Botox

(Botulinum toxin type A)

PL 00426/0074-0105
PL 00426/0118-0025
PL 00426/0119-0007

UKPAR

TABLE OF CONTENTS

Lay summary .......................................................... P2
Scientific discussion .................................................. P3
Steps taken for assessment ....................................... P46
Steps taken after assessment .................................... P47
Summary of product characteristics .......................... P48
Product information leaflet ....................................... P99
Labelling .................................................................... P115
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Allergan Limited a variation for the medicinal products Botox 50, 100 and 200 Allergan units – powder for solution for injection (PL 00426/0118, PL 00426/0074, and PL 00426/0119) on 8th July 2010 to add the new indication of “prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)”.

This medicine is subject to restricted medical prescription and is already indicated for the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis); for the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics; and for focal spasticity, including the treatment of dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older; and wrist and hand disability due to upper limb spasticity associated with stroke in adults.

Botox contains the active ingredient botulinum toxin type A from Clostridium botulinum at strength of 50, 100 or 200 Allergan units/vial. Botox blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals. It also blocks the release of neurotransmitters associated with the genesis of pain, which is the presumed mechanism for headache prophylaxis.

A critical review of the non-clinical and clinical data presented to the MHRA demonstrated that Botox is effective for the prophylaxis of headaches in adults with chronic migraine. No new safety risks were identified and the safety profile of Botox was considered to be acceptable. It was therefore judged that the benefits of using this product outweigh the risks, hence the variation has been granted.
Botox

(Botulinum toxin type A)

PL 00426/0074-0105
PL 00426/0118-0025
PL 00426/0119-0007

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction  P4
Pharmaceutical assessment  P5
Pre-clinical assessment  P6
Clinical assessment  P9
Overall conclusions and risk benefit assessment  P46
Annex 1  P118
Annex 2  P152
Annex 3  P187
Annex 4  P261
Based on the review of data on safety and efficacy the UK granted a variation to Allergan Limited for the medicinal product Botox – powder for solution for injection – on 8th July 2010 in order to add the new indication of “prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)”. This product is a restricted prescription only medicine. This variation application was submitted as a complex type II (extended) national variation.

Botox is already indicated for the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis); for the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics; and for focal spasticity, including the treatment of dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older; and wrist and hand disability due to upper limb spasticity associated with stroke in adults.

Botox is presented as a white powder for solution for injection in a clear glass vial, with rubber stopper and tamper-proof aluminium seal. Following reconstitution with sterile saline, Botox is injected using a sterile, 27-30 gauge needle. A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. Botox is available as Botox 50 Allergan Units/vial (PL 00426/0118), Botox 100 Allergan Units/vial (PL 00426/0074), and Botox 200 Allergan Units/vial (PL 00426/0119).

The active constituent in Botox is a protein complex derived from \textit{Clostridium botulinum}. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin. \textit{Clostridium botulinum} toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals. It also blocks the release of neurotransmitters associated with the genesis of pain.

The original licence for Botox was granted on 17th May 1994 and this subsequent variation to extend the indication to include “prophylaxis of headaches in adults with chronic migraine” was granted on 8th July 2010.
QUALITY ASSESSMENT

No new pharmaceutical data have been supplied with these applications and none are required for applications of this type.
NON-Clinical Assessment

Introduction
The applicant has submitted this extended complex type II national variation in order to add an indication for the prophylaxis of headaches in adults with chronic migraine to all strengths on the licence.

Supporting Evidence
The applicant has submitted four non-clinical pharmacology studies to support the rationale for the above proposed indication. The non-clinical data are also supported by clinical data.

Botox blocks the release of neurotransmitters associated with the genesis of pain. It is now known that Botox acts both directly on preventing sensitization of pain nerves in the periphery and consequently, indirectly modulates central sensory nerve function. It is believed that reducing excess pain signals to the central nervous system indirectly prevents (and reverses) the development of central sensitization and that this is the mechanism by which Botox has its headache prophylaxis effect. This pharmacologic action aligns well with current understanding of the pathophysiology of chronic migraine, whereby there is a pervasive and/or persistent cortical hyperexcitability. The non-clinical data discussed further below support the hypotheses regarding the proposed mechanism of action for prevention of headache in chronic migraine. These hypotheses are also supported by clinical data.

Several non-clinical studies in the literature report that Botox or botulinum neurotoxin type A (BoNT/A) inhibits the peripheral release of nociceptive, inflammatory mediators such as glutamate, calcitonin gene-related peptide and substance P. An indirect reduction of central sensitization is supported by studies investigating the early expression of c-Fos immunoreactivity (an indicator of activation of neurons) in the spinal cord, using the formalin-challenged rat model. In these studies, activation of c-Fos gene and expression of its protein product, Fos, indicate rapid neuronal firing in response to increased peripheral stimuli. Subcutaneous Botox pre-treatment reduced Fos protein expression after formalin challenge in a dose-dependent manner, indicating a reduction in the peripheral stimuli and an indirect effect on central sensitization, leading to a reduction in pain. A conceptual mechanism of the effect of Botox in preventing peripheral and central sensitization is shown in Figure 1.
Evidence supporting Figure 1 is summarised in the following three Allergan pharmacology studies:

**BOTOX Pharmacological Efficacy in Rat Models of Thermal Nociception**
This study evaluated the ability of Botox to reduce pain in two models in rats. Botox did not alter perception of acute thermal pain in the Hargreaves model but was effective in reducing capsaicin-induced thermal hyperalgesia.

i) In the classic acute radiant thermal pain withdrawal response (Hargreaves model), pretreatment of rats with Botox (15 units/kg, intraplantar) did not change the nociceptive response, whereas morphine (10 mg/kg, s.c.) significantly alleviated the acute pain.

ii) Intraplantar capsaicin (10 microliter of a 0.3% solution) elicited a thermal hyperalgesic response in the Hargreaves model. Pretreatment with Botox (0.3 to 15 U/kg, intraplantar) prevented capsaicin-induced thermal hyperalgesia in a dose related manner. The highest dose, 15 U/kg was selected to avoid distal muscle weakness. Local administration of lidocaine (0.6 and 1.2 mg, intraplantar) prevented capsaicin-induced thermal hyperalgesia in the treat paw and did not affect the contralateral paw. Reference analgesic agents prevented capsaicin-induced thermal hyperalgesia as expected: acetamenophen (600 and 900 mg/kg, orally), morphine (5 and 10 mg/kg, SC), gabapentin (10, 30, 100 mg/kg, intraplantar), and naproxen (30, 100, 300 mg/kg, orally).
This study evaluated the ability of Botox to inhibit capsaicin-induced mechanical allodynia as measured by paw withdrawal.

The time taken to induce mechanical allodynia in rats following administration of capsaicin (10 microliter of 0.3%) was within 15 minutes. Botox (3.5, 7, 15 U/kg, subcutaneous) administered 24 hours before the capsaicin challenge prevented development of cutaneous allodynia in a dose-related manner. Pretreatment of the rats with Botox (15 U/kg, subcutaneous) at 1 day, 2 weeks, 4 weeks or 8 weeks prevented development of cutaneous allodynia. The effect of Botox was evident out to 8 weeks, albeit with an approximately 50% reduction of efficacy.

This study evaluated the ability of Botox to inhibit mechanical allodynia in a streptozocin-induced diabetic neuropathic pain model in rats as measured by paw withdrawal.

Intravenous streptozocin (65 mg/kg, IV) elicited a sustained hyperglycemia in rats which resulted in the development of a progressive mechanical allodynia. A single injection of Botox (15 units/kg, SC) was associated with an increase in paw withdrawal threshold (PWT) in STZ-treated rats, starting and peaking at day 1, and gradually decreasing after day 8 in ipsilateral paws, but not in contralateral paws, indicating no systemic effects. Unlike Botox, gabapentin acts systemically and showed an increase in PWT in both paws. These data were consistent with previous results regarding the antinociceptive effect of peripherally administered Botox and support a role for peripheral mechanisms in the establishment and maintenance of chronic pain states.

**Evaluation**

The pharmacological data presented by the applicant appear to support the proposed indication. Section 5.1 of the SmPC is satisfactory from a non-clinical perspective.

No pharmacokinetic or toxicological data have been submitted. This is acceptable as the pharmacokinetic and toxicological data provided for previous applications support the current submission.
SCOPE OF THE VARIATION

The scope of this type II variation is the extension to a new indication for Botox: prophylaxis of headaches in adults with chronic migraine.

Other changes to the SmPC related to this variation concern section 4.2 (Posology and method of administration), section 4.8 (Undesirable effects), and 5.1 (Pharmacodynamic properties). The PIL has been revised accordingly.

Paediatric Investigation Plan (PIP)

Botox was first approved in Europe in 1992. It is not protected by a Supplementary Protection Certificate (SPC) or a patent which qualifies for the granting of the SPC. As a result, the product does not fall within the scope of Article 8 of the Paediatric Regulation.

SCIENTIFIC DISCUSSION

CLINICAL PHARMACOLOGY AND MECHANISM OF ACTION

Migraine attacks are characterised by unilateral throbbing, pulsating headache associated with nausea, vomiting, photophobia, phonophobia and cutaneous allodynia. The trigeminal nerves, which innervate intracranial and extracranial tissues, have been postulated to account for head pain and other symptoms in migraine. The first-order neurons in the trigeminal ganglion receive input from the dural blood vessels, which is transmitted to second-order neurons in the trigeminal brain stem nuclear complex and is finally sent to the third-order neurons in the thalamus. Studies in humans and animals have shown that migraine pain progresses along this neural pathway, with throbbing head pain occurring early in the attack (sensitisation of first-order neurons), followed by central sensitisation and cutaneous allodynia within the referred pain area (second-order) and finally extracephalic allodynia, e.g. neck stiffness (third-order).

It has been postulated that the development of throbbing in the initial phase of migraine is mediated by sensitisation of peripheral trigeminovascular neurons that innervate the meninges; it occurs when the nerve terminals (meningeal nociceptors) of the neurons of the trigeminal ganglion are soaked with the "inflammatory" soup (prostaglandin E2, bradykinin, serotonin and cytokines) along the vasculature of the cerebral dura mater. When stimulated these axon terminals release neuropeptides, such as substance P, neurokinin A, and calcitonin gene-related peptide (CGRP), which promote meningeal vasodilatation. However, CGRP effects do not seem sufficient to activate or sensitise meningeal nociceptors. The development and maintenance of cutaneous allodynia later in the attack is propelled by sensitisation of central trigeminovascular neurons which receive converging sensory input from the meninges as well as from the scalp and facial skin and become hyperexcitable.
According to the Marketing Authorisation Holder (MAH), Allergan Limited, the presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitisation, as confirmed by clinical and non-clinical studies. Clinical evidence suggests that Botox reduces or prevents local neuropeptide (NP) release and thus reduces NP-induced sensitisation of peripheral nociceptive (pain-conducting) nerve fibres, thereby reducing peripheral pain signals to the central nervous system. Additionally, Botox preferentially targets Cfibres and probably TRPV1-receptors, block neurotransmitter release and subsequently reduces pain, neurogenic inflammation and cutaneous heat pain thresholds. These hypotheses regarding the proposed mechanism of action for prevention of headaches in chronic migraine are supported by non-clinical data (see Non-clinical Assessment).

Assessor’s comment
Numerous pharmacodynamic studies have been conducted in healthy volunteers in order to provide some support to a potential effect of Botulinum neurotoxin A (BoNT/A) in the treatment of migraine. Indeed, the mechanism of a direct analgesic effect of BoNT/A is not fully clarified yet. However, it seems to be distinct from BoNT/A effect on muscles. This idea is supported by the evidences showing that the effect of BoNT/A on pain appears in the absence of muscle contraction or lasts for longer duration of time after relieving of muscle contraction. Sufficient in vitro exposure to BoNT/A has been shown to reduce the release of glutamate, substance P, CGRP and vasopressin from cultured cells or isolated materials. Non-clinical studies were also successful to demonstrate that BoNT/A is able to inhibit pain and neuropeptide release, e.g. in rat formalin test. Antinociceptive effects of BoNT/A were also seen in a rat capsaicin pain model (see Non-clinical Assessment).

Human experimental models of pain have provided more information about the analgesic effects of BoNT/A. Although the studies appeared well conducted (prospective, double-blind placebo-controlled) their findings have been highly inconsistent, which may suggest that the analgesic efficacy of BoNT/A may depend on the injection site, route of administration, dose and outcome measures as well as timing of the challenge, applied pain model and also the BoNT/A preparation itself. Blersch et al. [2002] and Voller et al. [2003] found no effect of BoNT/A on electrical and heat pain thresholds in human skin. The study by Krämer et al. [2003] also failed to detect any antinociceptive or antihyperalgesic effect of BoNT/A in an electrically induced pain model; however, a reduction of the neurogenic flare was observed. In an Ultraviolet B pain model no analgesic or anti-inflammatory effect of BoNT/A was seen [Sycha T. 2006]. In contrast to the above-mentioned studies, Gazerani P et al. [2006] showed that intramuscular BoNT/A inhibits the capsaicin-evoked pain and neurogenic vasodilatation in human skin mostly due to toxin leakage to the skin in the forehead. Tognoli et al. [2007] showed pain and flare reduction in the forearm skin; however, such result could not be repeated by Schulte-Mattler et al. [2007] in a similar model. Subsequently, Gazerani P et al. [2009] investigated the effect of subcutaneous (forehead) administration of BoNT/A on capsaicin-induced...
trigeminal pain, neurogenic inflammation and experimentally induced cutaneous pain modalities. The study demonstrated that BoNT/A reduced capsaicin-induced trigeminal pain, sensitisation and neurogenic inflammation, altered cutaneous heat pain threshold, but had no effect on electrical or pressure pain thresholds. The earliest analgesic effect of BoNT/A was recorded at 24 h after its application. Of note, most published negative studies were conducted with Dysport whereas most published positive results were found by teams using Botox.

In conclusion, there is limited information supporting the effect of subcutaneous administration of Botox on peripheral nociceptive nerve fibres in the skin.

CLINICAL EFFICACY

An overview of the clinical development conducted by the MAH in the indication of headache and migraine is shown in figure 2.

Figure 2. Overview of all migraine clinical studies

Rationale and early development of Botox in migraine

Rationale

A myogenic nociceptive mechanism for primary headache has been postulated, especially in tension-type headache (TTH). The most prominent clinical finding in patients with TTH is considerably increased tenderness to palpation of pericranial myofascial tissues and also trapezius muscle hardness, even during attack free periods. Botulinum toxin has been shown to be effective in reducing myogenic pain associated with cervical dystonia, chronic limb spasticity, and hand dystonia. In early reports, it was also observed that after treatment of torticollis by Botox therapy, the relief of pain exceeded the reduction of inappropriate muscle contraction, suggesting that Botox may act via a different pathophysiologic pathway to alleviate or eliminate generalised pain other than that related to muscle dysfunction.
While performing initial clinical trials of Botox treatment for hyperfunctional lines of the face, some physicians discovered a correlation between pericranial Botox administration and the alleviation of migraine headache symptoms. The use of Botox to reduce migraine pain was not immediately obvious because there is no clear cut mechanism of action that could explain its clinical effect. Patients with concomitant headache disorders as well as other patients requiring treatment only for headaches were then prospectively treated to determine whether the relationship between Botox treatment and the alleviation of migraine symptoms was meaningful and could be replicated by other physicians. Botox was injected into glabellar, temporal, and frontal regions of the head in 106 patients. Among 77 true migraine subjects treated prophylactically, 51% reported complete response with a mean duration of 4 months. A minimal dose of approximately 50 units distributed over the glabella (5 injection sites), bitemporal (3 injection sites per side), and upper forehead (4 injection sites) at a dilution of 4 cc per 100 units became the most frequent dose/volume/site ratio used (Binder, 2000).

**Early phase II trials in episodic migraine (studies 005, 009, 024, 026, 036)**

All studies were negative except for the first trial (study 005), where a low dose (25 U) injected into several muscles in the front of the head (frontalis, temporalis, corrugator, procerus) was the only one to show any benefit but this was not subsequently reproduced.

**Study in chronic tension-type headache (study 027)**

This study was designed to explore and compare various dose and injection site combinations (frontal and posterior) with total doses ranging from 50 U to 150 U. The frequency of tension headache-free days increased in all treatment groups, but no significant differences favouring Botox were observed.

The next step was a massive increase in doses with more muscle groups injected (up to 260 U) in episodic migraine and chronic headache. The major distinction between these two entities is the number of headache days per month: ≤ 15 in episodic migraine and ≥ 16 in chronic headache.

**Later phase II trials in episodic migraine**

- **Study 037**
  
  **Treatment: follow the pain paradigm**

  In contrast to the fixed site/fixed dosage approach used in other studies, physicians participating in this study were allowed to determine the number of injection sites and dosage to be administered for the specified frontal and posterior muscle areas, depending on the location and severity of the patient’s headache pain. Dose levels also were higher than those used in previous studies due to the injection of larger, posterior muscles (table 1 and figure 3). The protocol included 3 blinded treatment cycles because, based on physicians’ feedback, it was anticipated that additional treatments might increase benefit. Finally, it was thought that a dosing interval of every 4 months may be too long; treatment intervals of 3 months for other Botox muscle-related indications have been shown to be optimal. Therefore, the treatment cycles were shortened to every 3 months.

<table>
<thead>
<tr>
<th>Muscle Area</th>
<th>Number of Units</th>
<th>Bilateral Injection</th>
<th>Total Dose (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal/Glabellar</td>
<td>25-40</td>
<td>No</td>
<td>25-40</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>10</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>Temporalis</td>
<td>10-25</td>
<td>Yes</td>
<td>20-50</td>
</tr>
<tr>
<td>Masseter (optional)</td>
<td>0-25</td>
<td>Yes</td>
<td>0-50</td>
</tr>
<tr>
<td>Trapezius</td>
<td>10-30</td>
<td>Yes</td>
<td>20-60</td>
</tr>
<tr>
<td>Semispinalis</td>
<td>5-10</td>
<td>Yes</td>
<td>10-20</td>
</tr>
<tr>
<td>Sphenius capitis</td>
<td>5-10</td>
<td>Yes</td>
<td>10-20</td>
</tr>
</tbody>
</table>

**TOTAL**

105-260

Note: Patients were injected with the minimum dose of 103U of BOTOX® or placebo in the specified muscles as defined above; total doses were determined by the investigator using a follow the pain paradigm.

Botox
Design
First administration: placebo (run-in period)
Separate randomisation for placebo responders and non-responders to 3 consecutive administrations, 3 months apart, of placebo or active

Results
In the analyses of the protocol-designated primary efficacy variable (number of migraine headaches per 30-day period), there were no statistically significant differences between the Botox and placebo groups, including Day 180 (the primary time point) for either the placebo non-responders (population of primary interest) or placebo responders, or for the pooled population of patients (placebo non-responders and placebo responders).

In the analyses of the protocol-designated secondary and other efficacy variables, there were only occasional statistically significant differences between treatment groups for the pooled population. No treatment-by-responder group interaction was statistically significant; therefore, stratification by this factor did not help in identifying a subpopulation in which Botox benefits patients better than placebo. Further post hoc analyses were performed to identify subgroups of patients and variables where the efficacy of Botox relative to placebo was demonstrated. These analyses did not find any consistent and statistically significant differences between the Botox and placebo groups.

- **Study 509**
  Treatment: fixed-site, fixed-dose paradigm; comparison of 3 doses (75 U, 150 U, 225 U) vs. placebo
  Same design as previous study

<table>
<thead>
<tr>
<th>Table 2. Study medication dose and injection sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Frontalis</td>
</tr>
<tr>
<td>Corrugator</td>
</tr>
<tr>
<td>Temporalis</td>
</tr>
<tr>
<td>Splenius capitis</td>
</tr>
<tr>
<td>Trapezius</td>
</tr>
<tr>
<td>Semispinalis capitis</td>
</tr>
<tr>
<td>Suboccipital region</td>
</tr>
<tr>
<td>Total injected</td>
</tr>
</tbody>
</table>

*Botox*® or placebo were injected bilaterally into the identified pericranial muscle groups at the indicated Units (U)/Volume (mL) injected per bilateral muscle groups.
Results
All treatment groups, including the placebo group, showed substantial reductions in the frequency and duration of migraine headaches following each treatment cycle. No statistically significant differences were seen between the Botox groups and placebo at most time points for most of the efficacy parameters evaluated, with the strength of the placebo response being generally of the same order as that seen in the Botox groups.

Assessor’s comment
In spite of massively increased doses of Botox, the two trials in episodic migraine were negative.

Later phase II trials in chronic headache

- **Study 038**
  Treatment: *follow the pain paradigm* and design similar to study 037
  Inclusion criteria: Primary headache disorder with ≥ 16 headache days per month by history and confirmed by diary during baseline, which could include any combination of migraines with or without aura, episodic/chronic tension-type headaches, and/or migrainous headaches (as defined by 1988 ICHD criteria)

Results
A total of 355 patients entered the placebo run-in period and were subsequently randomised to treatment. At the end of the run-in period (Day 0), 279 (78.6%) patients were classified as placebo non-responders and 76 (21.4%) patients as placebo responders. Subsequently patients were randomised within each stratum (placebo non-responders and placebo responders) to receive either Botox or placebo. Within the placebo non-responder stratum, 134 patients received Botox and 145 patients received placebo. Within the placebo responder stratum, 39 patients received Botox and 37 patients received placebo. The study was completed by 76.9% (133/173) of Botox patients and by 76.9% (140/182) of placebo patients.

The 2 treatment groups were similar in demographic characteristics, with no statistically significant differences between the groups. Patients were 19 to 65 years of age (mean, 43.5 years), 62.4% (174/279) were > 40 years of age, most were Caucasian (88.5%, 247/279), and most were female (84.9%, 237/279).

There were no statistically significant differences between Botox and placebo in the prespecified analyses of the primary efficacy variable: *frequency of headache-free days per 30-day period in the placebo non-responder strata*. However, the secondary endpoint of the proportion of patients with a *decrease from baseline of 50% or more headache days per 30-day period in the placebo non-responder strata* was met. There were occasional statistically significant differences in the analyses of other protocol-designated variables (eg, frequency of headaches, incidence of subjects with a decrease from baseline of 50% or more headaches per 30-day period, frequency of migraines per 30-day period) when analyses were performed on both placebo non-responder and placebo responder subpopulations. No treatment-by-responder interaction was statistically significant; therefore, stratification by responder/nonresponder was not necessary.

- **Study 039**
  Treatment: *fixed-site, fixed-dose paradigm* and design similar to Study 509
  Inclusion criteria: same as Study 038

Results
A total of 702 patients entered the placebo run-in period and were subsequently randomised. At the end of the run-in period (Day 0), 538 (76.6%) patients were classified as placebo non-responders and 164 (23.4%) were classified as placebo responders. A total of 182 patients received Botox 225 U, 168 received Botox 150 U, 174 received Botox 75 U, and 178 received placebo. Overall, 71.9% of the 538 placebo non-responders and 75.6% of the 164 placebo responders completed the study. For both

Botox
placebo non-responders and placebo responders, discontinuation rates were higher in the placebo group (33.7%) compared with the Botox groups (23.2% to 26.4%), primarily due to lack of efficacy.

The treatment groups were similar in demographic characteristics, with no statistically significant differences among the groups. Patients were 18 to 65 years of age (mean, 43.4 years), 66.2% (465/702) were > 40 years of age, most were Caucasian (94.0%, 660/702), and most were female (82.9%, 582/702).

There were no consistent and statistically significant differences among the treatment groups in the prespecified or post hoc analyses of the primary efficacy variable (number of headache-free days), secondary efficacy variable (decrease from baseline of 50% or more headache days per 30-day period), and other efficacy variables. For most of these variables, there were consistent improvements in the Botox and placebo groups over the entire treatment period. Greater improvements were observed in 1 or more Botox groups compared with the placebo group for most efficacy variables, although there were few statistically significant differences among the treatment groups. There was no evidence of a relationship between the dose of Botox and the response to treatment in the analyses of any of the efficacy variables.

**Assessor’s comment**

Overall, these two trials in chronic headache did not seem very promising, but the MAH “identified a specific patient population, dose, treatment regimen and efficacy endpoint that awaited confirmation in pivotal phase 3 trials”. Indeed, an analysis of a subgroup of patients from the chronic migraine phase II trials (referred as the ‘phase 2 subgroup’) who met key phase III study criteria was performed and presented to support the phase III trials results.

**Pivotal Phase III studies**

Two identical multicentre, double-blind, placebo-controlled trials were conducted in parallel from Feb-Mar 2006 to Jul-Aug 2008. **Study 079** was conducted in 51 centres in US (51) and Canada (5); **study 080** was conducted in 66 centres in US (44), Germany (8), Canada (6), UK (3), Croatia (3), and Switzerland (2). They were performed in compliance to GCP. Since they were identical, they will be described together in the rest of the document.

**Methods**

**Design**

- 4-week run-in phase (baseline)
- 24-week double-blind, randomised, placebo-controlled, parallel-group phase: patients received either 2 treatments of Botox or 2 treatments of placebo
- 32-week open-label phase: patients received 3 treatments with Botox
Objective
- Double-blind Phase: to evaluate the efficacy and safety of Botox compared with placebo as headache prophylaxis in migraine patients with 15 or more headache days per 4-week period
- Open-label Phase: to evaluate the long-term safety of Botox

Selection criteria
- Main inclusion criteria
  - Male or female, 18 to 65 years old
  - History of migraine headache disorder meeting any of the diagnostic criteria listed in ICHD-II (2004) section 1, Migraine, with the exception of “complicated migraine” (e.g., hemiplegic migraine [1.2.4, 1.2.5], basilar migraine [1.2.6], ophthalmoplegic migraine [13.17] or migrainous infarction [1.5.4])
  - Four (4) or more distinct headache episodes each with a duration of at least 4 hours during the 4-week baseline phase
  - Fifteen (15) or more headache days during the 4-week baseline phase, with each day consisting of 4 or more hours of continuous headache
• At least 50% of baseline headache days are migraine or probable migraine days (ICHD-II 2004 sections 1)

- Main exclusion criteria
  o Uncontrolled clinically significant medical condition other than the condition under evaluation (including alcohol/illicit substance abuse)
  o Headache diagnosis of chronic tension-type headache (ICHD-II 2.3), hypnic headache (ICHD-II 4.5), hemicrania continua (ICHD-II 4.7) or new daily persistent headache (ICHD-II 4.8)
  o Headache attributed to another disorder (eg, cervical dystonia, craniotomy, head/neck trauma)
  o Unremitting headache lasting continuously throughout the 4-week baseline period
  o Patients with a known or suspected Temporomandibular Disorder (TMD)
  o Any medical condition that may put the patient at increased risk with exposure to Botox
  o Use of any headache prophylactic medication within 28 days prior to Week -4
  o Acupuncture, TENS (transcutaneous electrical nerve stimulation), cranial traction, nociceptive trigeminal inhibition or occipital nerve block treatments, or injection of anaesthetics or steroids into the study target muscles within 4 weeks prior to Week -4, or, on or after Week -4

**Assessor’s comment**

The diagnostic criteria for chronic migraine published in 2004 by the Headache Classification Committee (ICHD) of the International Headache Society (IHS) were rapidly recognised as not optimal and in June 2006 revised criteria (ICHD-2R) were proposed (Olesen et al, 2006). When Allergan initiated the phase III studies in the beginning of 2006, the revised criteria had not yet been finalised and published but their protocol criteria were defined by headache experts who were members of the IHS Headache Classification Committee.

Although not exactly the same, the study criteria and current ICHD criteria are similar and overlap. Importantly, the ICHD classification excludes medication-overuse headache (MOH) from chronic migraine (CM) while these subjects were not excluded from the trials. However, the Task Force of the IHS Clinical Trials Subcommittee published guidelines for controlled trials of prophylactic treatment of chronic migraine in adults (Silberstein, 2008), where they recommend that subjects with MOH may be included provided the randomisation is stratified accordingly. Such stratification was indeed performed in Allergan’s trials. Other selection criteria such as age, coexistent disorders, and concomitant therapies are also in line with these guidelines. No criterion was formally mentioned about the duration of CM at study entry (more than 6 months is recommended) but the description of the patients actually enrolled showed that this must have been the case in the great majority of patients (mean duration of about 18 years).

In conclusion, the population selected in these trials is considered representative of the target population of patients with chronic migraine as currently defined (ICHD-2R).

**Treatment**

The test product used was Botox (formulation 9060X, which contained 100 U botulinum toxin type A), which was reconstituted with 2 mL of 0.9% sodium chloride (preservative free).

For each treatment, patients received a minimum dose of 155 U Botox or placebo administered intramuscularly (IM) as 31 fixed-site, fixed-dose injections across 7 specific head/neck muscle areas. At the investigator’s discretion, additional injections of Botox or placebo could be administered up to a maximum dose of 195 U (39 injection sites), using a follow-the-pain paradigm across only 3 of the specified head/neck muscle areas. These optional additional injections did not have to be consistent across treatment visits with respect to dose or number of injection sites, but could not exceed the maximum dose allowed.

Botox  

17/117
Thus, the minimum total cumulative dose planned for the study was 465 U (155 U × [0 double-blind treatments + 3 open-label treatments]) and the maximum total cumulative dose was 975 U (195 U × [2 double-blind treatments + 3 open-label treatments]).

The reference therapy was Placebo (formulation 9379X, which contained 0.9 mg of sodium chloride), which was reconstituted with 2.0 mL of 0.9% sodium chloride (preservative free) and injected in an identical way to the test product.
Assessor’s comment

The maximum allowed dose (195 U per treatment session) was lower than the maximum doses tested in the phase II trials because there had been an increased incidence of adverse reactions at the highest dose of 225 U. Also, arm pain (shoulder pain) had been a newly identified adverse event that was felt to be secondary to the injection of the trapezius muscles in these studies. Injection of this muscle had not been a part of the treatment paradigm in earlier phase II studies, and no adverse events for arm pain had been reported in those trials.

Randomisation

Upon entry into the 4-week baseline phase, patients were assigned a unique 5-digit patient number that was provided to the site via a central validated interactive voice response system (IVRS). At Day 0, patients were randomised within each strata of medication overuse to Treatment 1 (Botox or placebo); the definition of medication overuse was in line with ICHD criteria. Vials of medication were provided in kits that were individually assigned to patients via the validated electronic telephone system prior to each treatment. The medication kits were also randomised within blocks balanced by treatment. Blocks of medication kits were assigned to investigator sites and blocks were not broken across sites.

Efficacy endpoints

Efficacy measures were variables derived from the information recorded by patients for the duration of the study using a validated electronic headache diary that captured data using a telephone IVRS.

Primary endpoint

Frequency of headache episodes per 28-day period at week 24 (during the 28-day period ending with week 24). A headache episode was defined as patient-reported headache pain with a start and stop time that indicated that the pain lasted at least 4 continuous hours per patient diary.

Secondary endpoints

Secondary efficacy variables summarised for each 28-day period included:

- Frequency of headache days (days (00:00 to 23:59) with 4 or more continuous hours of headache)
- Frequency of migraine/probable migraine days (days (00:00 to 23:59) with 4 or more continuous hours of migraine headache (ICHD-II criteria 1.1 or 1.2) or probable migraine (ICHD-II 1.6))
- Frequency of migraine/probable migraine episodes (patient reported headache pain with a start and stop time that indicated that the pain lasted at least 4 continuous hours and met ICHD-II 1.1, 1.2 or 1.6)
- Frequency of acute headache pain medication intakes (defined as a patient reported intake of medication(s) to treat headache pain per patient diary)

Other efficacy variables

- Percentage of patients with at least a 25%, 50%, 75%, and 100% decrease from baseline in the frequency of headache episodes
- Percentage of patients with at least a 25%, 50%, 75%, and 100% decrease from baseline in the frequency of headache days
- Percentage of patients with at least a 25%, 50%, 75%, and 100% decrease from baseline in the frequency of migraine/probable migraine episodes
- Percentage of patients with at least a 25%, 50%, 75%, and 100% decrease from baseline of the frequency of migraine/probable migraine days
- Frequency of days with acute headache pain medication use
- Incidence of use and overuse of acute headache pain medication, including baseline incidence of use and overuse of specific types of acute headache pain medication, displayed separately for ergotamines, triptans, simple analgesics, opioids, and combination analgesics

Patient Reported Outcomes Measures

- The Headache Impact Test (HIT-6) comprises 6 items that assess pain, role functioning, social functioning, cognitive functioning, vitality, and psychological distress. A total score is created by summing across all items, and ranges from 36 (no impact) to 78 (severe impact).
Score categories are based on the total score and include “little to no impact” (total score 36 to 49), “some impact” (total score 50 to 55), “substantial impact” (total score 56 to 59) and “severe impact” (total score 60 to 78).

- The Migraine-Specific Quality of Life Questionnaire (MSQ) is comprised of 14 items measuring the following 3 domains: Role Function - Restrictive (RFR), which measures the degree to which performance of daily activities is limited by migraines; Role Function – Preventive (RFP), which measures the degree to which performance of daily activities is interrupted by migraines; and Emotional Function (EF), which examines feelings of frustration and helplessness due to migraines. Scores range from 0 (high function) to 100 (low function).

- The Euro-Qual-5 Dimensions (EQ-5D) includes a visual analog scale (VAS) for eliciting a self-rating of health status with a range of 0 (worst imaginable health state) to 100 (best imaginable health state).

**Assessor’s comment**

The EU guideline (dated 2003) recommends the frequency of migraine attacks as primary endpoint while requiring an interval of at least 48 hours to distinguish between two attacks. Secondary endpoints may be responder rate (≥ 50% reduction in attack frequency), migraine days, average intensity of headache, drug consumption.

The IHS guidelines published after the trials had been conducted (2008) recommend that the primary endpoint includes headache days with moderate or severe intensity, migraine (including probable migraine) days, or frequency of migraine episodes without expressing any preference between these three outcomes. Of note, they also emphasise that the duration of pain-free period between episodes must be predefined. Secondary endpoints may be headache days (any intensity), responder rate (≥ 50% or ≥ 30% reduction in the primary endpoints), or acute treatment utilization. Validated disease-specific quality of life and disability instruments are also recommended as secondary endpoints; HIT or MIDAS may be useful.

Overall, no primary endpoint emerges as clearly consensual and the debate between headache days and episodes remains open. The selection of headache episodes was certainly based on the phase II trials results, where the only significant differences were observed on episodes rather than days. Of note, the MAH did not define any pain-free period between two episodes, which potentially allows for reporting of several episodes per day. In addition, the primary endpoint of headache episodes included headache of any severity.

In February 2008, the primary analysis for the double-blind phase of study 079 was performed. Although there was a large mean improvement from baseline for the primary endpoint (frequency of headache episodes), no between-group difference was found at any double-blind phase timepoint whereas highly significant differences for improvement from baseline were observed for both headache days and migraine/probable migraine days. As a result, on 05 August 2008 and prior to the primary database lock and treatment unblinding, the protocol and statistical analysis plan for study 080 were officially amended to change the primary endpoint to frequency of headache days. To control the type 1 error rate for multiple secondary endpoints, a fixed-sequence gate keeping approach was used for the 5 ranked secondary variables at the week 24 primary visit.

In conclusion, it would seem acceptable to consider the totality and the consistency of the results between the various endpoints for both trials, which are generally in line with various recommendations, without putting too much emphasis on their prioritisation.

**Statistical analysis**

The ITT population for efficacy data analyses consisted of all randomised patients. Patients were analysed according to the randomisation assignment regardless of the actual treatment received. All safety analyses were performed using the safety population, consisting of all patients who received at least 1 injection of the study treatment. Patients were analysed according to the actual treatment received regardless of randomisation assignment at day 0.
The ITT analysis was the primary analysis. Comparisons between treatment groups were done by analysis of covariance (ANCOVA) for the change from baseline, including treatment, baseline and medication overuse (the stratification variables).

A thorough description as to how missing data has been handled in the studies was provided.

- If there are at least 20 days for which the patient has reported headache data (for either headache days or headache-free days), but less than 28 days in a diary period, the data for counts will be prorated accordingly and rounded to the nearest whole number. The prorating will be based on the number of days with reported data in that period. For example, if there are 24 days with reported data in the third diary period, the data will be multiplied by 28/24 and rounded to a whole number.

- If a patient reports any diary data for less than 10 days of a 28-day period, such a patient’s score for that period will be imputed by a modified last observation carried forward (mLOCF) analysis and rounded to the nearest whole number. Specifically, the substitution will be the patient’s previous 28-day period score multiplied by the ratio of the mean over all patients in the 28-day period of interest divided by the mean over all patients in the previous 28-day period.

- If a patient reports diary data for at least 10 days but less than 20 of a 28-day period, the scores for the period will instead be imputed by taking the average of the two estimated scores resulting from the simple prorating method and the mLOCF method (discussed above) and rounding to the nearest whole number.

Sensitivity analyses for the primary variable and key secondary variables were done by comparing the change from baseline between treatment groups using a Wilcoxon rank-sum test, by ANCOVA of observed data, and by ANCOVA of ranked mLOCF data. A secondary analysis of the primary efficacy variable included the changes from baseline to other timepoints.

Post hoc efficacy analyses included the following: total cumulative hours of headache that occurred on headache days, frequency of moderate/severe headache days, and proportion of patients with severe headache impact test (HIT-6) impact category scores.

**Statistical Assessor’s comment**
The methods used to analyse the data are appropriate and acceptable. The imputation technique to handle missing data is understood although it is not clear whether this would give an appropriately conservative method for handling the missing data. This is discussed further in the patient disposition section.

**Results**

**Patient disposition**
A combined total of 1384 patients (679 in study 079 and 705 in study 080) were enrolled and randomised to receive study treatment: 688 patients (341 in study 079 and 347 in study 080) were randomised to receive Botox (ie, the Botox/Botox group) and 696 patients (338 in study 079 and 358 in study 080) were randomised to receive placebo (ie, the placebo/Botox group) in the double-blind phase. The majority of patients (65.5% [906/1384]) were stratified to the group that was overusing acute headache pain medications at baseline.

A total of 88.2% (607/688) of patients treated with Botox and 90.4% (629/696) of patients treated with placebo completed the double-blind phase. Only 10.7% (148/1384) of the patients discontinued the study prior to the open-label phase. Only 0.7% (5/688) of patients treated with Botox and 0.1% (1/696) of patients treated with placebo discontinued the double-blind phase due to lack of efficacy.

A total of 72.6% (1005/1384) of all patients completed the open-label phase, and therefore, the entire study: 74.6% (513/688) in the Botox/Botox group and 70.7% (492/696) in the placebo/Botox group. Only 2.3% (16/688) of patients in the Botox/Botox group and 3.0% (21/696) in the placebo/Botox group discontinued the entire study due to lack of efficacy.
Table 5. Patient disposition

<table>
<thead>
<tr>
<th>Disposition</th>
<th>Study 191622-080</th>
<th>Study 191622-079</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX®/ BOTOX®</td>
<td>Placebo/ BOTOX®</td>
<td>BOTOX®/ BOTOX®</td>
</tr>
<tr>
<td>Enrolled a</td>
<td>347 (89.6%)</td>
<td>334 (93.3%)</td>
<td>341</td>
</tr>
<tr>
<td>Completed double-blind phase (week 24)</td>
<td>311 (88.2%)</td>
<td>334 (93.3%)</td>
<td>296 (86.8%)</td>
</tr>
<tr>
<td>Discontinued prior to week 24 b</td>
<td>36 (10.4%)</td>
<td>24 (6.7%)</td>
<td>45 (13.2%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>8 (2.3%)</td>
<td>3 (0.8%)</td>
<td>11 (3.2%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>4 (1.2%)</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1 (0.3%)</td>
<td>1 (0.3%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>7 (2.0%)</td>
<td>8 (2.2%)</td>
<td>6 (1.8%)</td>
</tr>
<tr>
<td>Personal reasons</td>
<td>7 (2.0%)</td>
<td>5 (1.4%)</td>
<td>12 (3.5%)</td>
</tr>
<tr>
<td>Protocol violations</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (2.3%)</td>
<td>6 (1.7%)</td>
<td>13 (3.8%)</td>
</tr>
<tr>
<td>Completed open-label phase (week 50) and entire study</td>
<td>261 (75.2%)</td>
<td>261 (72.9%)</td>
<td>252 (73.9%)</td>
</tr>
<tr>
<td>Discontinued entire study c</td>
<td>85 (24.8%)</td>
<td>97 (27.1%)</td>
<td>89 (26.1%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>20 (5.8%)</td>
<td>18 (5.0%)</td>
<td>18 (5.3%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>10 (2.9%)</td>
<td>15 (4.2%)</td>
<td>6 (1.8%)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>4 (1.2%)</td>
<td>2 (0.6%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>10 (2.9%)</td>
<td>22 (6.1%)</td>
<td>14 (4.1%)</td>
</tr>
<tr>
<td>Personal reasons</td>
<td>20 (5.8%)</td>
<td>13 (3.6%)</td>
<td>21 (6.2%)</td>
</tr>
<tr>
<td>Protocol violations</td>
<td>2 (0.6%)</td>
<td>1 (0.3%)</td>
<td>2 (0.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (5.8%)</td>
<td>26 (7.3%)</td>
<td>26 (7.6%)</td>
</tr>
</tbody>
</table>

Source: Module 5.3.3 ISE Table 1-1

a Includes all randomized patients.
b Discontinued patients only include those who discontinued before open label phase.
c Discontinuation prior to week 35 is cumulative (ie, includes discontinuations prior to week 24).
d Two patients completed the study at week 52 (Module 5.3.3.1 Report 191622-080 Table 14.1-2-1)
e Four patients completed the study at week 52 (Module 5.3.3.1 Report 191622-080 Table 14.1-2-1)
f Three patients completed the study at week 52 (Module 5.3.5.1 Report 191622-079 Table 14.1-2-1)

Statistical Assessor's comment

There was a slightly higher rate of drop-outs due to adverse events in the Botox group, which may be expected. It is perhaps surprising that more patients dropped out on the active treatment due to lack of efficacy, but this is consistent with it being a chance finding. There were slightly more missing data in study 79 compared to study 80 but overall the amount of missing data was small.

It was not clear from the study report how the missing data for patients who discontinued before week 20 were handled in the analysis. The MAH subsequently provided data on the proportion of patients who had more than 20 days of diary data, 10 to 20 days of diary data and less than 10 days of diary data over the period Week 20 to Week 24. This provided reassurance that there was no difference between the groups relating to the total amount of data that each patient actually contributes. This helped to support the argument that any missing data were not driving the results seen.

Baseline demographic characteristics

There were no statistically significant differences between the treatment groups with respect to their baseline demographic characteristics either within each study individually or in the pooled phase 3 analyses (table 6). Overall, patients were 18 to 65 years of age (mean, 41.3 years), 58.0% (803/1384)
were ≥ 40 years of age, and 90.1% (1247/1384) were Caucasian. As expected in this patient population, the majority of patients were female (86.4% [1196/1384]).

Table 6. Baseline demographic characteristics

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Study 191622-080</th>
<th>Study 191622-079</th>
<th>Pooled Phase 3 Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX® (N = 347)</td>
<td>Placebo (N = 358)</td>
<td>BOTOX® (N = 341)</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>41.0 ± 10.39</td>
<td>40.9 ± 10.82</td>
<td>41.2 ± 10.49</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (13.8%)</td>
<td>55 (15.4%)</td>
<td>37 (10.9%)</td>
</tr>
<tr>
<td>Female</td>
<td>299 (86.2%)</td>
<td>303 (84.6%)</td>
<td>304 (89.1%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>312 (89.9%)</td>
<td>321 (89.7%)</td>
<td>305 (89.4%)</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>35 (10.1%)</td>
<td>37 (10.3%)</td>
<td>36 (10.6%)</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>73.51 ± 18.36</td>
<td>74.72 ± 19.21</td>
<td>72.97 ± 17.97</td>
</tr>
<tr>
<td>Body mass index (kg/m²), mean ± SD</td>
<td>26.7 ± 6.55</td>
<td>27.1 ± 6.39</td>
<td>26.7 ± 6.18</td>
</tr>
<tr>
<td>Baseline overuse of acute headache medications (yes), n (%) a</td>
<td>220 (63.4%)</td>
<td>224 (62.9%)</td>
<td>226 (66.3%)</td>
</tr>
<tr>
<td>Pre-study headache prophylactic medication use (yes), n (%) b</td>
<td>222 (64.0%)</td>
<td>237 (66.2%)</td>
<td>203 (59.5%)</td>
</tr>
</tbody>
</table>

Baseline disease characteristics

In study 079, as well as the pooled phase 3 population, a statistically significant imbalance at baseline was observed for the following efficacy variables: frequency of headache episodes (fewer headache episodes with Botox than with placebo, p ≤ 0.023), frequency of migraine/probable migraine headache episodes (fewer migraine/probable migraine headache episodes with Botox than with placebo, p ≤ 0.006), and total cumulative hours of headache occurring on headache days (more hours of headache with Botox than with placebo, p ≤ 0.022). No such baseline differences were observed in study 080. All other baseline disease characteristics were similar between study groups in the phase 3 studies (table 7).

In the total pooled phase 3 study population (N = 1384), the mean number of headache days was 19.9, composed predominantly of headache days that were migraine/probable migraine (mean, 19.0) and of moderate/severe intensity (mean, 18.0).

Assessor’s comment

From these last figures, it can be deduced that the migraine sufferers of the study population were severely affected. This is fortunate since the IHS guidelines recommend to consider primarily moderate/severe headaches rather than headaches of any severity (primary endpoint chosen by the MAH).
Table 7. Baseline disease characteristics

<table>
<thead>
<tr>
<th>Disease Characteristic</th>
<th>Study 191622-080</th>
<th>Study 191622-079</th>
<th>Pooled Phase 3 Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX&lt;sup&gt;a&lt;/sup&gt; Placebo</td>
<td>BOTOX&lt;sup&gt;a&lt;/sup&gt; Placebo</td>
<td>BOTOX&lt;sup&gt;a&lt;/sup&gt; Placebo</td>
</tr>
<tr>
<td></td>
<td>(N = 347)</td>
<td>(N = 358)</td>
<td>(N = 341)</td>
</tr>
<tr>
<td>Baseline headache days, mean ± SD</td>
<td>19.9 ± 3.69</td>
<td>19.7 ± 3.65</td>
<td>20.0 ± 3.73</td>
</tr>
<tr>
<td>Baseline MPM headache days, mean ± SD</td>
<td>19.2 ± 5.94</td>
<td>18.7 ± 4.05</td>
<td>19.1 ± 4.04</td>
</tr>
<tr>
<td>Baseline moderate/ severe headache days, mean ± SD</td>
<td>18.1 ± 4.03</td>
<td>17.7 ± 4.26</td>
<td>18.1 ± 4.22</td>
</tr>
<tr>
<td>Total cumulative hours of headache on headache days, mean ± SD</td>
<td>296.18 ± 121.043</td>
<td>287.20 ± 118.089</td>
<td>295.66 ± 116.811&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Proportion of patients with severe HIT-6 category scores, n (%)</td>
<td>321 (92.5%)</td>
<td>325 (90.8%)</td>
<td>322 (94.4%)</td>
</tr>
<tr>
<td>Baseline headache episodes, mean ± SD</td>
<td>12.0 ± 5.27</td>
<td>12.7 ± 5.29</td>
<td>12.3 ± 5.23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baseline MPM headache episodes, mean ± SD</td>
<td>11.3 ± 4.99</td>
<td>11.7 ± 5.08</td>
<td>11.5 ± 5.06&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baseline acute headache pain medication intakes, mean ± SD</td>
<td>24.7 ± 18.76</td>
<td>25.4 ± 18.87</td>
<td>29.1 ± 19.27</td>
</tr>
</tbody>
</table>

Efficacy results

Study 079
There was a large mean decrease from baseline at all timepoints for the primary efficacy variable, the frequency of headache episodes in the Botox and placebo groups; however, there were no statistically significant between-group differences at any timepoint other than baseline. There was a statistically significant imbalance at baseline for this primary efficacy variable, with the Botox group having significantly fewer headache episodes than the placebo group (p = 0.023). Even after ANCOVA analysis adjustment for the baseline difference, as well as non-parametric rank test with mLOCF and ANCOVA using observed data, the primary efficacy endpoint of reduction in frequency of headache episodes was not met.

Statistically significant reductions from baseline favouring the Botox group over the placebo group were observed for the prospectively defined secondary efficacy variables that evaluated the frequency of headache days (p = 0.006) and frequency of migraine/probable migraine days (p = 0.002) at the primary timepoint. Even when controlling for multiple comparisons, the differences observed for these endpoints were highly statistically significant.

Statistical Assessor’s comment
The data from study 079 suggest that although there is no difference in the decrease in headache episodes, there is a difference in the decrease in headache days. Therefore one might expect that there are differences in the duration of episodes.
Study 080

The primary endpoint (after amendment of the statistical analysis plan) was met. Botox was highly statistically significantly more effective than placebo in reducing from baseline the frequency of headache days at week 24 (p < 0.001) and at all other timepoints starting at week 4 during the double-blind phase (p ≤ 0.001).

At the primary week 24 timepoint, Botox was also highly statistically significantly more effective than placebo in reducing from baseline all 5 of the secondary efficacy variables: frequency of migraine/probable migraine headache days (p < 0.001), frequency of moderate/severe headache days (p < 0.001), number of total cumulative hours of headache that occurred on headache days (p < 0.001), proportion of patients with severe HIT-6 category scores (p = 0.003), and frequency of headache episodes (p = 0.003).

**Statistical Assessor’s comment**

The decision to switch primary endpoint in trial 080 is understandable and it is of note that both the original and the final primary endpoint were highly significant in this trial. One explanation of why there are differences between the studies is the baseline imbalance observed in Study 079. Details on the duration of headache episodes for both trials were subsequently provided by the MAH. It was noted that there was a substantial baseline imbalance between the 2 treatment groups in terms of the average headache episode duration. This imbalance helps to explain the results seen: even if at the end of the study both groups had a similar length of duration, the difference between the groups would still favour Botox. Given that the average duration was less in the Botox group, it can be concluded that any differences seen in terms of total headache time and number of headache episodes has not been confounded by the duration of headache episodes.

The results of the per-protocol analyses are broadly similar to the mLOCF analyses, which does provide some reassurance that the method may be acceptable. Sensitivity analyses were subsequently performed by the MAH, which assumed that there were no migraine or headache episodes on a diary day with missing data. The results of these analyses showed the results are broadly similar in terms of the point estimate and significance for the difference between treatment arms although it was expected a priori that the results in each arm may differ slightly. Given that these analyses could be considered to cover a potential worst case scenario, they add to the robustness of the results.

Integrated summary of efficacy (ISE)

The MAH presented an integrated summary of efficacy (ISE) of Botox in the prophylaxis of headaches in adults with chronic migraine based on the two phase III studies and a similar subset of the two phase II studies. This subset includes patients who met the following phase III study constraints: 28-day analysis periods; no baseline prophylactic headache pain medication use; headache episodes and days counted only if they included at least 4 hours continuous headache duration; at least 4 baseline headaches; at least 15 baseline headache days at least half of which were migraine/probable migraine, and at least 150 Units dosing for patients in the Botox group.

The intent-to-treat (ITT) population, consisting of all randomised patients, has been used; the patients were analysed according to randomisation assignment for the phase III studies and according to treatment received for the phase II studies (in line with initial analysis plans).

The primary ISE analysis was on the change from baseline in the frequency of headache days per 4 weeks and the primary visit was Week 24. Secondary endpoints included the changes from baseline to other time points (Weeks 4, 8, 12, 16, 20, 28, 32, 36, 40, 44, 48, 52 and 56) in the frequency of headache days per 4-week period.

The secondary efficacy variables were identified as follows:
- Frequency of migraine/probable migraine days
- Frequency of moderate/severe headache days
- Total cumulative hours of headache occurring on headache days
- Proportion of patients with severe HIT-6 category scores
- Frequency of headache episodes
- Frequency of migraine/probable migraine episodes
- Frequency of acute headache pain medication intakes

Other efficacy variables included:
- Incidence of patients with a decrease from baseline of 50% or more of the frequency of headache episodes
- Incidence of patients with a decrease from baseline of 50% or more of the frequency of headache days

These results are summarised in table 8 and figures 5-6.
<table>
<thead>
<tr>
<th>Efficacy Variable (per 28 days)</th>
<th>Phase 3 Study 191622-080</th>
<th>Phase 3 Study 191622-079</th>
<th>Pooled Phase 3 191622-080 + 191622-079</th>
<th>Pooled Phase 2 Subgroup 191622-038 + 191622-039</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache days *</td>
<td>-9.0 -6.7 &lt;0.001</td>
<td>-7.8 -6.4 0.006</td>
<td>-8.4 -6.6 &lt;0.001</td>
<td>-9.8 -7.9 0.008</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine headache days</td>
<td>-8.7 -6.3 &lt;0.001</td>
<td>-7.6 -6.1 0.002</td>
<td>-8.2 -6.2 &lt;0.001</td>
<td>-8.9 -7.3 0.027</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-8.3 -5.8 &lt;0.001</td>
<td>-7.2 -5.8 0.004</td>
<td>-7.7 -5.8 &lt;0.001</td>
<td>-9.0 -7.9 0.153</td>
</tr>
<tr>
<td>Total cumulative hours of headache on headache days</td>
<td>-132.41 -90.01 &lt;0.001</td>
<td>-106.70 -70.40 0.003</td>
<td>-119.67 -80.49 &lt;0.001</td>
<td>-127.73 -124.50 0.294</td>
</tr>
<tr>
<td>Proportion of patients with severe HIT-6 category scores, % (^d)</td>
<td>66.3% 76.5% 0.003 (^d)</td>
<td>68.9% 79.9% 0.001 (^d)</td>
<td>67.6% 78.2% &lt;0.001 (^d) NA NA NA</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Frequency of headache episodes  (^k)</td>
<td>-5.3 -4.6 0.003</td>
<td>-5.2 -5.3 0.344</td>
<td>-5.2 -4.9 0.009</td>
<td>-5.4 -4.6 0.096</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine headache episodes</td>
<td>-4.9 -4.2 0.003</td>
<td>-4.8 -4.9 0.206</td>
<td>-4.9 -4.5 0.004</td>
<td>-4.8 -3.9 0.062</td>
</tr>
<tr>
<td>Frequency of acute headache pain medication inks</td>
<td>-9.9 -8.4 0.132</td>
<td>-10.3 -10.4 0.795</td>
<td>-10.1 -9.4 0.247</td>
<td>-13.2 -10.7 0.178</td>
</tr>
<tr>
<td>Frequency of acute headache pain medication days (^*)</td>
<td>-6.4 -4.8 &lt;0.001</td>
<td>-5.7 -5.8 0.996</td>
<td>-6.1 -5.3 0.016</td>
<td>-7.7 -5.1 0.019</td>
</tr>
<tr>
<td>Total HIT-6 scores  (^f)</td>
<td>-4.9 -2.4 &lt;0.001</td>
<td>-4.7 -2.4 &lt;0.001</td>
<td>-4.8 -2.4 &lt;0.001</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Proportion of patients with 50% reduction in headache days  (^*)</td>
<td>50.5% 34.4% &lt;0.001 (^d)</td>
<td>43.5% 36.0% 0.082 (^d)</td>
<td>47.1% 35.1% &lt;0.001 (^d) 50.0% 36.8% 0.129 (^d)</td>
<td>53.8% 50.9% 0.733 (^d)</td>
</tr>
<tr>
<td>Proportion of patients with 50% reduction in headache episodes  (^*)</td>
<td>50.2% 39.1% 0.008 (^d)</td>
<td>46.9% 47.5% 0.905 (^f)</td>
<td>48.6% 43.1% 0.065 (^f) 53.8% 50.9% 0.733 (^d)</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>MSQ RFR scores  (^*)</td>
<td>-17.2 -8.4 &lt;0.001</td>
<td>-16.8 -8.8 &lt;0.001</td>
<td>-17.0 -8.6 &lt;0.001</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>MSQ RFP scores  (^*)</td>
<td>-13.5 -5.4 &lt;0.001</td>
<td>-12.6 -7.6 0.005</td>
<td>-13.1 -6.4 &lt;0.001</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>MSQ EF scores  (^*)</td>
<td>-19.0 -9.1 &lt;0.001</td>
<td>-16.9 -10.0 0.001</td>
<td>-17.9 -9.5 &lt;0.001</td>
<td>NA NA NA</td>
</tr>
<tr>
<td>Daily headache impact scores  (^*)</td>
<td>-0.7 -0.4 &lt;0.001</td>
<td>-0.6 -0.4 0.002</td>
<td>-0.6 -0.4 &lt;0.001</td>
<td>NA NA NA</td>
</tr>
</tbody>
</table>
EF = Role Function–Emotional Function; HIT-6 = Headache Impact Test; MSQ = Migraine-Specific Quality of Life Questionnaire; NA = Not collected, and therefore not applicable; RFP = Role Function–Preventive; RFR = Role Function–Relaxation.

Unless otherwise noted, p-values for between-treatment comparisons are from ANCOVA, with baseline values as covariate. The main effects in the ANCOVA included treatment and medication-overuse strata, where the type III sum of squares was used. Missing values were estimated using nlme.

a Primary efficacy variable in study 191622-009 and secondary efficacy variable in study 191622-079.
b Primary efficacy variable in study 191622-079 and secondary efficacy variable in study 191622-080.
c P-values from statistical comparisons are for raw values, not for changes from baseline.
d P-values for between-treatment comparisons were determined by Pearson's chi-square or Fisher's exact tests (if ≥ 25% of the expected cell counts were less than 5).
e Observed data, without imputation for missing values.
f P-values for between-treatment comparisons were determined by logistic regression with the unranked baseline frequency as covariate.
g P-values for between-treatment comparisons were determined by Wilcoxon rank-sum test.

Figure 5. Pooled phase 3 studies
Figure 6. Mean change from baseline in the number of headache days (pooled phase 3 studies)

**Assessor’s comment**

In both phase III studies, the improvement in terms of days was significantly higher on Botox than on placebo whatever the type of pain considered (headache, headache of moderate/severe intensity, migraine/probable migraine). In the placebo group, the mean decrease was about 6 days while it was about 7-8 days in study 079 and 8-9 days in study 080. As expected, the placebo effect was high in these studies and the effect size (around 2 days) appears far from dramatic; however, it is similar to that reported for topiramate (Silberstein, 2007). In relative terms, the number of headache days was decreased by 33% with placebo and 42% with Botox in the pooled phase III analysis, a difference which is again far from impressive. Likewise, the overall proportion of patients with at least 50% reduction in the headache days was significantly higher on Botox (47%) than on placebo (35%; p < 0.001); while the placebo results were similar in both studies, they were better for Botox in study 080 (50%) than in study 079 (43%). This figure is also within the range of what has been reported with other prophylactic migraine treatments.

The improvement in terms of episodes was only significantly higher on Botox than on placebo in study 080, which drove the results of the pooled analysis. For this endpoint also, the effect size (less than 1 episode) appears to be small. Furthermore, the reliability of this endpoint may be questionable given the absence of definition of pain-free interval between two episodes.

The consumption of acute headache medications is important to consider, especially given the high percentage of patients with MOH (around 65%). Change in acute medication use may reflect a change in headache status provided subjects are not counselled to change the type or frequency of their medications during treatment, so that any fluctuation in use can be evaluated. Indeed, change or restricted use of acute medication can lead to a reduction in headache frequency/severity (detoxification effect) and potentially confound the interpretation of the results. A decrease in acute headache medication use was observed in both placebo and Botox groups, whether expressed as intakes or days; no difference was observed between the treatment groups in study 079 while a statistically significant difference in terms of days was reported in study 080. This likely reflects the slightly better results generally seen in the latter study but the
small difference observed between Botox and placebo is unlikely to have confounded the key endpoint results.

Regarding patient reported outcomes baseline total HIT-6 scores (mean of 65) indicated severe impact and results were consistent in both studies. It has been suggested that the minimum important difference for within-person clinical improvement is ~ 3.7 units while it is ~ 2.3 units for a between-groups comparison (Coeytaux, 2006). The mean decrease was 2.4 units on placebo (not considered clinically meaningful) as opposed to a meaningful improvement of 4.8 units on Botox (p < 0.001). The effect size (2.5 units) would also appear clinically meaningful. Likewise, the mean decreases in the three functions of the MSQ exceeded the established minimally important within-group differences from baseline of -10.9 (RFR), -8.3 (RFP) and -12.2 (EF) (Dodick, 2007) only in the Botox group whereas none of the placebo group scores met these minimally important differences.

The effects of treatment over time are important to consider since subjects received 2 double-blind treatments followed by 3 Botox treatments, all treatments being separated by 3-month intervals. As shown in figure 6, the group of patients that received Botox since the start of the studies continued to improve during the open-label phase so that the difference between the two patient groups (Botox/Botox and Placebo/Botox) was still significant after one year. From a mean baseline of 19.9 headache days/28 in the Botox/Botox group, the mean reduction was 7.4 days after the first treatment and 11.8 days after the 5th treatment (i.e. a reduction by ~60%); in contrast, during the double-blind part of the studies, the placebo effect appeared to plateau after the second administration. Thus, although the second part of the studies was open-label, this substantial improvement suggests that the effect of repeated Botox administrations is sustained at least over one year. Regarding the frequency of Botox treatments, it appears that after each treatment, its benefit increases over the first two weeks and reaches a plateau or even starts waning during the third week (figure 6); hence the 3-week interval seems appropriate.
Subgroup analyses
For the phase III studies only, headache days and headache episodes were summarised for the primary time point by the following subgroup factors:

- acute headache pain medication overuse group (yes versus no; with the overuse group as stratified during randomisation assignment)
- age (<40 years vs. ≥40 years)
- gender
- race (Caucasian vs. non-Caucasian)
- history of headache pain prophylactic medication use (yes versus no).

These results are summarised in tables 9 and 10.

Table 9. Subgroup analysis: baseline and mean change at week 24 in headache days

<table>
<thead>
<tr>
<th>Subgroup Categories</th>
<th>Pooled 191622-079 + 191622-080 Studies</th>
<th>Baseline</th>
<th>Week 24</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BOTOX®</td>
<td>Placebo</td>
<td>BOTOX®</td>
</tr>
<tr>
<td><strong>Overuse of Acute Headache Pain Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>20.1 ± 3.73</td>
<td>19.8 ± 3.60</td>
<td>-8.2 ± 6.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =443; Placebo N = 459</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>19.6 ± 3.57</td>
<td>19.7 ± 3.83</td>
<td>-8.8 ± 6.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =243; Placebo N = 237</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td></td>
<td>20.3 ± 3.65</td>
<td>19.9 ± 3.79</td>
<td>-9.0 ± 6.63</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =293; Placebo N = 288</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 40 years</td>
<td></td>
<td>19.6 ± 3.67</td>
<td>19.7 ± 3.60</td>
<td>-8.0 ± 6.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =395; Placebo N = 408</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>20.5 ± 3.42</td>
<td>20.4 ± 3.75</td>
<td>-7.9 ± 6.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =85; Placebo N = 103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>19.8 ± 3.71</td>
<td>19.7 ± 3.66</td>
<td>-8.5 ± 6.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =603; Placebo N = 593</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td>19.9 ± 3.64</td>
<td>19.8 ± 3.68</td>
<td>-8.4 ± 6.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =617; Placebo N = 630</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td></td>
<td>20.2 ± 3.98</td>
<td>19.7 ± 3.69</td>
<td>-8.6 ± 6.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =71; Placebo N = 66</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History of Headache Medication Prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>20.1 ± 3.64</td>
<td>20.1 ± 3.74</td>
<td>-7.9 ± 6.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =423; Placebo N = 454</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>19.7 ± 3.72</td>
<td>19.3 ± 3.50</td>
<td>-9.2 ± 6.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BOTOX® N =263; Placebo N = 242</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: JSE Tables 3-2, 3-8, 3-10, 3-12, 3-14
Note: All values are presented as mean ± SD

* P-values for between-group comparisons at week 24 and are from ANCOVA with baseline values as covariate.
Table 10. Subgroup analysis: baseline and mean change at week 24 in headache episodes

<table>
<thead>
<tr>
<th>Subgroup Categories</th>
<th>Baseline</th>
<th>Week 24</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>( \text{Pooled 191622-079 + 191622-080 Studies:} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX*</td>
<td>Placebo</td>
<td>BOTOX*</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>Overuse of Acute Headache Pain Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.8 ± 5.35</td>
<td>13.8 ± 5.49</td>
<td>-5.4 ± 5.51</td>
<td>-5.1 ± 5.39</td>
</tr>
<tr>
<td>BOTOX* N = 445; Placebo N = 459</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10.9 ± 4.81</td>
<td>11.4 ± 5.18</td>
<td>-5.0 ± 4.53</td>
<td>-4.6 ± 5.29</td>
</tr>
<tr>
<td>BOTOX* N = 243; Placebo N = 237</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40 years</td>
<td>11.9 ± 5.52</td>
<td>12.9 ± 5.69</td>
<td>-5.3 ± 5.20</td>
<td>-5.6 ± 5.11</td>
</tr>
<tr>
<td>BOTOX* N = 293; Placebo N = 288</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 40 years</td>
<td>12.3 ± 5.04</td>
<td>13.1 ± 5.37</td>
<td>-5.2 ± 5.18</td>
<td>-4.4 ± 5.48</td>
</tr>
<tr>
<td>BOTOX* N = 395; Placebo N = 408</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13.3 ± 5.74</td>
<td>13.5 ± 5.97</td>
<td>-5.2 ± 4.95</td>
<td>-5.2 ± 4.90</td>
</tr>
<tr>
<td>BOTOX* N = 85; Placebo N = 103</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12.0 ± 5.16</td>
<td>12.9 ± 5.42</td>
<td>-5.2 ± 5.22</td>
<td>-4.9 ± 5.43</td>
</tr>
<tr>
<td>BOTOX* N = 603; Placebo N = 593</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>12.3 ± 5.27</td>
<td>13.2 ± 5.52</td>
<td>-5.3 ± 5.30</td>
<td>-4.9 ± 5.38</td>
</tr>
<tr>
<td>BOTOX* N = 617; Placebo N = 630</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>10.5 ± 4.82</td>
<td>11.1 ± 5.05</td>
<td>-4.5 ± 4.01</td>
<td>-4.7 ± 5.12</td>
</tr>
<tr>
<td>BOTOX* N = 71; Placebo N = 66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History of Headache Medication Prophylaxis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.7 ± 5.31</td>
<td>13.6 ± 5.44</td>
<td>-5.2 ± 5.33</td>
<td>-4.5 ± 5.35</td>
</tr>
<tr>
<td>BOTOX* N = 423; Placebo N = 434</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11.2 ± 5.02</td>
<td>12.0 ± 5.49</td>
<td>-5.2 ± 4.96</td>
<td>-5.7 ± 5.30</td>
</tr>
<tr>
<td>BOTOX* N = 263; Placebo N = 242</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: ISE Tables 3.1, 3.7, 3.9, 3.11, 3.13
Note: All values are presented as mean ± SD
<sup>a</sup> P-values for between-group comparisons at week 24 and are from ANCOVA with baseline values as covariate.

Additional analyses in male subjects

Detailed results for most efficacy variables in male subjects were provided. In the subgroup of 123 males (N=57 Botox; N=66 Placebo) with medication overuse at baseline, week 24 mean improvements from baseline were always numerically larger, although not statistically significant, in the Botox group versus the placebo group across multiple efficacy measures including frequency of headache episodes, headache days, migraine/probable migraine days, moderate/severe headache days, cumulative hours of headache on headache days, and the incidence of subjects with severe total HIT-6 category scores. The Migraine Specific Quality of Life (MSQ) scale scores at week 24 for the Botox group exceeded the established minimally important within-group difference (MID) from baseline of -10.9 (Role Function Restrictive [RFR] and -8.3 (Role Function Preventative [RFP]), whereas none of the placebo group scores met these minimally important differences. Mean improvements from baseline in total HIT-6 scores were also higher in the Botox than placebo group.
Even with a higher placebo response, similar efficacy trends were observed across multiple efficacy measures in the subgroup of 65 males (N=28 Botox; N=37 Placebo) without baseline medication overuse. The MSQ scale scores at week 24 for the Botox group but not the placebo group exceeded the established MID from baseline for RFR and EF. Both treatment arms exceeded the MID for RFP. Mean improvements from baseline in total HIT6 scores were also higher in the Botox than placebo group.

**Assessor’s comment**

The evidence is far from convincing in male subjects, who are underrepresented in this trial (14%) as compared with the prevalence in the population of chronic migraine, i.e. 21% according to a publication referred to by the MAH. In the group with medication overuse, where the placebo response was similar to the response in the whole ITT population, the response to Botox appeared smaller than the response in the whole ITT population for most outcomes, including primary outcome. However, there was some evidence of effect on other secondary relevant endpoints, such as the frequency of migraine days, the cumulative hours of headache or the QoL scores. Overall, since there is a trend towards benefit in this subpopulation, it can be agreed that it should not be excluded from the indication. However, a statement in section 5.1 of the SmPC should highlight this finding as long as the MAH does not provide further confirmatory data in male subjects.

Additional analyses according to prior migraine headache prophylaxis use

In January 2006, at the time that the Allergan phase 3 studies were initiated, there was no international and/or agreed upon local guidelines of ‘proven effective’ migraine headache prophylaxis treatments. Investigators were instructed to record the past use of any of the medications listed in a guideline provided, irrespective of whether the treatment was prescribed as headache prophylaxis or not. Furthermore, if a patient reported that they had taken any other headache prophylactic drug/herbal not listed in the guideline, then it was also to be recorded in the case report form. Overall, approximately 64% of enrolled subjects had a history of prior headache prophylaxis medication use when this broad list of possible medications was used. The protocol specified subgroup analysis for the subjects without prior headache prophylaxis medication use did not find differences between treatment groups for change from baseline in frequency of headache days or headache episodes (see tables 9 and 10).

The British Association for the Study of Headache (BASH) issued a guideline in April 2007 that identifies 16 medications that are considered to be effective migraine headache prophylaxis treatments. These medications have been further sub-divided by BASH as first, second or third-line treatments. All of these medications were included on the phase 3 guideline of headache prophylaxis medications, with the exception of clonidine (third line treatment per BASH). A new subgroup analysis has been performed to re-categorize subjects as yes/no to first-line prior migraine headache prophylaxis medication use according to the BASH guideline of migraine headache prophylaxis medications. Results from this analysis show that 41.5% of enrolled subjects had a history of prior BASH first-line migraine headache prophylaxis medication use.

Across multiple headache symptom measures the efficacy results were consistent regardless of whether subjects had previously tried a First Line BASH Medication (table 11). Significant improvements from baseline favouring Botox over placebo were observed for headache days, migraine/probable migraine days, moderate/severe headache days, total cumulative hours of headache on headache days, and 50% or more improvement from baseline in headache days in both sub-groups. Significant results were not consistent between the two subgroups for headache episodes and migraine episodes (significant in the yes subgroup only). There were no significant differences in either subgroup for acute medication intakes and acute medication days.
There were also statistically significant improvements from baseline always favouring Botox over placebo at week 24 for all of the patient reported disability and quality of life measures including the proportion of subjects with severe HIT-6 category scores, all 3 domains of the MSQ, total HIT-6 scores and the incidence of subjects with ≥ 5 point improvement from baseline on total HIT-6 score (table 12). For both subgroups, MSQ scale scores at week 24 for the Botox group all exceeded the established minimally important within group difference from baseline of -10.9 (RFR), -8.3 (RFP) and -12.2 (EF), whereas none of the placebo group scores in either subgroup met these minimally important differences. For both subgroups, the incidence of subjects with the minimally important within group improvement from baseline of ≥ 5 points on the total HIT6 score significantly favoured Botox over placebo treatment.

Assessment of the MAH response
The MAH has provided convincing evidence that when results were analysed according to previous use of recognised prophylactic medications, the treatment effect was substantial and statistically significant for most outcomes regardless of previous use. Interestingly, the response to placebo was notably higher in naïve patients.
CLINICAL SAFETY

Patient exposure

The safety profile of Botox in the Phase 3 Chronic Migraine population was based on a pooled analysis of 1,300 chronic migraine patients who were exposed to at least 1 Botox treatment in the phase 3 studies, providing a total of 12,379 patient-months of exposure. A total of 518 patients were exposed to 5 treatment cycles of Botox.

Among the 1,300 chronic migraine patients, the total actual Botox dosages received per cycle ranged from 15 U to 195 U when averaged across cycles 1 to 5 for each patient, with a mean of 164 U. A total of 1,137 patients were exposed to Botox for ≥ 24 weeks and 544 patients were exposed for ≥ 48 weeks at a dose range of 150 U to 200 U (tables 13 & 14). Based on the 4648 actual Botox doses administered across all treatment visits, all but 18 Botox doses were administered at 155 U or higher. The majority were within the target label dose of 155 U to 195 U. Across treatment cycles, the majority of patients continued in subsequent treatment cycles to receive their initial study drug dose; few patients increased, decreased or had their dosage changed from cycle to cycle.

The safety profile in the All Migraine population was based on a pooled analysis of 3,235 patients exposed to Botox for up to 26,685 patient-months of exposure. The total actual Botox dosages received per cycle ranged from 6 U to 260 U when averaged across cycles 1 to 5 for each patient, with a mean of 135.4 U (table 13). A total of 1,777 patients (54.9%) received any Botox treatment, and had their initial dose in the range of 150 U to 200 U; however, across treatment cycles, the majority of Botox treatments were administered at doses < 155 U, which were not inclusive of the target label dose. A total of 2,289 patients were exposed for ≥ 24 weeks and 810 patients were exposed for ≥ 48 weeks. The mean treatment cycle duration was similar across treatment cycles, irrespective of the dose administered.

Table 13. Overall Botox doses (units) in the three safety populations

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Phase 3 Chronic Migraine (N = 1300)</th>
<th>All Chronic Migraine (N = 1997)</th>
<th>All Migraine (N = 3235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (U)³</td>
<td>164.0</td>
<td>163.0</td>
<td>135.4</td>
</tr>
<tr>
<td>Median (U)b</td>
<td>158.3 (15 – 195) c</td>
<td>158.3 (15 – 260)</td>
<td>155.0 (6 – 260)</td>
</tr>
<tr>
<td>&lt; 150 U (%)²</td>
<td>0.1%</td>
<td>9.5%</td>
<td>31.1%</td>
</tr>
<tr>
<td>150 to 200 U (%)²</td>
<td>99.9%</td>
<td>77.6%</td>
<td>54.9%</td>
</tr>
<tr>
<td>&gt; 200 U (%)²</td>
<td>0.0%</td>
<td>12.9%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>

Source: Module 5.3.5.3, ISS Tables 2-2.3, 2-4.2, 2-6.2

a Based on the average of each patient over all cycles, which was then averaged over all patients.

b Based on the average for each patient.

c Based on a patient’s initial BOTOX® dose.
Table 14. Duration of exposure (Phase 3 CM population)

<table>
<thead>
<tr>
<th>Duration</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX®</td>
</tr>
<tr>
<td></td>
<td>(N = 687)</td>
</tr>
<tr>
<td>&lt; 12 Weeks</td>
<td>41 (6.0%)</td>
</tr>
<tr>
<td>12 to &lt; 24 Weeks</td>
<td>100 (14.6%)</td>
</tr>
<tr>
<td>≥ 24 Weeks</td>
<td>546 (79.5%)</td>
</tr>
<tr>
<td>Open-label Exposure</td>
<td>BOTOX®/BOTOX®*</td>
</tr>
<tr>
<td>(N = 592)</td>
<td>(N = 613)</td>
</tr>
<tr>
<td>&lt; 12 Weeks</td>
<td>19 (3.2%)</td>
</tr>
<tr>
<td>12 to &lt; 24 Weeks</td>
<td>33 (5.6%)</td>
</tr>
<tr>
<td>24 to &lt; 36 Weeks</td>
<td>475 (80.2%)</td>
</tr>
<tr>
<td>≥ 36 Weeks</td>
<td>65 (11.0%)</td>
</tr>
<tr>
<td>Any BOTOX® Exposure</td>
<td>Any BOTOX®*</td>
</tr>
<tr>
<td></td>
<td>(N = 1390)</td>
</tr>
<tr>
<td>&lt; 12 Weeks</td>
<td>76 (5.8%)</td>
</tr>
<tr>
<td>12 to &lt; 24 Weeks</td>
<td>87 (6.7%)</td>
</tr>
<tr>
<td>24 to &lt; 36 Weeks</td>
<td>495 (38.1%)</td>
</tr>
<tr>
<td>36 to &lt; 48 Weeks</td>
<td>98 (7.5%)</td>
</tr>
<tr>
<td>≥ 48 Weeks</td>
<td>544 (41.8%)</td>
</tr>
</tbody>
</table>

Source: Module 3.3.5.5. IS Tables 2-1.1, 2-1.2, and 2-1.3

a BOTOX®/BOTOX® patients received BOTOX® during the double-blind phase and BOTOX® during the open-label phase. Placebo/BOTOX® patients received placebo during the double-blind phase and BOTOX® during the open-label phase.

Adverse events

Adverse events from all 11 studies were converted to MedDRA version 11.0 coding conventions and integrated across the 3 safety populations. Adverse events for the 3 safety populations were analysed by 3 “exposure groups”: 1) double-blind, placebo-controlled [DBPC] exposure; 2) open-label exposure [presented for the Phase 3 Chronic Migraine population only]; and 3) any Botox exposure.

The results of the safety analyses of the Phase 3 Chronic Migraine population, the All Chronic Migraine population, and the All Migraine population were consistent across the 3 safety populations. These analyses revealed a higher frequency of adverse events with Botox than with placebo (table 15). The nature of adverse events observed was consistent with the known safety and tolerability profile of Botox with multiple IM injections to the head and/or neck. Compared with all other Botox clinical indications, no new safety findings emerged from these analyses across the 11 migraine studies that included 3,235 patients exposed to 6 U to 260 U of Botox.
Table 15. Adverse events across the 3 safety populations

<table>
<thead>
<tr>
<th>Placebo-controlled Exposure</th>
<th>Phase 3 Chronic Migraine Population</th>
<th>All Chronic Migraine Population</th>
<th>All Migraine Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (a/N)</td>
<td>% (a/N)</td>
<td>% (a/N)</td>
</tr>
<tr>
<td>BOTOX&lt;sup&gt;a&lt;/sup&gt;</td>
<td>62.4% (429/687)</td>
<td>71.4% (988/1384)</td>
<td>69.3% (1754/2532)</td>
</tr>
<tr>
<td>Placebo</td>
<td>51.7% (358/692)</td>
<td>56.8% (598/1052)</td>
<td>56.4% (871/1544)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Open-label Exposure</th>
<th>% (a/N)</th>
<th>% (a/N)</th>
<th>% (a/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX&lt;sup&gt;a&lt;/sup&gt;/BOTOX&lt;sup&gt;b&lt;/sup&gt;</td>
<td>55.6% (329/592)</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Placebo/BOTOX&lt;sup&gt;b&lt;/sup&gt;</td>
<td>61.0% (374/613)</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total</td>
<td>58.3% (703/1203)</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any BOTOX&lt;sup&gt;a&lt;/sup&gt; Exposure</th>
<th>% (a/N)</th>
<th>% (a/N)</th>
<th>% (a/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX&lt;sup&gt;a&lt;/sup&gt;</td>
<td>68.9% (896/1300)</td>
<td>72.9% (1455/1997)</td>
<td>73.7% (2383/3235)</td>
</tr>
</tbody>
</table>

Source: Module 5.3.5.3. ISS Tables 3-2.1, 3-2.2, 3-2.3, 3-2.4, 3-2.5, 3-2.6, 3-2.7

n/N = number of patients reporting adverse events/total number of patients; NA = not applicable

<sup>a</sup> Only the phase 3 chronic migraine studies had open-label exposure; therefore open-label exposure analyses were not conducted for the All Chronic Migraine and All Migraine populations.

Table 16. Adverse events reported by ≥ 2% of patients in either treatment group (Phase 3 CM population)

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>BOTOX&lt;sup&gt;a&lt;/sup&gt; (N = 687)</th>
<th>Placebo (N = 692)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERALL</td>
<td>429 (62.4%)</td>
<td>358 (51.7%)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>38 (5.5%)</td>
<td>10 (1.4%)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (3.6%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>49 (7.1%)</td>
<td>54 (7.8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (2.0%)</td>
<td>17 (2.5%)</td>
</tr>
<tr>
<td>General Disorders &amp; Administration Site Conditions</td>
<td>60 (8.7%)</td>
<td>57 (8.2%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>23 (3.3%)</td>
<td>14 (2.0%)</td>
</tr>
<tr>
<td>Infections &amp; Infestations</td>
<td>170 (24.7%)</td>
<td>167 (24.1%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>28 (4.1%)</td>
<td>30 (4.3%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>28 (4.1%)</td>
<td>27 (3.9%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>27 (3.9%)</td>
<td>37 (5.3%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>17 (2.3%)</td>
<td>11 (1.6%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>11 (1.6%)</td>
<td>16 (2.3%)</td>
</tr>
<tr>
<td>Musculoskeletal &amp; Connective Tissue Disorders</td>
<td>169 (24.6%)</td>
<td>85 (12.3%)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (8.7%)</td>
<td>19 (2.7%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (3.6%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (3.5%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3.1%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (2.6%)</td>
<td>10 (1.4%)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>117 (17.0%)</td>
<td>74 (10.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (4.7%)</td>
<td>22 (3.2%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>26 (3.8%)</td>
<td>18 (2.6%)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>15 (2.2%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Botox 37
Phase 3 Chronic Migraine population, DBPC exposure

The only individual adverse event occurring at a rate ≥ 5% in the Botox group was neck pain (8.7%). Among the 60 Botox-treated patients who reported neck pain, 8 reported events that were mild and 33 reported events that were moderate in severity. Neck pain is not unexpected based on the known pharmacology and tolerability profile of Botox in indications that involve IM injections to neck muscles.

The most frequently reported adverse events reported at a higher incidence in the Botox than placebo group were: neck pain, headache, migraine, eyelid ptosis, musculoskeletal stiffness, and muscular weakness. Only 3.3% of Botox- and 2.0% of placebo-treated patients reported injection site pain (table 16).

The adverse events of interest that may be related to an exaggerated local pharmacological effect of Botox, such as eyelid ptosis, muscular weakness, facial paresis, and dysphagia, occurred at low rates of 3.6%, 3.5%, 2.2%, and 0.7%, respectively, in Botox-treated patients. Notably, eyelid ptosis, muscular weakness, and dysphagia were also reported among placebo-treated patients at rates of 0.3%, 0.3%, and 0.1%, respectively.

All Chronic Migraine population

While the overall nature of the adverse events was similar between the All Chronic Migraine population and Phase 3 Chronic Migraine population, the incidences of most adverse events were lower in the Phase 3 Chronic Migraine population. Neck pain was again the most frequently reported adverse event during DBPC exposure in the All Chronic Migraine population with an incidence of 13.8% (vs. 8.7% in the Phase 3 Chronic Migraine population). The incidence of dysphagia during DBPC exposure was 2.1% in the All Chronic Migraine population vs. 0.7% in the Phase 3 Chronic Migraine population. The lower incidence of adverse events in the Phase 3 Chronic Migraine population may be related to an optimised dosing and injection paradigm. This includes:

1) a lower maximum dose used per treatment cycle in the phase 3 studies (195 U vs. 260 U);
2) a more defined injection paradigm in the phase 3 studies, which specified a fixed-site, fixed-dose injection regimen in the forehead region, no masseter injections, and injection of the upper cervical paraspinal muscles rather than deeper splenius capitis and semispinalis cervical muscles; uniform use of a 30-gauge (0.5-inch) needle in the phase 3 studies vs. the use of a 30-gauge, 1-inch needle required in one of the phase 2 chronic migraine studies and optional use of either a 27-gauge or 30-gauge needle (0.5 to 1.5 inches) in the other phase 2 chronic migraine study.

All Adverse Events by Treatment Cycle

The overall nature of adverse events by treatment cycle was similar in all 3 safety populations. Irrespective of which population was evaluated, the overall safety and tolerability profile of Botox showed improvement with subsequent treatments. The incidences of overall adverse events and most individual adverse events decreased with repeated treatments. In the All Migraine Population, DBPC Exposure, in the Botox group, the incidence of adverse events decreased from 60.2% in the first cycle to 45.4% in the third cycle. In the placebo group, the incidence of all adverse events was similar during cycles 1, 2, and 3 (43.8%, 39.8%, 39.1%, respectively). Compared with the first Botox treatment cycle, no new safety findings emerged in patients receiving up to 5 treatment cycles over 56 weeks, suggesting that there is no cumulative toxicity with long-term Botox exposure. This is consistent with the known reversibility of the pharmacological effects of Botox when injected into target tissue.

All Adverse Events by Dose Group

In order to evaluate potential dose relationships of the frequently reported adverse events seen with Botox exposure, several analyses were performed by 3 Botox dose groups utilized during the
migraine clinical development program (< 150 U, 150 U to 200 U, and > 200 U). Patients were assigned to a dose group based on the dose received in treatment cycle 1. The middle dose group (150 U to 200 U) approximates the target label dose range of 155 U to 195 U (ie, the dose range utilized in the phase 3 chronic migraine studies). The adverse event analyses by dose group were performed for the All Chronic Migraine and the All Migraine populations; this analysis was not performed for the Phase 3 Chronic Migraine population because 99.9% of patients in this population received doses of 150 U to 200 U.

Analysis of the All Chronic Migraine population during DBPC exposure did not identify increasing frequencies of adverse events by increasing dose group for the overall incidence of adverse events nor any individual adverse event with a frequency of ≥ 2%, with the exception of eyelid ptosis and myalgia. The middle dose group consistently showed the lowest incidence of adverse events, and the highest dose group consistently showed the highest incidence of adverse events. The highest rates reported for eyelid ptosis and myalgia (6.2% and 3.1%, respectively) were in the highest (> 200 U) dose group. Neck pain (the most frequently occurring adverse event in every dose group during any exposure) and dysphagia had the lowest incidence in the middle dose group (11.1% and 1.3%, respectively), which represents the phase 3 target label dose range of 155 U to 195 U. These adverse events did not result in any medical sequelae. A similar pattern was observed for other frequently reported adverse events such as muscular weakness, headache, facial paresis, and musculoskeletal stiffness, whereby the middle dose group had the lowest incidence compared with the other 2 dose groups.

Analysis of the All Migraine population during DBPC exposure identified increasing frequencies by increasing dose group for the clinically relevant adverse events of neck pain, eyelid ptosis, myalgia, musculoskeletal stiffness, muscular weakness, musculoskeletal pain, headache, depression, and insomnia. Of these events, depression and insomnia occurred at rates similar to placebo, and therefore were not considered to be of clinical significance.

**Adverse reactions**

The MAH has developed an algorithm to define ADRs, which was applied to the Phase 3 Chronic Migraine population during DBPC exposure; 17 ADRs were identified and are proposed for the prescribing information (table 17). All proposed ADRs, except for migraine, have been observed with the use of Botox in other indications.

Migraine, including worsening migraine, was reported in a small number (3.8%) of Botox-treated patients, with the onset occurring in the majority within the first month after treatment. The incidence of migraine observed in placebo-treated patients was 2.6%. Although in a few patients, these reactions recurred at some subsequent treatment cycles, the overall incidences decreased with repeated treatments.
Table 17. Adverse drug reactions (Phase 3 CM population, DBPC exposure)

<table>
<thead>
<tr>
<th>Adverse Drug Reaction</th>
<th>BOTOX® N = 687</th>
<th>Placebo N = 692</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common (≥ 1% to &lt; 10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck pain</td>
<td>60 (8.7%)</td>
<td>19 (2.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (4.7%)</td>
<td>22 (3.2%)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>25 (3.6%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>25 (3.6%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>26 (3.8%)</td>
<td>18 (2.6%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>24 (3.5%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>23 (3.3%)</td>
<td>14 (2.0%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>21 (3.1%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>18 (2.6%)</td>
<td>10 (1.4%)</td>
</tr>
<tr>
<td>Facial paresis</td>
<td>15 (2.2%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13 (1.9%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Muscle tightness</td>
<td>9 (1.3%)</td>
<td>3 (0.4%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (1.0%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (1.0%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Uncommon (≥ 0.1% to &lt;1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>5 (0.7%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Pain of jaw</td>
<td>5 (0.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pain of skin</td>
<td>5 (0.7%)</td>
<td>2 (0.3%)</td>
</tr>
</tbody>
</table>

Assessor’s comment

Intramuscular administration of Botox to muscles of the face, head and neck is not essentially different from other indications and the recommended dose tested in the phase III clinical studies is not higher either. Not surprisingly, no new adverse reaction emerged in this development, with the exception of migraine.

The proposed list of ADRs is endorsed. As expected, the most frequent reactions involved the muscular system (myalgia, stiffness, tightness, spasms, weakness) with some locations specifically identified (eyelid ptosis, facial paresis, dysphagia, neck pain, pain of jaw). They occurred at or near the site of injection (e.g. corrugator, procerus, and trapezius muscles). The other ADRs were injection site and skin reactions.

Hypersensitivity reactions were subsequently detailed. Eyelid oedema was the only AE reported more frequently with Botox (1.7%) than with placebo (0.2%) in the All migraine population. Although this is unlikely to be an allergic reaction, it is already listed as an ADR in the SmPC for the treatment of blepharospasm, but with a “rare” frequency. Based on the phase 3 studies data, “eyelid oedema” should be added in the migraine indication with a frequency of “uncommon” (3/687 = 0.4%).

Additional data on the adverse events of headache/migraine

- Migraine/headache AEs were reported more frequently on Botox (64 subjects; 9.3%) than on placebo (40; 5.8%) (p = 0.013) during the double-blind phase of the phase 3 CM trials and in a total of 169 subjects (12.3%) over the whole duration of these trials.
- No baseline characteristics allowed distinguishing these subjects from the whole population of the trials.
• Overall, these subjects seemed to respond to Botox similarly to the whole population of the trial although a few subjects reported a greater frequency of headache days at the time of the AE compared to baseline (1.5% vs. 0.7% in the Botox and placebo groups, respectively) or a longer average headache episode duration (4.7% vs. 3.2%, respectively).
• Like for other ADRs, the incidence of migraine/headache AEs declined over time. It was higher during the first cycle: 7.0% vs. 3.9% in the Botox and placebo groups, respectively (p = 0.012) than during the following cycles (e.g. 3.5% during cycle 3).
• The onset of the migraine/headache AEs was observed preferably in the first week after the injection: in cycle1, 1.7% vs. 0.9% (in the Botox and placebo groups, respectively) on the day of the injection, then 2.3% vs. 1.4% between Day 1-7, and subsequent decrease.
• There were also more SAEs of migraine/headache, reported as intractable migraine/headache, worsening/exacerbation of migraine, or status migrainous, and prompting hospitalisation in the Botox group (6 cases; 0.9%) than in the placebo group (1 case; 0.1% - but unclear because hospitalisation on the day of the 2nd injection was pre-arranged). There was an additional 5 cases during the open phase of the trials, including a second event in a subject previously affected. Overall, the proportion of subjects with this type of SAE on Botox was 0.7%. Most of them had hospitalisation for migraine prior to the trial. Nevertheless, it is noteworthy that all hospitalisations for migraine/headache occurred in the Botox group (if the pre-arranged hospitalisation is not taken into account).
• Finally, two patients discontinued Botox due to this serious ADR.

**Assessor’s comment**

Although unexpected, migraine and headache are clearly ADRs to BOTOX as they were reported significantly more often on Botox than on placebo. They are listed in section 4.8. of the SmPC and a descriptive comment should mention the occurrence of serious ADRs reported as intractable or worsening of headache/migraine.

**Serious adverse events and deaths**

Across all clinical studies of the program, one death was reported in a patient who received placebo.

In the Phase 3 Chronic Migraine population during DBPC exposure, serious adverse events were reported in 4.8% (33/687) of patients in the Botox group and 2.3% (16/692) of patients in the placebo group. The incidence of serious adverse events in the Phase 3 Chronic Migraine population was consistent across the DBPC, open-label, and any Botox exposure groups. The most frequently reported serious adverse events with any Botox exposure were migraine (0.6%), uterine leiomyoma (0.4%), and pneumonia and non-cardiac chest pain (both 0.3%). A majority of the remaining serious adverse events were reported only once (0.1%) and were either evenly distributed between the Botox and placebo groups or higher in the placebo group.

Two of the serious adverse events in patients receiving Botox were considered to be treatment-related by the investigator. Both of these were migraine, both resolved without sequelae, one led to study discontinuation, and the other patient completed the study. Uterine leiomyoma and pneumonia are frequently experienced in the general population with the demographic profile included in these studies. There were no serious adverse events related to the injection procedure. There was no particular pattern or clustering of events to indicate a potential safety signal in relationship to Botox.

The incidence and pattern of serious adverse events in the All Chronic Migraine and All Migraine populations was similar to that of the Phase 3 Chronic Migraine population, and no new safety findings emerged in these analyses.
Adverse Events Leading to Discontinuation

The incidence of adverse events leading to discontinuation in the Phase 3 Chronic Migraine population was consistent across the DBPC, open-label, and any Botox exposure groups. During DBPC exposure, 3.8% (26/687) in the Botox group and 1.2% (8/692) in the placebo group discontinued due to adverse events. Neck pain was the single most frequent adverse event that led to discontinuation in the Phase 3 Chronic Migraine population. There was no other identified pattern of adverse events that led to discontinuation.

Immunogenicity and antibody formation

Immunogenicity manifested as antibody formation has been reported with the use of botulinum toxins in other indications. The clinical development of Botox has included the collection and analysis of serum samples for the presence of neutralizing antibodies.

Serum samples for toxin-neutralizing antibody (TNA) titre analysis were collected in 4 of the 11 migraine studies (phase 2 chronic migraine studies 191622-038 and 191622-039 and phase 2 episodic migraine studies 191622-037 and 191622-509). Serum samples were collected at study exit and analyzed using the mouse protection assay. Samples were analyzed for 3 of these 4 studies: 191622-037 (with Botox doses of 105 U to 260 U per treatment cycle), 191622-038 (with Botox doses of 105 U to 260 U per treatment cycle), and 191622-039 (with Botox doses of 75 U, 150 U, and 225 U per treatment cycle). All of these studies included 3 repeated treatment cycles at approximately 12-week intervals. Since sufficient data were available indicating that there is no heightened risk for immunogenicity in this patient population, and to limit unnecessary animal testing, samples from study 191622-509 were not analyzed and have been destroyed.

The TNA titre analysis included 505 Botox-treated patients, of whom 496 had analyzable samples. In all 3 studies, there were no positive serum antibody tests for botulinum toxin type A antibodies at study exit. There was 1 Botox-treated patient among the 496 patients (0.2%) with a sample with inconclusive results. In conclusion, the formation of toxin neutralizing antibodies to the current Botox formulation is very low.

Assessor’s comment

Due to the choice of an in vivo test in mice for the determination of neutralising antibodies, the MAH decided to stop the tests after 505 Botox-treated patients with 496 analysable samples had been tested with only one inconclusive result. These patients had received 3 treatments at 3-month intervals. It is acknowledged that the risk of developing neutralising antibodies is low based on these data (estimate of less than 2%).

Pharmacovigilance System

An updated DDPS has been provided. It is considered acceptable.

Risk Management Plan

An updated RMP has been submitted and is considered acceptable. The MAH has committed to conduct a drug utilisation survey in the UK to describe the utilisation patterns of Botox in chronic migraine and collect additional safety data.
CONCLUSION AND BENEFIT-RISK ASSESSMENT

In the Guidelines of the British Association for the Study of Headache (2007) prophylaxis is used to reduce the number of attacks when acute therapy gives inadequate symptom control. Although overuse of acute therapy is also a criterion for migraine prophylaxis, prophylactic drugs are inappropriate and ineffective in case of medication overuse. The first-line prophylactic medications are:

- beta-adrenergic blockers without partial agonism such as atenolol (preferred but off-label use), metoprolol and propranolol;
- amitryptiline (off-label use) or other less sedative alternatives.

The second- and third-line medications are topiramate and sodium valproate (off-label use), gabapentin (off-label use) and methysergide.

The use of all these medications is greatly limited by their contraindications and their systemic side-effects, which affect treatment compliance and impair their efficacy. Thus, there is a need for prophylactic treatment, especially of chronic migraine, a disabling disorder that substantially interferes with quality of life.

Benefits

Beneficial effects

- Significant improvements have been shown with Botox in comparison with placebo for multiple headache symptom measures, which are considered valid endpoints (e.g. frequency of headache days and migraine days). Although the effect size appears small, it is similar to that of oral prophylactic medications.
- These improvements resulted in a clinically significant impact on quality of life (HIT-6, MSQ), which was not observed on placebo.
- Sustained benefit was observed with repeated treatments every 3 months over one year.
- Unlike most other prophylactic medications, Botox showed evidence of benefit in subjects with medication-overuse headache.

Uncertainty in the knowledge about the beneficial effects

- The mechanism of action is speculative.
- No evidence of efficacy has been shown in episodic migraine, while the major distinction between episodic and chronic migraine is based on a cut-off value of 15 days for the number of headache days per month. The MAH argues that this may be due to a different underlying disease pathophysiology (but does not propose any hypotheses and this seems rather unlikely) or to the non-optimal design of the clinical trials.
- The effects of Botox appear small in male subjects but the size of the male population studied in the clinical trials was limited.

Risks

Unfavourable effects

- The safety profile of Botox is well known and the incidence of adverse reactions of concern is low.
- Compliance with Botox treatment compares favourably with compliance reported for most current oral prophylactic migraine medications.
Uncertainty in the knowledge about the unfavourable effects

- It is unclear why Botox can induce worsening of migraine/headaches in a small number of cases.
- Although uncommon, the development of neutralising antibodies is a possible risk.

Benefit-risk balance

Botox is a unique approach in the prophylaxis of chronic migraine. In contrast to oral therapies with systemic side-effects, it acts locally (although its mechanism of action is currently mainly speculative) and has generally a more favourable safety profile. Based on the evidence provided, its efficacy in chronic migraine is clinically relevant even if not dramatic; open-label data suggest that efficacy may improve over time with repeated treatment sessions. Therefore, the benefit-risk balance of Botox in the prophylaxis of headaches in adults with chronic migraine is considered positive.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
No new quality data were submitted and none are required for this type of application.

NON-Clinical
The pharmacological data submitted support the rationale for the addition of the proposed indication for the prophylaxis of headaches in adults with chronic migraine. No pharmacokinetic or toxicological data have been submitted. This is acceptable as the pharmacokinetic and toxicological data provided for previous applications support the current submission.

Efficacy and Safety
Significant improvements have been shown with Botox in comparison with placebo for multiple headache symptom measures, which are considered valid endpoints and resulted in a clinically significant impact on quality of life, which was not observed on placebo.

The safety profile of Botox is well known and no new or unexpected safety concerns arose from these applications.

The changes to the SmPC, PIL and labelling are acceptable.

Benefit-risk Assessment
No new non-clinical or clinical safety concerns have been identified. Sufficient clinical experience with Botox is considered to have demonstrated the therapeutic value of the compound in this new indication. The benefit-risk balance is, therefore, considered to be positive.
**Botox**

*(Botulinum toxin type A)*

PL 00426/0074-0105  
PL 00426/0118-0025  
PL 00426/0119-0007

**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the marketing authorisation application on 11\textsuperscript{th} December 2009
2. Following standard checks the MHRA informed the applicant that its application was considered valid on 22\textsuperscript{nd} December 2009
3. Following assessment of the submitted data including advice from the Commission of Human Medicines, a request for supplementary information was sent to the applicant on 17\textsuperscript{th} March 2010
4. The applicant submitted its response to the supplementary information request in a letter dated 13\textsuperscript{th} May 2010
5. Following assessment of the submitted data, a further request for supplementary information was sent to the applicant on 24\textsuperscript{th} June 2010
6. The applicant submitted its response to the supplementary information request in a letter dated 1\textsuperscript{st} July 2010
7. The application was finalised on 8\textsuperscript{th} July 2010
### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.05.11</td>
<td>Type II national variation</td>
<td>To update the SPC in line with the agreed wording of Vistabel (PL 05179/0010) with regards to the indications relating to glabellar lines. Consequential updates are made to the PIL.</td>
<td>Granted 24.11.11</td>
</tr>
<tr>
<td>04.07.13</td>
<td>Type II national variation</td>
<td>To update sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC due to the addition of a new indication for the temporary improvement in the appearance of moderate to severe lateral canthal lines (crow's feet lines) in adults treated either alone or simultaneously with glabellar lines, when the severity of these lines has an important psychological impact for the patient. Consequentially, the leaflet is updated.</td>
<td>Granted 20.12.13</td>
</tr>
<tr>
<td>25.06.13</td>
<td>Type II national variation</td>
<td>To add an indication for focal spasticity, including the treatment of “ankle disability due to lower limb spasticity associated with stroke in adults” to the product licence. As a consequence, section 4.1 (therapeutic indications) of the SPC has been updated.</td>
<td>Granted 25.01.14</td>
</tr>
</tbody>
</table>
1 NAME OF THE MEDICINAL PRODUCT

BOTOX
50 Allergan Units
Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Botulinum toxin* type A, 50 Allergan units/vial.
* from Clostridium botulinum
Botulinum toxin units are not interchangeable from one product to another.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTOX is indicated for:
- the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
- the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

BOTOX is also indicated for focal spasticity, including the treatment of:
- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older and
- wrist and hand disability due to upper limb spasticity associated with stroke in adults.

The injections should be administered by appropriately trained personnel in hospital specialist centres.

The safety and effectiveness of BOTOX in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia, chronic migraine and focal hyperhidrosis have not been demonstrated in children.

4.2 Posology and method of administration

Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin.
Adequate studies on geriatric dosing have not been performed. Dose selection should be the same; however, the lowest effective dose is recommended.

**Blepharospasm**

After reconstitution, BOTOX is injected using a sterile, 27-30 gauge needle. Electromyographic guidance is not necessary. The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. The initial dose should not exceed 25 Units per eye. Normally no additional benefit is conferred by treating more frequently than every three months. It is rare for the effect to be permanent.

In the management of blepharospasm total dosing should not exceed 100 Units every 12 weeks.

**Hemifacial spasm**

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

**Cervical dystonia**

Several dosing regimens have been used in clinical trials for treatment of cervical dystonia with BOTOX. Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response.

In practice, the maximum total dose is not usually more than 200 Units. No more than 50 Units should be given at any one injection site. The dilutions suggested are indicated in the following table:

<table>
<thead>
<tr>
<th>Diluent added</th>
<th>Resulting dose in units per 0.1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>20 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>10 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>5 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>8 ml</td>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

The following doses are recommended:

<table>
<thead>
<tr>
<th>Type I Head rotated toward side of shoulder</th>
<th>Type II Neck</th>
<th>Type III Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head rotated toward side of shoulder</td>
<td>Sternomastoid</td>
<td>50 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td>Levator scapulae</td>
<td>50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td>Scalene</td>
<td>25 - 50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td>Splenius capitis</td>
<td>25 - 75 Units; 1 - 3 sites</td>
</tr>
<tr>
<td></td>
<td>Trapezius</td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
<tr>
<td>Type</td>
<td>Description</td>
<td>Muscle(s)</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>II</td>
<td>Head rotation only</td>
<td>Sternomastoid</td>
</tr>
<tr>
<td>III</td>
<td>Head tilted toward side of shoulder elevation</td>
<td>Sternomastoid, Levator scapulae,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalene, Trapezius</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Bilateral posterior cervical muscle spasm with elevation of the face</td>
<td>Splenius capitis and cervicis</td>
</tr>
</tbody>
</table>

The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s). The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose.

The sternocleidomastoid muscle should not be injected bilaterally as there is an increased risk of adverse effects (in particular dysphagia) when bilateral injections or doses in excess of 100 Units are administered to this muscle.

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. For cervical dystonia, localisation of the involved muscles with electromyographic guidance may be useful.

Multiple injection sites allow BOTOX to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

**Hyperhidrosis of the axillae**

The recommended injection volume for intradermal injection in axillary hyperhidrosis is 0.1-0.2 ml. Reconstituted BOTOX (100 Units/4 mL) is injected using a 30 gauge needle. 50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor’s iodine-starch test.

Clinical improvement generally occurs within the first week after injection. Repeat injections of axillary hyperhidrosis should be administered when effects from previous injections subside. Treatment response has been reported to persist for 4-7 months.

**Paediatric cerebral palsy**

Diluted BOTOX is injected using a sterile 23-26 gauge needle. It is administered into each of two sites in the medial and lateral heads of the affected gastrocnemius muscle. The recommended total dose is 4 Units/kg body weight. When both lower limbs are to be injected on the same occasion this dose should be divided between the two limbs.
Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every two months.

**Focal spasticity associated with stroke**
Reconstituted BOTOX is injected using a sterile 25, 27 or 30 gauge needle for superficial muscles, and a longer needle for deeper musculature. Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles. The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved the severity of spasticity, and the presence of local muscle weakness.

In the controlled Phase 3 clinical trial the following doses were administered:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum profundus</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>50 Units</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units</td>
</tr>
</tbody>
</table>

In all clinical trials, the doses did not exceed 360 Units divided among selected muscles at any treatment session.

Clinical improvement in muscle tone generally occurs within two weeks following treatment and the peak effect is generally seen within four to six weeks following treatment. Data on the repeated and long-term treatment are limited.

**Chronic Migraine**
The recommended reconstituted BOTOX dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5-inch needle as 0.1 ml (5 U) injections to 31 and up to 39 sites. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the **injection sites**:
BOTOX Dosing By Muscle:

<table>
<thead>
<tr>
<th>Head/Neck Area</th>
<th>Recommended Dose</th>
<th>Total Dosage (number of sites(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis(^a)</td>
<td>20 U</td>
<td>4 sites</td>
</tr>
<tr>
<td>Corrugator(^b)</td>
<td>10 U</td>
<td>2 sites</td>
</tr>
<tr>
<td>Procerus</td>
<td>5 U</td>
<td>1 site</td>
</tr>
<tr>
<td>Occipitalis(^b)</td>
<td>30 U (6 sites)</td>
<td>up to 40 U (up to 8 sites)</td>
</tr>
<tr>
<td>Temporalis(^b)</td>
<td>40 U (8 sites)</td>
<td>up to 50 U (up to 10 sites)</td>
</tr>
<tr>
<td>Trapezius(^b)</td>
<td>30 U (6 sites)</td>
<td>up to 50 U (up to 10 sites)</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group(^b)</td>
<td>20 U (4 sites)</td>
<td>155 U to 195 U 31 to 39 sites</td>
</tr>
</tbody>
</table>

\(^a\)1IM injection site = 0.1 mL = 5 U BOTOX
\(^b\)Dose distributed bilaterally

The recommended re-treatment schedule is every 12 weeks.

4.3 Contraindications

BOTOX is contraindicated:
- in individuals with a known hypersensitivity to botulinum toxin type A or to any of the excipients;
- in the presence of infection at the proposed injection site(s).

4.4 Special warnings and precautions for use

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX. The recommended dosages and frequencies of administration of BOTOX should not be exceeded.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted (see section 4.8c additional information).

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.
Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including swallowing difficulties are at increased risk of these side effects. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 ‘Cervical Dystonia’).

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation.

As with any treatment with the potential to allow previously-sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually.

Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Eaton Lambert Syndrome; such patients may have an increased sensitivity to agents such as BOTOX, which may result in excessive muscle weakness. Patients with neuromuscular disorders may be at an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX.

BOTOX contains human serum albumin. When medicinal products derived from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of blood donors and donations. In addition, virus inactivation procedures are included in the production process.

As with any injection, procedure-related injury could occur. An injection could result in localized infection, pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc. Care should be taken when injecting near vulnerable anatomic structures.

**Blepharospasm**
Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal pathology. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma.

**Cervical dystonia**
Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 Units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the oesophageal musculature. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia may contribute to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX injection.

**Hyperhidrosis of the axillae**
Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

**Focal spasticity associated with paediatric cerebral palsy and spasticity of the hand and wrist in adult post-stroke patients**
BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

**Chronic migraine**
No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

### 4.5 Interaction with other medicinal products and other forms of interaction
Theoretically, the effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. tubocurarine-type muscle relaxants).

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

No interaction studies have been performed. No interactions of clinical significance have been reported.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. BOTOX should not be used during pregnancy unless clearly necessary.

Lactation
There is no information on whether BOTOX is excreted in human milk. The use of BOTOX during lactation cannot be recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, BOTOX may cause asthenia, muscle weakness, somnolence, dizziness and visual disturbance, which could affect driving and the operation of machinery.

4.8 Undesirable effects

a) General
In controlled clinical trials adverse events considered by the investigators to be related to BOTOX were reported in 35% of the patients with blepharospasm, 28% with cervical dystonia, 17% with paediatric cerebral palsy 11% with primary hyperhidrosis of the axillae and16% with focal spasticity of the upper limb associated with stroke. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In general, adverse reactions occur within the first few days following injection and are transient.

In rare cases, adverse reactions may have a duration of several months or longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue.

As is expected for any injection procedure, localised pain, tenderness and/or bruising may be associated with the injection. Fever and flu syndrome have also been reported after injections of botulinum toxin.
b) Adverse reactions - frequency by indication
For each indication the frequency of adverse reactions arising from clinical experience is given. The frequency is defined as follows:
Very Common (> 1/10); Common (>1/100 to <1/10); Uncommon (>1/1,000 to <1/100);
Rare (>1/10,000 to <1/1,000); Very Rare (<1/10,000).

**Blepharospasm/hemifacial spasm**

Nervous system disorders
Uncommon: Dizziness, facial paresis and facial palsy.

Eye Disorders:
Very common: Eyelid ptosis.
Common: Punctate keratitis, lagophthalmos, dry eye, photophobia and lacrimation increase.
Uncommon: Keratitis, ectropion, diplopia, entropion, visual disturbance and vision blurred.
Rare: Eyelid oedema.
Very rare: Corneal ulceration.

Skin and subcutaneous tissue disorders
Uncommon: Rash/dermatitis.

General disorders and administration site conditions
Common: Irritation and face oedema.
Uncommon: Fatigue.

**Cervical dystonia**

Infections and infestations
Common: Rhinitis and upper respiratory infection.

Nervous system disorders
Common: Dizziness, hypertonia, hypoaesthesia, somnolence and headache.

Eye Disorders:
Uncommon: Diplopia and eyelid ptosis.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea and dysphonia.

Gastrointestinal disorders
Very common: Dysphagia (see section c. below).
Common: Dry mouth and nausea.

Musculoskeletal and connective tissue disorders
Very common: Muscular weakness.
Common: Musculoskeletal stiffness and soreness.

General disorders and administration site conditions
Very common: Pain.
Common: Asthenia, influenza like illness and malaise.
Uncommon: Pyrexia.

*Paediatric cerebral palsy*

Infections and infestations
Very common: Viral infection and ear infection.

Nervous system disorders
Common: Somnolence and paraesthesia.

Skin and subcutaneous tissue disorders
Common: Rash.

Musculoskeletal and connective tissue disorders
Common: Myalgia and muscular weakness.

Renal and urinary disorders
Common: Urinary incontinence.

General disorders and administration site conditions
Common: Gait disturbance and malaise.

*Focal upper limb spasticity associated with stroke*

Psychiatric disorders
Uncommon: Depression and insomnia.

Nervous system disorders
Common: Hypertonia
Uncommon: Hypoaesthesia, headache, paraesthesia, incoordination and amnesia.

Ear and labyrinth disorders
Uncommon: Vertigo.

Vascular disorders
Uncommon: Orthostatic hypotension.

Gastrointestinal disorders
Uncommon: Nausea and paraesthesia oral.

Skin and subcutaneous tissue disorders
Common: Ecchymosis and purpura.
Uncommon: Dermatitis, pruritus and rash.

Musculoskeletal and connective tissue disorders
Common: Pain in extremity and muscle weakness.
Uncommon: Arthralgia and bursitis.

General disorders and administration site conditions
Common: Injection site hemorrhage and injection site irritation.
Uncommon: Asthenia, pain, injection site hypersensitivity, malaise and oedema peripheral.
Some of the uncommon events may be disease related.

Primary hyperhidrosis of the axillae

Nervous system disorders
Common: Headache

Vascular disorders
Common: Hot flushes.

Gastrointestinal disorders
Uncommon: Nausea

Skin and subcutaneous tissue disorders
Common: Hyperhidrosis (non-axillary sweating).
Uncommon: Pruritus.

Musculoskeletal and connective tissue disorders
Uncommon: Muscular weakness, myalgia, arthropathy and pain in extremity.

General disorders and administration site conditions
Common: Injection site reactions and pain.
Uncommon: Asthenia, injection site oedema and injection site pain

In the management of primary axillary hyperhidrosis, increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

Chronic Migraine

Nervous system disorders
Common: Headache*, migraine*, facial paresis

Eye disorders
Common: Eyelid ptosis
Uncommon: Eyelid oedema

Skin and subcutaneous tissue disorders
Common: Pruritus, rash
Uncommon: Pain of skin

Musculoskeletal and connective tissue disorders
Common: Neck pain, myalgia, musculoskeletal pain
musculoskeletal stiffness, muscle spasms, muscle tightness,
muscular weakness

Uncommon: Pain in jaw

General disorders and administration site conditions
Common: Injection site pain

Gastrointestinal disorders
Uncommon: Dysphagia

* In placebo-controlled trials, headache and migraine, including serious cases of
  intractable or worsening of headache/migraine, were reported more frequently with
  BOTOX (9%) than with placebo (6%). They typically occurred within the first month
  after the injections and their incidence declined with repeated treatments.

c) Additional information

Dysphagia ranges in severity from mild to severe, with potential for aspiration, which
occasionally may require medical intervention (see section 4.4).

Side effects related to spread of toxin distant from the site of administration have been
reported very rarely (exaggerated muscle weakness, dysphagia, aspiration/aspiration
pneumonia, with fatal outcome in some cases) (see section 4.4).

The following other adverse events have been reported since the drug has been marketed:
  dysarthria; abdominal pain; vision blurred; pyrexia; focal facial paralysis; hypoesthesia;
  malaise; myalgia; pruritus; hyperhidrosis; diarrhoea; anorexia; hypoacusis; tinnitus;
  radiculopathy; syncope; myasthenia gravis; erythema multiforme; dermatitis
  psoriasiform; vomiting and brachial plexopathy.

There have also been rare reports of adverse events involving the cardiovascular system,
including arrhythmia and myocardial infarction, some with fatal outcomes. Some of
these patients had risk factors including cardiovascular disease.

Serious and/or immediate hypersensitivity reactions have been rarely reported, including
anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these
reactions have been reported following the use of BOTOX either alone or in conjunction
with other agents known to cause similar reactions.

A case of peripheral neuropathy has been reported in a large adult male after receiving
four sets of BOTOX injections, totalling 1800 Units (for neck and back spasm, and
severe pain) over an 11 week period.

Angle closure glaucoma has been reported very rarely following botulinum toxin
treatment for blepharospasm.

New onset or recurrent seizures have been reported, typically in patients, who are
predisposed to experiencing these events. The exact relationship of these events to the
botulinum toxin injection has not been established. The reports in children were reports
predominantly from cerebral palsy patients treated for spasticity.

Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope,
hypotension, etc.
4.9 Overdose

No cases of systemic toxicity resulting from accidental injection of BOTOX have been observed. No cases of ingestion of BOTOX have been reported. Signs of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically supervised for several days for signs and symptoms of systemic weakness or muscle paralysis.

Patients presenting with the symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles) should be considered for admission to hospital.

With increasing dosage, generalised and profound muscular paralysis occurs. When the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed, intubation and assisted respiration will be required until recovery takes place.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from *Clostridium botulinum*. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.

*Clostridium botulinum* toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.

Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse transmission is by newly formed nerve endings and motor end plates. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical and clinical pharmacodynamic studies.

Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.
During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.

<table>
<thead>
<tr>
<th>Mean change from baseline at Week 24</th>
<th>BOTOX</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache days</td>
<td>-8.4</td>
<td>-6.6</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47%</td>
<td>35%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Total cumulative hours of headache on headache days</td>
<td>120</td>
<td>80</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8</td>
<td>-2.4</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance:
Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the extreme toxicity of botulinum toxin type A.

b) Characteristics in patients:
Human ADME studies have not been performed due to the nature of the product. It is believed that little systemic distribution of therapeutic doses of BOTOX occurs. BOTOX is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways.

5.3 Preclinical safety data

Acute toxicity
In monkeys receiving a single intramuscular (i.m.) injection of BOTOX, the No Observed Effect Level (NOEL) ranged from 4 to 24 Units/kg. The i.m. LD₅₀ was reported to be 39 Units/kg.

Toxicity on repeated injection
In three different studies (six months in rats; 20 weeks in juvenile monkeys; 1 year in monkeys) where the animals received i.m. injections, the NOEL was at the following respective BOTOX dosage levels: < 4 Units/kg, 8 Units/kg and 4 Units/kg. The main systemic effect was a transient decrease in body weight gain.

There was no indication of a cumulative effect in the animal studies when BOTOX was given at dosage intervals of 1 month or greater.

Local toxicity
BOTOX was shown not to cause ocular or dermal irritation, or give rise to toxicity when injected into the vitreous body in rabbits.

Botox
Allergic or inflammatory reactions in the area of the injection sites are rarely observed after BOTOX administration. However, formation of haematoma may occur.

**Reproduction toxicology**

**Teratogenic effects**
When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL of BOTOX was at 4 Units/kg. Reductions in ossification were observed at 8 and 16 Units/kg (mice) and reduced ossification of the hyoid bone at 16 Units/kg (rats). Reduced foetal body weights were observed at 8 and 16 Units/kg (rats).

In a range-finding study in rabbits, daily injections at dosages of 0.5 Units/kg/day (days 6 to 18 of gestation), and 4 and 6 Units/kg (administered on days 6 and 13 of gestation), caused death and abortions among surviving dams. External malformations were observed in one foetus each in the 0.125 Units/kg/day and the 2 Units/kg dosage groups. The rabbit appears to be a very sensitive species to BOTOX treatment.

**Impairment of fertility and reproduction**
The reproductive NOEL following i.m. injection of BOTOX was 4 Units/kg in male rats and 8 Units/kg in female rats. Higher dosages were associated with dose-dependent reductions in fertility. Provided impregnation occurred, there were no adverse effects on the numbers or viability of the embryos sired or conceived by treated male or female rats.

**Pre- and post-natal developmental effects**
In female rats, the reproductive NOEL was 16 Units/kg. The developmental NOEL was 4 Units/kg.

**Mutagenicity**
BOTOX has been evaluated and shown to be non-mutagenic in a number of *in vitro* and *in vivo* systems including the Ames test, the AS52/XPRT Mammalian Cell Forward Gene Mutation assay and the CHO test, and non-clastogenic in the mouse PCE test.

**Carcinogenicity**
No animal studies have been conducted.

**Antigenicity**
BOTOX showed antigenicity in mice only in the presence of adjuvant. BOTOX was found to be slightly antigenic in the guinea pig.

**Blood compatibility**
No haemolysis was detected up to 100 Units/ml of BOTOX in normal human blood.

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**
Human albumin
Sodium chloride

6.2 **Incompatibilities**
In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.

### 6.3 Shelf life

3 years.  
After reconstitution, stability has been demonstrated for 24 hours at 2°C – 8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C), or store in a freezer (at or below -5°C).

For storage conditions of the reconstituted medicinal product see section 6.3.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (see also section 6.6).

### 6.5 Nature and contents of container

Clear glass vial, with rubber stopper and tamper-proof aluminium seal, containing white powder for solution for injection.  
Pack size:  
- Carton comprising one 50 Allergan Unit vial and package leaflet.  
- Packs containing one, two, three or six cartons.  

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

BOTOX is reconstituted prior to use with sterile unpreserved normal saline (0.9% sodium chloride for injection). It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of diluent (see dilution table below) is drawn up into a syringe. The exposed portion of the rubber septum of the vial is cleaned with alcohol (70%) prior to insertion of the needle. Since BOTOX is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. When reconstituted, BOTOX may be stored in a refrigerator (2-8°C) for up to 24 hours prior to use. After this period used or unused vials should be discarded.

Each vial is for single use only.

Dilution table: **Diluent added**  
<table>
<thead>
<tr>
<th>Diluent added</th>
<th>Resulting dose in units per 0.1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>10 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>5 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

Botox
The 'unit' by which the potency of preparations of BOTOX is measured should be used to calculate dosages of BOTOX only and is not transferable to other preparations of botulinum toxin.

An injection volume of approximately 0.1 ml is recommended. A decrease or increase in the BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For safe disposal, unused vials should be reconstituted with a small amount of water then autoclaved. Any used vials, syringes, and spillages etc. should be autoclaved, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%).

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Allergan Ltd.,
Marlow International,
The Parkway, Marlow,
Bucks, SL7 1YL, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00426/0118

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/09/2007

10 DATE OF REVISION OF THE TEXT

08/07/2010
NAME OF THE MEDICINAL PRODUCT

BOTOX
100 Allergan units
Powder for solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Botulinum toxin* type A, 100 Allergan Units/vial.
* from Clostridium botulinum
Botulinum toxin units are not interchangeable from one product to another.

For a full list of excipients, see section 6.1.

PHARMACEUTICAL FORM

Powder for solution for injection.

CLINICAL PARTICULARS

Therapeutic indications

BOTOX is indicated for:

- the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
- the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

BOTOX is also indicated for focal spasticity, including the treatment of:

- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older
- and
- wrist and hand disability due to upper limb spasticity associated with stroke in adults.

The injections should be administered by appropriately trained personnel in hospital specialist centres.

The safety and effectiveness of BOTOX in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia, chronic migraine and focal hyperhidrosis have not been demonstrated in children.

Posology and method of administration

Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin.
Adequate studies on geriatric dosing have not been performed. Dose selection should be the same; however, the lowest effective dose is recommended.

**Blepharospasm**

After reconstitution, BOTOX is injected using a sterile, 27-30 gauge needle. Electromyographic guidance is not necessary. The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. The initial dose should not exceed 25 Units per eye. Normally no additional benefit is conferred by treating more frequently than every three months. It is rare for the effect to be permanent.

In the management of blepharospasm total dosing should not exceed 100 Units every 12 weeks.

**Hemifacial spasm**

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

**Cervical dystonia**

Several dosing regimens have been used in clinical trials for treatment of cervical dystonia with BOTOX. Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response.

In practice, the maximum total dose is not usually more than 200 Units. No more than 50 Units should be given at any one injection site. The dilutions suggested are indicated in the following table:

<table>
<thead>
<tr>
<th>Diluent added</th>
<th>Resulting dose in units per 0.1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>20 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>10 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>5 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>8 ml</td>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

The following doses are recommended:

<table>
<thead>
<tr>
<th>Type</th>
<th>Head rotated</th>
<th>Nerve</th>
<th>Dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Head rotated</td>
<td>Sternomastoid</td>
<td>50 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td>toward side of</td>
<td>Levator scapulae</td>
<td>50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td>shoulder elevation</td>
<td>Scalen</td>
<td>25 - 50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Splenius capitis</td>
<td>25 - 75 Units; 1 - 3 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trapezius</td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
</tbody>
</table>
The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s). The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose.

The sternocleidomastoid muscle should not be injected bilaterally as there is an increased risk of adverse effects (in particular dysphagia) when bilateral injections or doses in excess of 100 Units are administered to this muscle.

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. For cervical dystonia, localisation of the involved muscles with electromyographic guidance may be useful.

Multiple injection sites allow BOTOX to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

**Hyperhidrosis of the axillae**

The recommended injection volume for intradermal injection in axillary hyperhidrosis is 0.1-0.2 ml. Reconstituted BOTOX (100 Units/4 mL) is injected using a 30 gauge needle. 50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor’s iodine-starch test.

Clinical improvement generally occurs within the first week after injection. Repeat injections of axillary hyperhidrosis should be administered when effects from previous injections subside. Treatment response has been reported to persist for 4-7 months.

**Paediatric cerebral palsy**

Diluted BOTOX is injected using a sterile 23-26 gauge needle. It is administered into each of two sites in the medial and lateral heads of the affected gastrocnemius muscle. The recommended total dose is 4 Units/kg body weight. When both lower limbs are to be injected on the same occasion this dose should be divided between the two limbs.
Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every two months.

**Focal spasticity associated with stroke**
Reconstituted BOTOX is injected using a sterile 25, 27 or 30 gauge needle for superficial muscles, and a longer needle for deeper musculature. Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles. The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved the severity of spasticity, and the presence of local muscle weakness.

In the controlled Phase 3 clinical trial the following doses were administered:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum profundus</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>50 Units</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units</td>
</tr>
</tbody>
</table>

In all clinical trials, the doses did not exceed 360 Units divided among selected muscles at any treatment session.

Clinical improvement in muscle tone generally occurs within two weeks following treatment and the peak effect is generally seen within four to six weeks following treatment. Data on the repeated and long-term treatment are limited.

**Chronic Migraine**
The recommended reconstituted BOTOX dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5-inch needle as 0.1 ml (5 U) injections to 31 and up to 39 sites. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the injection sites:
BOTOX Dosing By Muscle:

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis</td>
<td>20 U (4 sites)</td>
</tr>
<tr>
<td>Corrugator</td>
<td>10 U (2 sites)</td>
</tr>
<tr>
<td>Procerus</td>
<td>5 U (1 site)</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>30 U (6 sites) up to 40 U (up to 8 sites)</td>
</tr>
<tr>
<td>Temporalis</td>
<td>40 U (8 sites) up to 50 U (up to 10 sites)</td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 U (6 sites) up to 50 U (up to 10 sites)</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group</td>
<td>20 U (4 sites)</td>
</tr>
</tbody>
</table>

**Total Dose Range:**

<table>
<thead>
<tr>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>155 U to 195 U</td>
</tr>
<tr>
<td>31 to 39 sites</td>
</tr>
</tbody>
</table>

\[^{a}]1IM injection site = 0.1 mL = 5 U BOTOX  
\[^{b}]Dose distributed bilaterally

The recommended re-treatment schedule is every 12 weeks.

### 4.3 Contraindications

BOTOX is contraindicated:

- in individuals with a known hypersensitivity to botulinum toxin type A or to any of the excipients;

- in the presence of infection at the proposed injection site(s).

### 4.4 Special warnings and precautions for use

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX. The recommended dosages and frequencies of administration of BOTOX should not be exceeded.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted (see section 4.8c additional information).

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including swallowing difficulties are at increased risk of these side effects. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.
Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 ‘Cervical Dystonia’).

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation.

As with any treatment with the potential to allow previously-sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually.

Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Eaton Lambert Syndrome; such patients may have an increased sensitivity to agents such as BOTOX, which may result in excessive muscle weakness. Patients with neuromuscular disorders may be at an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX.

BOTOX contains human serum albumin. When medicinal products derived from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of blood donors and donations. In addition, virus inactivation procedures are included in the production process.

As with any injection, procedure-related injury could occur. An injection could result in localized infection, pain, inflammation, paraesthesia, hypoesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc. Care should be taken when injecting near vulnerable anatomic structures.

**Blepharospasm**
Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal pathology. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.
Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma.

**Cervical dystonia**

Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 Units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the oesophageal musculature. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia may contribute to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX injection.

**Hyperhidrosis of the axillae**

Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

**Focal spasticity associated with paediatric cerebral palsy and spasticity of the hand and wrist in adult post-stroke patients**

BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

**Chronic migraine**

No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

**4.5 Interaction with other medicinal products and other forms of interaction**

Theoretically, the effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. tubocurarine-type muscle relaxants).

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.
No interaction studies have been performed. No interactions of clinical significance have been reported.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. BOTOX should not be used during pregnancy unless clearly necessary.

Lactation
There is no information on whether BOTOX is excreted in human milk. The use of BOTOX during lactation cannot be recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, BOTOX may cause asthenia, muscle weakness, somnolence, dizziness and visual disturbance, which could affect driving and the operation of machinery.

4.8 Undesirable effects

a) General

In controlled clinical trials adverse events considered by the investigators to be related to BOTOX were reported in 35% of the patients with blepharospasm, 28% with cervical dystonia, 17% with paediatric cerebral palsy 11% with primary hyperhidrosis of the axillae and 16% with focal spasticity of the upper limb associated with stroke. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In general, adverse reactions occur within the first few days following injection and are transient.

In rare cases, adverse reactions may have a duration of several months or longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue.

As is expected for any injection procedure, localised pain, tenderness and/or bruising may be associated with the injection. Fever and flu syndrome have also been reported after injections of botulinum toxin.

b) Adverse reactions - frequency by indication

For each indication the frequency of adverse reactions arising from clinical experience is given. The frequency is defined as follows:

Very Common (> 1/10); Common (>1/100 to <1/10); Uncommon (>1/1,000 to <1/100); Rare (>1/10,000 to <1/1,000); Very Rare (<1/10,000).

Blepharospasm/hemifacial spasm
Nervous system disorders
Uncommon: Dizziness, facial paresis and facial palsy.

Eye Disorders:
Very common: Eyelid ptosis.
Common: Punctate keratitis, lagophthalmos, dry eye, photophobia and lacrimation increase.
Uncommon: Keratitis, ectropion, diplopia, entropion, visual disturbance and vision blurred.
Rare: Eyelid oedema.
Very rare: Corneal ulceration.

Skin and subcutaneous tissue disorders
Uncommon: Rash/dermatitis.

General disorders and administration site conditions
Common: Irritation and face oedema.
Uncommon: Fatigue.

*Cervical dystonia*

Infections and infestations
Common: Rhinitis and upper respiratory infection.

Nervous system disorders
Common: Dizziness, hypertonia, hypoaesthesia, somnolence and headache.

Eye Disorders:
Uncommon: Diplopia and eyelid ptosis.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea and dysphonia.

Gastrointestinal disorders
Very common: Dysphagia (see section c. below).
Common: Dry mouth and nausea.

Musculoskeletal and connective tissue disorders
Very common: Muscular weakness.
Common: Musculoskeletal stiffness and soreness.

General disorders and administration site conditions
Very common: Pain.
Common: Asthenia, influenza like illness and malaise.
Uncommon: Pyrexia.

*Paediatric cerebral palsy*

Infections and infestations
Very common: Viral infection and ear infection.

Nervous system disorders
Common: Somnolence and paraesthesia.

Skin and subcutaneous tissue disorders
Common: Rash.

Musculoskeletal and connective tissue disorders
Common: Myalgia and muscular weakness.

Renal and urinary disorders
Common: Urinary incontinence.

General disorders and administration site conditions
Common: Gait disturbance and malaise.

Focal upper limb spasticity associated with stroke

Psychiatric disorders
Uncommon: Depression and insomnia.

Nervous system disorders
Common: Hypertonia
Uncommon: Hypoaesthesia, headache, paraesthesia, incoordination and amnesia.

Ear and labyrinth disorders
Uncommon: Vertigo.

Vascular disorders
Uncommon: Orthostatic hypotension.

Gastrointestinal disorders
Uncommon: Nausea and paraesthesia oral.

Skin and subcutaneous tissue disorders
Common: Ecchymosis and purpura.
Uncommon: Dermatitis, pruritus and rash.

Musculoskeletal and connective tissue disorders
Common: Pain in extremity and muscle weakness.
Uncommon: Arthralgia and bursitis.

General disorders and administration site conditions
Common: Injection site hemorrhage and injection site irritation.
Uncommon: Asthenia, pain, injection site hypersensitivity, malaise and oedema peripheral.

Some of the uncommon events may be disease related.

Primary hyperhidrosis of the axillae

Nervous system disorders
Common: Headache
Vascular disorders
Common: Hot flushes.

Gastrointestinal disorders
Uncommon: Nausea.

Skin and subcutaneous tissue disorders
Common: Hyperhidrosis (non-axillary sweating).
Uncommon: Pruritus.

Musculoskeletal and connective tissue disorders
Uncommon: Muscular weakness, myalgia, arthropathy and pain in extremity.

General disorders and administration site conditions
Common: Injection site reactions and pain.
Uncommon: Asthenia, injection site oedema and injection site pain.

In the management of primary axillary hyperhidrosis, increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

**Chronic Migraine**

Nervous system disorders
Common: Headache*, migraine*, facial paresis

Eye disorders
Common: Eyelid ptosis
Uncommon: Eyelid oedema

Skin and subcutaneous tissue disorders
Common: Pruritus, rash
Uncommon: Pain of skin-

Musculoskeletal and connective tissue disorders
Common: Neck pain, myalgia, musculoskeletal pain
musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness
Uncommon: Pain in jaw

General disorders and administration site conditions
Common: Injection site pain

Botox
Gastrointestinal disorders
Uncommon: Dysphagia

* In placebo-controlled trials, headache and migraine, including serious cases of intractable or worsening of headache/migraine, were reported more frequently with BOTOX (9%) than with placebo (6%). They typically occurred within the first month after the injections and their incidence declined with repeated treatments.

c) Additional information
Dysphagia ranges in severity from mild to severe, with potential for aspiration, which occasionally may require medical intervention (see section 4.4).

Side effects related to spread of toxin distant from the site of administration have been reported very rarely (exaggerated muscle weakness, dysphagia, aspiration/aspiration pneumonia, with fatal outcome in some cases) (see section 4.4).

The following other adverse events have been reported since the drug has been marketed: dysarthria; abdominal pain; vision blurred; pyrexia; focal facial paralysis; hypoesthesia; malaise; myalgia; pruritus; hyperhidrosis; diarrhoea; anorexia; hypoacusis; tinnitus; radiculopathy; syncope; myasthenia gravis; erythema multiforme; dermatitis psoriasiform; vomiting and brachial plexopathy.

There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. Serious and/or immediate hypersensitivity reactions have been rarely reported, including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other agents known to cause similar reactions.

A case of peripheral neuropathy has been reported in a large adult male after receiving four sets of BOTOX injections, totalling 1800 Units (for neck and back spasm, and severe pain) over an 11 week period.

Angle closure glaucoma has been reported very rarely following botulinum toxin treatment for blepharospasm.

New onset or recurrent seizures have been reported, typically in patients, who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. The reports in children were reports predominantly from cerebral palsy patients treated for spasticity.

Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.

4.9 Overdose

No cases of systemic toxicity resulting from accidental injection of BOTOX have been observed. No cases of ingestion of BOTOX have been reported. Signs of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically supervised for several days for signs and symptoms of systemic weakness or muscle paralysis.
Patients presenting with the symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles) should be considered for admission to hospital.

With increasing dosage, generalised and profound muscular paralysis occurs. When the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed, intubation and assisted respiration will be required until recovery takes place.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from *Clostridium botulinum*. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.

*Clostridium botulinum* type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.

Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse transmission is by newly formed nerve endings and motor end plates. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical and clinical pharmacodynamic studies.

Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.

During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.
<table>
<thead>
<tr>
<th>Mean change from baseline at Week 24</th>
<th>BOTOX</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=688</td>
<td>N=696</td>
<td>p</td>
</tr>
<tr>
<td>Frequency of headache days</td>
<td>-8.4</td>
<td>-6.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47%</td>
<td>35%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cumulative hours of headache on headache days</td>
<td>120</td>
<td>80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>= 0.009</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8</td>
<td>-2.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance:
Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the extreme toxicity of botulinum toxin type A.

b) Characteristics in patients:
Human ADME studies have not been performed due to the nature of the product. It is believed that little systemic distribution of therapeutic doses of BOTOX occurs. BOTOX is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways.

5.3 Preclinical safety data

Acute toxicity
In monkeys receiving a single intramuscular (i.m.) injection of BOTOX, the No Observed Effect Level (NOEL) ranged from 4 to 24 Units/kg. The i.m. LD₅₀ was reported to be 39 Units/kg.

Toxicity on repeated injection
In three different studies (six months in rats; 20 weeks in juvenile monkeys; 1 year in monkeys) where the animals received i.m. injections, the NOEL was at the following respective BOTOX dosage levels: < 4 Units/kg, 8 Units/kg and 4 Units/kg. The main systemic effect was a transient decrease in body weight gain.

There was no indication of a cumulative effect in the animal studies when BOTOX was given at dosage intervals of 1 month or greater.

Local toxicity

BOTOX was shown not to cause ocular or dermal irritation, or give rise to toxicity when injected into the vitreous body in rabbits.

Allergic or inflammatory reactions in the area of the injection sites are rarely observed after BOTOX administration. However, formation of haematoma may occur.

Reproduction toxicology
**Teratogenic effects**
When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL of BOTOX was at 4 Units/kg. Reductions in ossification were observed at 8 and 16 Units/kg (mice) and reduced ossification of the hyoid bone at 16 Units/kg (rats). Reduced foetal body weights were observed at 8 and 16 Units/kg (rats).

In a range-finding study in rabbits, daily injections at dosages of 0.5 Units/kg/day (days 6 to 18 of gestation), and 4 and 6 Units/kg (administered on days 6 and 13 of gestation), caused death and abortions among surviving dams. External malformations were observed in one foetus each in the 0.125 Units/kg/day and the 2 Units/kg dosage groups. The rabbit appears to be a very sensitive species to BOTOX treatment.

**Impairment of fertility and reproduction**
The reproductive NOEL following i.m. injection of BOTOX was 4 Units/kg in male rats and 8 Units/kg in female rats. Higher dosages were associated with dose-dependent reductions in fertility. Provided impregnation occurred, there were no adverse effects on the numbers or viability of the embryos sired or conceived by treated male or female rats.

**Pre- and post-natal developmental effects**
In female rats, the reproductive NOEL was 16 Units/kg. The developmental NOEL was 4 Units/kg.

**Mutagenicity**
BOTOX has been evaluated and shown to be non-mutagenic in a number of *in vitro* and *in vivo* systems including the Ames test, the AS52/XPRT Mammalian Cell Forward Gene Mutation assay and the CHO test, and non-clastogenic in the mouse PCE test.

**Carcinogenicity**
No animal studies have been conducted.

**Antigenicity**
BOTOX showed antigenicity in mice only in the presence of adjuvant. BOTOX was found to be slightly antigenic in the guinea pig.

**Blood compatibility**
No haemolysis was detected up to 100 Units/ml of BOTOX in normal human blood.

---

6 **PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

- Human albumin
- Sodium chloride

6.2 **Incompatibilities**

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.
6.3 **Shelf life**

3 years. After reconstitution, stability has been demonstrated for 24 hours at 2°C–8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (see also section 6.6).

6.4 **Special precautions for storage**

Store in a refrigerator (2°C-8°C), or store in a freezer (at or below -5°C).

For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 **Nature and contents of container**

Clear glass vial, with rubber stopper and tamper-proof aluminium seal, containing white powder for solution for injection.

Pack size:

- Carton comprising one 100 Allergan Unit vial and package leaflet.
- Packs containing two, three or six cartons.

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**

BOTOX is reconstituted prior to use with sterile unpreserved normal saline (0.9% sodium chloride for injection). It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of diluent (see dilution table below) is drawn up into a syringe. The exposed portion of the rubber septum of the vial is cleaned with alcohol (70%) prior to insertion of the needle. Since BOTOX is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. When reconstituted, BOTOX may be stored in a refrigerator (2-8°C) for up to 24 hours prior to use. After this period used or unused vials should be discarded.

Each vial is for single use only.

<table>
<thead>
<tr>
<th>Diluent added</th>
<th>Resulting dose in units per 0.1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>20 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>10 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>5 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>8 ml</td>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

The 'unit' by which the potency of preparations of BOTOX is measured should be used to calculate dosages of BOTOX only and is not transferable to other preparations of botulinum toxin.
An injection volume of approximately 0.1 ml is recommended. A decrease or increase in the BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For safe disposal, unused vials should be reconstituted with a small amount of water then autoclaved. Any used vials, syringes, and spillages etc. should be autoclaved, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%).

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Allergan Ltd.,
Coronation Road,
High Wycombe,
Bucks HP12 3SH

8 MARKETING AUTHORISATION NUMBER(S)
PL 00426/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
17 May 1994

10 DATE OF REVISION OF THE TEXT
08/07/2010
1 NAME OF THE MEDICINAL PRODUCT

BOTOX
200 Allergan Units
Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Botulinum toxin* type A, 200 Allergan units/vial.
* from Clostridium botulinum
Botulinum toxin units are not interchangeable from one product to another.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTOX is indicated for:
➢ the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
➢ the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
➢ the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine).

BOTOX is also indicated for focal spasticity, including the treatment of:
➢ dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older
and
➢ wrist and hand disability due to upper limb spasticity associated with stroke in adults.

The injections should be administered by appropriately trained personnel in hospital specialist centres.

The safety and effectiveness of BOTOX in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia, chronic migraine and focal hyperhidrosis have not been demonstrated in children.

4.2 Posology and method of administration

Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin.
Adequate studies on geriatric dosing have not been performed. Dose selection should be the same; however, the lowest effective dose is recommended.

**Blepharospasm**
After reconstitution, BOTOX is injected using a sterile, 27-30 gauge needle. Electromyographic guidance is not necessary. The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. The initial dose should not exceed 25 Units per eye. Normally no additional benefit is conferred by treating more frequently than every three months. It is rare for the effect to be permanent.

In the management of blepharospasm total dosing should not exceed 100 Units every 12 weeks.

**Hemifacial spasm**
Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

**Cervical dystonia**
Several dosing regimens have been used in clinical trials for treatment of cervical dystonia with BOTOX. Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response.

In practice, the maximum total dose is not usually more than 200 Units. No more than 50 Units should be given at any one injection site. The dilutions suggested are indicated in the following table:

<table>
<thead>
<tr>
<th>Diluent added</th>
<th>Resulting dose in units per 0.1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>20 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>10 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>5 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>8 ml</td>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

The following doses are recommended:

<table>
<thead>
<tr>
<th>Type I Head rotated toward side of shoulder elevation</th>
<th>Sternomastoid</th>
<th>Levator scapulae</th>
<th>Scalene</th>
<th>Splenius capitis</th>
<th>Trapezius</th>
<th>50 - 100 Units; at least 2 sites</th>
<th>50 Units; 1 - 2 sites</th>
<th>25 - 50 Units; 1 - 2 sites</th>
<th>25 - 75 Units; 1 - 3 sites</th>
<th>25 - 100 Units; 1 - 8 sites</th>
</tr>
</thead>
</table>

Botox
<table>
<thead>
<tr>
<th>Type II</th>
<th>Head rotation only</th>
<th>Sternomastoid</th>
<th>25 - 100 Units; at least 2 sites if &gt;25 Units given</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type III</td>
<td>Head tilted toward side of shoulder elevation</td>
<td>Sternomastoid, Levator scapulae, Scalenae, Trapezius</td>
<td>25 - 100 Units at posterior border; at least 2 sites if &gt;25 Units given</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 75 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
<tr>
<td>Type IV</td>
<td>Bilateral posterior cervical muscle spasm with elevation of the face</td>
<td>Splenius capitis and cervicis</td>
<td>50 - 200 Units; 2 - 8 sites, treat bilaterally</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(This is the total dose and not the dose for each side of the neck)</td>
</tr>
</tbody>
</table>

The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, and/or the trapezius muscle(s). The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose.

The sternocleidomastoid muscle should not be injected bilaterally as there is an increased risk of adverse effects (in particular dysphagia) when bilateral injections or doses in excess of 100 Units are administered to this muscle.

A 25, 27 or 30 gauge needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. For cervical dystonia, localisation of the involved muscles with electromyographic guidance may be useful.

Multiple injection sites allow BOTOX to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

**Hyperhidrosis of the axillae**

The recommended injection volume for intradermal injection in axillary hyperhidrosis is 0.1-0.2 ml. Reconstituted BOTOX (100 Units/4 mL) is injected using a 30 gauge needle. 50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor’s iodine-starch test.

Clinical improvement generally occurs within the first week after injection. Repeat injections of axillary hyperhidrosis should be administered when effects from previous injections subside. Treatment response has been reported to persist for 4-7 months.

**Paediatric cerebral palsy**

Diluted BOTOX is injected using a sterile 23-26 gauge needle. It is administered into each of two sites in the medial and lateral heads of the affected gastrocnemius muscle. The recommended total dose is 4 Units/kg body weight. When both lower limbs are to be injected on the same occasion this dose should be divided between the two limbs.
Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every two months.

**Focal spasticity associated with stroke**

Reconstituted BOTOX is injected using a sterile 25, 27 or 30 gauge needle for superficial muscles, and a longer needle for deeper musculature. Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles. The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved the severity of spasticity, and the presence of local muscle weakness.

In the controlled Phase 3 clinical trial the following doses were administered:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum profundus</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>50 Units</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>50 Units</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units</td>
</tr>
</tbody>
</table>

In all clinical trials, the doses did not exceed 360 Units divided among selected muscles at any treatment session.

Clinical improvement in muscle tone generally occurs within two weeks following treatment and the peak effect is generally seen within four to six weeks following treatment. Data on the repeated and long-term treatment are limited.

**Chronic Migraine**

The recommended reconstituted BOTOX dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5-inch needle as 0.1 ml (5 U) injections to 31 and up to 39 sites. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the injection sites:
BOTOX Dosing By Muscle:

<table>
<thead>
<tr>
<th>Head/Neck Area</th>
<th>Recommended Dose</th>
<th>Total Dosage (number of sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis</td>
<td>20 U (4 sites)</td>
<td></td>
</tr>
<tr>
<td>Corrugator</td>
<td>10 U (2 sites)</td>
<td></td>
</tr>
<tr>
<td>Procerus</td>
<td>5 U (1 site)</td>
<td></td>
</tr>
<tr>
<td>Occipitalis</td>
<td>30 U (6 sites) up to 40 U (up to 8 sites)</td>
<td></td>
</tr>
<tr>
<td>Temporalis</td>
<td>40 U (8 sites) up to 50 U (up to 10 sites)</td>
<td></td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 U (6 sites) up to 50 U (up to 10 sites)</td>
<td></td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group</td>
<td>20 U (4 sites)</td>
<td></td>
</tr>
<tr>
<td><strong>Total Dose Range:</strong></td>
<td><strong>155 U to 195 U</strong></td>
<td><strong>31 to 39 sites</strong></td>
</tr>
</tbody>
</table>

a) IM injection site = 0.1 mL = 5 U BOTOX
b) Dose distributed bilaterally

The recommended re-treatment schedule is every 12 weeks.

4.3 Contraindications

BOTOX is contraindicated:
- in individuals with a known hypersensitivity to botulinum toxin type A or to any of the excipients,
- in the presence of infection at the proposed injection site(s).

4.4 Special warnings and precautions for use

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX. The recommended dosages and frequencies of administration of BOTOX should not be exceeded.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted (see section 4.8c additional information).

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including swallowing difficulties are at increased risk of these side effects. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.
Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 ‘Cervical Dystonia’).

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation.

As with any treatment with the potential to allow previously-sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually.

Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Eaton Lambert Syndrome; such patients may have an increased sensitivity to agents such as BOTOX, which may result in excessive muscle weakness. Patients with neuromuscular disorders may be at an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX.

BOTOX contains human serum albumin. When medicinal products derived from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. To reduce the risk of transmission of infective agents, stringent controls are applied to the selection of blood donors and donations. In addition, virus inactivation procedures are included in the production process.

As with any injection, procedure-related injury could occur. An injection could result in localized infection, pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc. Care should be taken when injecting near vulnerable anatomic structures.

**Blepharospasm**
Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal pathology. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.
Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma.

**Cervical dystonia**
Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 Units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the oesophageal musculature. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia may contribute to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX injection.

**Hyperhidrosis of the axillae**
Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

**Focal spasticity associated with paediatric cerebral palsy and spasticity of the hand and wrist in adult post-stroke patients**
BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

**Chronic migraine**
No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

4.5 **Interaction with other medicinal products and other forms of interaction**

Theoretically, the effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. tubocurarine-type muscle relaxants).

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

No interaction studies have been performed. No interactions of clinical significance have been reported.
4.6 Pregnancy and lactation

**Pregnancy**
There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). The potential risk for humans is unknown. BOTOX should not be used during pregnancy unless clearly necessary.

**Lactation**
There is no information on whether BOTOX is excreted in human milk. The use of BOTOX during lactation cannot be recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, BOTOX may cause asthenia, muscle weakness, somnolence, dizziness and visual disturbance, which could affect driving and the operation of machinery.

4.8 Undesirable effects

**a) General**
In controlled clinical trials adverse events considered by the investigators to be related to BOTOX were reported in 35% of the patients with blepharospasm, 28% with cervical dystonia, 17% with paediatric cerebral palsy 11% with primary hyperhidrosis of the axillae and 16% with focal spasticity of the upper limb associated with stroke. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In general, adverse reactions occur within the first few days following injection and are transient.

In rare cases, adverse reactions may have a duration of several months or longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue.

As is expected for any injection procedure, localised pain, tenderness and/or bruising may be associated with the injection. Fever and flu syndrome have also been reported after injections of botulinum toxin.

**b) Adverse reactions - frequency by indication**
For each indication the frequency of adverse reactions arising from clinical experience is given. The frequency is defined as follows:

Very Common (>1/10); Common (>1/100 to <1/10); Uncommon (>1/1,000 to <1/100); Rare (>1/10,000 to <1/1,000); Very Rare (<1/10,000).

*Blepharospasm/hemifacial spasm*

Nervous system disorders
Uncommon: Dizziness, facial paresis and facial palsy.

Eye Disorders:
Very common: Eyelid ptosis.
Common: Punctate keratitis, lagophthalmos, dry eye, photophobia and lacrimation increase.

Uncommon: Keratitis, ectropion, diplopia, entropion, visual disturbance and vision blurred.

Rare: Eyelid oedema.

Very rare: Corneal ulceration.

Skin and subcutaneous tissue disorders
Uncommon: Rash/dermatitis.

General disorders and administration site conditions
Common: Irritation and face oedema.
Uncommon: Fatigue.

*Cervical dystonia*

Infections and infestations
Common: Rhinitis and upper respiratory infection.

Nervous system disorders
Common: Dizziness, hypertonia, hypoaesthesia, somnolence and headache.

Eye Disorders:
Uncommon: Diplopia and eyelid ptosis.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea and dysphonia.

Gastrointestinal disorders
Very common: Dysphagia (see section c. below).
Common: Dry mouth and nausea.

Musculoskeletal and connective tissue disorders
Very common: Muscular weakness.
Common: Musculoskeletal stiffness and soreness.

General disorders and administration site conditions
Very common: Pain.
Common: Asthenia, influenza like illness and malaise.
Uncommon: Pyrexia.

*Paediatric cerebral palsy*

Infections and infestations
Very common: Viral infection and ear infection.

Nervous system disorders
Common: Somnolence and paraesthesia.

Skin and subcutaneous tissue disorders
Common: Rash.
Musculoskeletal and connective tissue disorders
Common: Myalgia and muscular weakness.

Renal and urinary disorders
Common: Urinary incontinence.

General disorders and administration site conditions
Common: Gait disturbance and malaise.

Focal upper limb spasticity associated with stroke

Psychiatric disorders
Uncommon: Depression and insomnia.

Nervous system disorders
Common: Hypertonia
Uncommon: Hypoaesthesia, headache, paraesthesia, incoordination and amnesia.

Ear and labyrinth disorders
Uncommon: Vertigo.

Vascular disorders
Uncommon: Orthostatic hypotension.

Gastrointestinal disorders
Uncommon: Nausea and paraesthesia oral.

Skin and subcutaneous tissue disorders
Common: Ecchymosis and purpura.
Uncommon: Dermatitis, pruritus and rash.

Musculoskeletal and connective tissue disorders
Common: Pain in extremity and muscle weakness.
Uncommon: Arthralgia and bursitis.

General disorders and administration site conditions
Common: Injection site hemorrhage and injection site irritation.
Uncommon: Asthenia, pain, injection site hypersensitivity, malaise and oedema peripheral.

Some of the uncommon events may be disease related.

Primary hyperhidrosis of the axillae

Nervous system disorders
Common: Headache

Vascular disorders
Common: Hot flushes.

Gastrointestinal disorders
Uncommon: Nausea
Skin and subcutaneous tissue disorders  
Common: Hyperhidrosis (non-axillary sweating).
Uncommon: Pruritus.

Musculoskeletal and connective tissue disorders  
Uncommon: Muscular weakness, myalgia, arthropathy and pain in extremity.

General disorders and administration site conditions  
Common: Injection site reactions and pain.  
Uncommon: Asthenia, injection site oedema and injection site pain.

In the management of primary axillary hyperhidrosis, increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

Chronic Migraine

Nervous system disorders  
Common: Headache*, migraine*, facial paresis

Eye disorders  
Common: Eyelid ptosis  
Uncommon: Eyelid oedema

Skin and subcutaneous tissue disorders  
Common: Pruritus, rash  
Uncommon: Pain of skin

Musculoskeletal and connective tissue disorders  
Common: Neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness  
Uncommon: Pain in jaw

General disorders and administration site conditions  
Common: Injection site pain

Gastrointestinal disorders  
Uncommon: Dysphagia
* In placebo-controlled trials, headache and migraine, including serious cases of intractable or worsening of headache/migraine, were reported more frequently with BOTOX (9%) than with placebo (6%). They typically occurred within the first month after the injections and their incidence declined with repeated treatments.

c) Additional information
Dysphagia ranges in severity from mild to severe, with potential for aspiration, which occasionally may require medical intervention (see section 4.4).

Side effects related to spread of toxin distant from the site of administration have been reported very rarely (exaggerated muscle weakness, dysphagia, aspiration/aspiration pneumonia, with fatal outcome in some cases) (see section 4.4).

The following other adverse events have been reported since the drug has been marketed: dysarthria; abdominal pain; vision blurred; pyrexia; focal facial paralysis; hypoaesthesia; malaise; myalgia; pruritus; hyperhidrosis; diarrhoea; anorexia; hypoacusis; tinnitus; radiculopathy; syncope; myasthenia gravis; erythema multiforme; dermatitis psoriasiform; vomiting and brachial plexopathy.

There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

Serious and/or immediate hypersensitivity reactions have been rarely reported, including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other agents known to cause similar reactions.

A case of peripheral neuropathy has been reported in a large adult male after receiving four sets of BOTOX injections, totalling 1800 Units (for neck and back spasm, and severe pain) over an 11 week period.

Angle closure glaucoma has been reported very rarely following botulinum toxin treatment for blepharospasm.

New onset or recurrent seizures have been reported, typically in patients, who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. The reports in children were reports predominantly from cerebral palsy patients treated for spasticity.

Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.

4.9 Overdose

No cases of systemic toxicity resulting from accidental injection of BOTOX have been observed. No cases of ingestion of BOTOX have been reported. Signs of overdose are not apparent immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically supervised for several days for signs and symptoms of systemic weakness or muscle paralysis.
Patients presenting with the symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles) should be considered for admission to hospital.

With increasing dosage, generalised and profound muscular paralysis occurs. When the musculature of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralysed, intubation and assisted respiration will be required until recovery takes place.

As a precaution against accidental overdose, care should be taken to use the correct diluent volume for the dosage chosen (See section 6.6).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from *Clostridium botulinum*. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.

*Clostridium botulinum* toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.

Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse transmission is by newly formed nerve endings and motor end plates. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical and clinical pharmacodynamic studies.

Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.

During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.
<table>
<thead>
<tr>
<th>Mean change from baseline at Week 24</th>
<th>BOTOX</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=688</td>
<td>N=696</td>
<td></td>
</tr>
<tr>
<td>Frequency of headache days</td>
<td>-8.4</td>
<td>-6.6</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47%</td>
<td>35%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Total cumulative hours of headache days on headache days</td>
<td>120</td>
<td>80</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8</td>
<td>-2.4</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance:
Classical absorption, distribution, biotransformation and elimination studies on the active substance have not been performed due to the extreme toxicity of botulinum toxin type A.

b) Characteristics in patients:
Human ADME studies have not been performed due to the nature of the product. It is believed that little systemic distribution of therapeutic doses of BOTOX occurs. BOTOX is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways.

5.3 Preclinical safety data

Acute toxicity
In monkeys receiving a single intramuscular (i.m.) injection of BOTOX, the No Observed Effect Level (NOEL) ranged from 4 to 24 Units/kg. The i.m. LD$_{50}$ was reported to be 39 Units/kg.

Toxicity on repeated injection
In three different studies (six months in rats; 20 weeks in juvenile monkeys; 1 year in monkeys) where the animals received i.m. injections, the NOEL was at the following respective BOTOX dosage levels: < 4 Units/kg, 8 Units/kg and 4 Units/kg. The main systemic effect was a transient decrease in body weight gain.

There was no indication of a cumulative effect in the animal studies when BOTOX was given at dosage intervals of 1 month or greater.

Local toxicity
BOTOX was shown not to cause ocular or dermal irritation, or give rise to toxicity when injected into the vitreous body in rabbits.

Allergic or inflammatory reactions in the area of the injection sites are rarely observed after BOTOX administration. However, formation of haematoma may occur.

Reproduction toxicology
Teratogenic effects
When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL of BOTOX was at 4 Units/kg. Reductions in ossification were observed at 8 and 16 Units/kg (mice) and reduced ossification of the hyoid bone at 16 Units/kg (rats). Reduced foetal body weights were observed at 8 and 16 Units/kg (rats).

In a range-finding study in rabbits, daily injections at dosages of 0.5 Units/kg/day (days 6 to 18 of gestation), and 4 and 6 Units/kg (administered on days 6 and 13 of gestation), caused death and abortions among surviving dams. External malformations were observed in one foetus each in the 0.125 Units/kg/day and the 2 Units/kg dosage groups. The rabbit appears to be a very sensitive species to BOTOX treatment.

Impairment of fertility and reproduction

The reproductive NOEL following i.m. injection of BOTOX was 4 Units/kg in male rats and 8 Units/kg in female rats. Higher dosages were associated with dose-dependent reductions in fertility. Provided impregnation occurred, there were no adverse effects on the numbers or viability of the embryos sired or conceived by treated male or female rats.

Pre- and post-natal developmental effects

In female rats, the reproductive NOEL was 16 Units/kg. The developmental NOEL was 4 Units/kg.

Mutagenicity
BOTOX has been evaluated and shown to be non-mutagenic in a number of in vitro and in vivo systems including the Ames test, the AS52/XPRT Mammalian Cell Forward Gene Mutation assay and the CHO test, and non-clastogenic in the mouse PCE test.

Carcinogenicity
No animal studies have been conducted.

Antigenicity
BOTOX showed antigenicity in mice only in the presence of adjuvant. BOTOX was found to be slightly antigenic in the guinea pig.

Blood compatibility
No haemolysis was detected up to 100 Units/ml of BOTOX in normal human blood.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sodium chloride

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products.
6.3 Shelf life

18 months.

After reconstitution, stability has been demonstrated for 24 hours at 2°C – 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (see also section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C), or store in a freezer (at or below -5°C). For storage conditions of the reconstituted medicinal product see section 6.3.

6.5 Nature and contents of container

Clear glass vial, with rubber stopper and tamper-proof aluminium seal, containing white powder for solution for injection.

Pack size:

- Carton comprising one 200 Allergan Unit vial and package leaflet.
- Packs containing two, three or six cartons.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

BOTOX is reconstituted prior to use with sterile unpreserved normal saline (0.9% sodium chloride for injection). It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of diluent (see dilution table below) is drawn up into a syringe. The exposed portion of the rubber septum of the vial is cleaned with alcohol (70%) prior to insertion of the needle. Since BOTOX is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. When reconstituted, BOTOX may be stored in a refrigerator (2-8°C) for up to 24 hours prior to use. After this period used or unused vials should be discarded.

Each vial is for single use only.

**Do not use more than one vial (200 Units) except for focal spasticity associated with stroke or cervical dystonia where a higher total dose may occasionally be administered.**

Care should be taken to use the correct diluent volume for the presentation chosen to prevent accidental overdose.

<table>
<thead>
<tr>
<th>Dilution table: Diluent added</th>
<th>Resulting dose in units per 0.1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>40 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>20 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>10 Units</td>
</tr>
</tbody>
</table>
The 'unit' by which the potency of preparations of BOTOX is measured should be used to calculate dosages of BOTOX only and is not transferable to other preparations of botulinum toxin.

An injection volume of approximately 0.1 ml is recommended. A decrease or increase in the BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For safe disposal, unused vials should be reconstituted with a small amount of water then autoclaved. Any used vials, syringes, and spillages etc. should be autoclaved, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%).

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Allergan Ltd.,
Marlow International,
The Parkway, Marlow,
Bucks, SL7 1YL, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00426/0119

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/03/2009

10 DATE OF REVISION OF THE TEXT

08/07/2010
Patient Information Leaflet

Botox

(Botulinum toxin type A)

PL 00426/0074-0105
PL 00426/0118-0025
PL 00426/0119-0007
Botox®

PACKAGE LEAFLET: INFORMATION FOR THE USER

1. WHAT BOTOX IS AND WHAT IT IS USED FOR

BOTOX is a muscle relaxant that is injected into the muscles or deep into the skin. It works by partially blocking the nerve impulses to any muscles that have been injected and

2. BEFORE YOU USE BOTOX

Do NOT use BOTOX

- if you are allergic (hypersensitive) to botulinum toxin type A or any of the other ingredients of BOTOX;
- if you have an infection at the proposed site of injection.

Take special care with BOTOX

Before using BOTOX

- tell your doctor if you:
  - have had any problems with injections (such as itching) in the past;
  - have inflammation in the muscles or skin area where your doctor plans to inject;
  - have significant weakness of swelling of the muscles which your doctor plans to inject;
  - have ever had problems with swallowing or food or liquid accidentally going into your lungs, especially if you will be treated for persistent muscle spasms in the neck and shoulders;
  - suffer from any other muscle problems or chronic diseases affecting your muscles (such as myasthenia gravis or Eaton Lambert Syndrome);
  - suffer from certain diseases affecting your nervous system (such as amyotrophic lateral sclerosis or motor neuropathy);
  - have had any surgery classified as closed-angle glaucoma (high pressure in the eye) or were told you are at risk for developing this type of glaucoma;
  - have had any surgery that may have in some way changed the muscle to be injected.

After you have been given BOTOX

Contact your doctor and seek medical attention immediately if you experience any of the following:

- difficulty breathing, swallowing, or speaking;
- trouble swallowing including swelling of the face or throat, wheezing, feeling faint and shortness of breath (possible symptoms of severe allergic reaction).

General precautions

If you are given BOTOX too often or the dose is too high, your body may start producing some antibodies, which can reduce the effect of BOTOX.

If you have not done much exercise for a long time before receiving BOTOX treatment, then after your injections you should start any activity gradually.

BOTOX contains a human albumin which comes from human blood. As with any medicine which is created from human blood there is a possibility of passing on infections. To reduce this risk, blood donors are screened very carefully. Furthermore, BOTOX is made in a way that should remove or destroy these viruses.

It is unlikely that this medicine will improve the range of motion of joints where the surrounding muscle has lost its ability to contract.

When BOTOX is used in the treatment of persistent muscle spasms in the eyelid, it could make your eyes blink less often, which may harm the surface of your eyes. In order to prevent this, you may need treatment with eye drops, ointments, or contact lenses to help maintain proper covering of the eye. Your doctor will tell you if this is required.

BOTOX does not prevent headaches in patients with episcleritis or episcleritis, which occurs less than 15 days a month.

Taking other medicines

Tell your doctor or pharmacist it

- you are taking any antibiotics (used to treat infections) or muscle relaxants. Some of these medicines may increase the effect of BOTOX;
- you have recently been injected with a medicine containing botulinum toxin (the active substance of BOTOX), as this may increase the effect of BOTOX too much.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including
Pregnancy and breast-feeding

The use of BOTOX is not recommended during pregnancy.

If you are pregnant or become pregnant whilst being treated, your doctor will discuss with you whether you should continue with your treatment.

BOTOX is not recommended in breast-feeding women.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

BOTOX may cause dizziness, sleepiness, tiredness or problems with your vision. If you experience any of these effects, do not drive or use any machines. If you are not sure, ask your doctor for advice.

3. HOW TO USE BOTOX

BOTOX must only be injected by healthcare professionals with specific skills on how to use the medicine.

Method and route of administration

BOTOX is injected into your muscles (intramuscularly) or into the skin (intradermally). It is injected directly into the affected area of your body; your doctor will usually inject BOTOX into several sites within the affected area.

General information about dosage

- The number of injections per muscle and the dose vary depending on the indications. Therefore, your doctor will decide how much, how often, and in which muscle(s) BOTOX will be given to you. It is recommended that your doctor uses the smallest effective dose.
- Dosages for the elderly are the same as for other adults.
- The dosage of BOTOX and the duration of its effect will vary depending on the condition for which you are treated.
- Below are details corresponding to each condition.

For persistent muscle spasms of the eyelid and face

Dosage

In the first treatment session, your doctor may give multiple injections in the affected muscles with 1.25 to 2.5 Units of BOTOX into each injection site. The maximum dose for the first treatment session is 25 Units per affected area (example per eye). For the following treatment sessions, the total maximum dose can be increased up to 100 Units, if needed.

Duration of treatment effect

You will usually see an improvement within 3 days after the injection.

The maximum effect is usually seen 1 to 2 weeks after treatment.

When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 9 months.

For persistent muscle spasms of the neck and shoulders

Dosage

Your doctor may give multiple injections in the affected muscles with up to 50 Units of BOTOX into each injection site.

The maximum dose for the first treatment session is 200 Units.

Duration of treatment effect

When the effect starts to wear off, you can have the treatment again if needed, normally not more often than every 12 weeks.

For persistent muscle spasms in the wrist and hand of patients who have had a stroke

Dosage

Your doctor may give multiple injections in the affected muscles. The dose and number of injections will vary depending on a number of factors, including your needs.

The muscles to be injected, the size of the muscles, severity of spasms, etc.

Duration of treatment effect

You will usually see an improvement within the first 2 weeks after the injection.

The maximum effect is usually seen about 4 to 6 weeks after treatment.

When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 12 weeks.

For excessive sweating of the axillae

Dosage

Your doctor will give multiple injections with a total of 50 Units of BOTOX in each armpit.

Duration of treatment effect

You will usually see an improvement within the first week after injection.

On average the effect usually lasts 4-7 months after the first injection.

When the effect starts to wear off, you can have the treatment again if needed.

For persistent muscle spasms in the legs of children who have cerebral palsy

Dosage

The doctor may give multiple injections in the affected muscles. The dose will depend on the weight of your child.

Duration of treatment effect

The improvement usually appears after the injection.

When the effect starts to wear off, it is possible, but not more often than every 2 months.

For the prevention of headache in adults who have chronic migraine

Dosage

Your doctor may give you multiple injections (between 3.1 and 3.9 Units) into each injection site. Injections are divided across muscles in your forehead, your temple on the side of your head, the back of your head, your upper neck area, and your shoulders.

The injections are given both the left and right side of these head and neck muscles, except for one injection given to the muscle that is between your eyebrows.

The total dose range is between 66.5 Units and 196 Units per treatment session.

Duration of treatment effect

When the effect starts to wear off, further treatment is possible, but not more often than every 12 weeks.

If you have received more BOTOX than you should

The signs of too much BOTOX may not appear for several days after the injection. Should you swallow BOTOX or have it accidentally injected, you should see your doctor who may keep you under observation for several days.

If you have received too much BOTOX, you may have any of the following symptoms and you must contact your doctor immediately. Has this if you have to go to hospital:
- difficulty in breathing, swallowing or speaking due to muscle paralysis,
- foaming at the mouth, or possibly cramps of the face or neck and other muscles,
- swallowing, change in voice or speaking.

If you have any further questions about the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, BOTOX can cause side effects, although not everybody gets them. In general, side effects occur within the first few days following injection and last only for a short time. In rare cases, they may last for several months or longer.

If you have any difficulty breathing, swallowing or speaking after receiving BOTOX,
contact your doctor immediately.

If you experience hives, swelling (including swelling of the face or throat), wheezing, feeling faint and shortness of breath, contact your doctor immediately.

The side effects are classified into the following categories, depending on how often they occur:

**Very common** occur in more than 1 out of 10 people who use the medicine

**Common** occur in more than 1 out of 10 people but more than 1 out of 100 people who use the medicine

**Uncommon** occur in less than 1 out of 10 people but more than 1 out of 1,000 people who use the medicine

**Rare** occur in less than 1 out of 1,000 people

**Very rare** occur in less than 1 out of 10,000 people who use the medicine

Below are lists of side effects which vary depending on the part of the body where BOTOX is injected:

### Injections in the eyelid and face

**Very common side effect:**
- drooping of one eyelid.

**Common side effects:**
- swelling of the face;
- mild inflammation of the cornea (transplant outer covering of the eye);
- difficulty in completely closing the eye;
- overflow of tears;
- itchy;
- dry eyes and sensitivity to light.

**Uncommon side effects:**
- dizziness;
- difficulty in seeing clearly;
- blurred vision;
- double vision;
- weakness;
- inflammation of the cornea (transplant outer covering of the eye);
- weakness of the facial muscles;
- drop of the muscles on one side of the face;
- rash;
- abnormal turning of the eyelids downwards or forwards.

**Rare side effect:**
- swelling of the eyelid.

**Very rare side effect:**
- ulcer of the cornea (transplant outer covering of the eye).

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### Injections in the neck and shoulder

**Very common side effects:**
- difficulty in swallowing;
- pain;
- muscle weakness.

**Common side effects:**
- dizziness;
- flu syndrome;
- sleepiness;
- muscle cramps;
- decreased skin sensation;
- feeling of weakness;
- feeling generally unwell;
- feeling sick;
- headache;
- stuffy or sore muscles;
- swelling and irritation inside the nose (mistletoe);
- blocked or runny nose, cough, sore throat, tickle or irritation in the throat;
- dry mouth.

**Uncommon side effects:**
- shortness of breath;
- dizziness;
- fever;
- drooping of the eyelid;
- changes in your voice.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### Injections in the wrist and hand of patients who have had a stroke

**Common side effects:**
- muscle weakness;
- muscle cramps;
- bruising and bleeding under the skin causing red patches (eczema or purpura);
- bleeding or bruising where the injection was given;
- pain in the hand and fingers.

**Uncommon side effects:**
- depression;
- a fall in blood pressure on standing up which causes dizziness, light headedness or fainting;
- feeling of dizziness or ‘spinning’ (vertigo);
- lack of coordination of movements;
- loss of memory;
- general weakness;
- pain;
- joint pain or inflammation;
- decreased skin sensation.

Some of these uncommon side effects may also be related to your illness.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### Injections for excessive sweating of the armpits

**Common side effects:**
- hot flashes;
- increased sweating at sites other than the armpit;
- reactions and pain where the injection was given;
- headache.

**Uncommon side effects:**
- muscle weakness;
- feeling of weakness;
- muscle pain;
- pain in the extremities, such as the hands and fingers;
- problem with the joints;
- feeling sick;
- swelling or pain where the injection was given;
- itching.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### Injections in the legs of children with cerebral palsy

**Very common side effects:**
- viral infection;
- ear infection.

**Common side effects:**
- sleepiness;
- muscle weakness;
- problems with walking;
- numbness;
- muscle pain;
- urinary incontinence (not being able to control when you empty your bladder);
- feeling generally unwell;
- rash.

If any of the side effects gets serious, or if you notice
any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Injections in the head and neck to prevent headache in patients who suffer from chronic migraine

Common side effects:
- headache; migraines;
- rash, itching;
- pain where the injection was given;
- dropping of the eyebrow;
- muscle weakness;
- neck pain;
- muscle pain, cramp;
- muscle stiffness, tightness;
- difficulty in swallowing;
- skin pain;
- jaw pain;
- swollen eyelid.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

General information about other side effects

Side effects related to the spread of BOTOX far away from the site of injection have been reported very rarely and include:
- muscle weakness;
- difficulty in swallowing or liquid accidentally going into the lungs which may cause pneumonia.

The difficulty in swallowing may range from mild to severe and in some cases you may need treatment. In rare cases, people have died because of swallowing difficulties.

Side effects affecting the heart have been rarely reported:
- irregular heartbeat;
- heart attack;
- Some of these people have died. However, some of these patients were already suffering from heart complaints.

Serious or immediate allergic reactions have been rarely reported, including:
- rashes;
- swelling including swelling of the face or throat;
- wheezing;
- feeling faint;
- shortness of breath.

There have been very rare reports of:
- glaucoma (high pressure in the eye).

BOTOX is available in 50 Allergan Units of Botulinum toxin type A.

Each vial contains 50 Allergan Units of Botulinum toxin type A. Each pack may contain 1, 2, 3, 6 or 12 vials.

6. FURTHER INFORMATION

What BOTOX contains
- The active substance is: Botulinum toxin type A from Clostridium botulinum;
- Other ingredients are: human albumin and sodium chloride.

What BOTOX looks like and content of the pack

BOTOX is presented as a white powder in a transparent glass vial. Prior to injection, the product must be dissolved in a sterile saline solution.

Each vial contains 50 Allergan Units of Botulinum toxin type A. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes are marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Allergan, plc.
Merrow Industrial, The Parkway, Merrow, Bury St Edmunds, UK.

Manufacturer:
Allergan Pharmaceuticals Ireland
Cathedral Road Westport County Mayo Ireland

This medicinal product is authorised in the Member States of the EEA under the following name: BOTOX Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom

This leaflet was last approved in MAR11YY

Deepest thanks to Dr. Michael B. Lacks, MD, for his assistance in the preparation of this leaflet.

Botox 103
The following information is intended for medical or healthcare professionals only:

Please refer to the Summary of Product Characteristics for complete prescribing information for BOTOX.

For all indications:

Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including swallowing difficulties are at increased risk of these side effects. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Reconstitution of the medicinal product:

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage.

Reconstitute BOTOX only in sterile preparation equipment, normal saline (0.9% sodium chloride for injection). Draw up an appropriate amount of diluent (see dilution table below) into a syringe.

<table>
<thead>
<tr>
<th>Amount of diluent added (0.9% Sodium chloride injection)</th>
<th>Resulting dose (Units per 0.1 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>0 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>0 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>0.5 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

Since BOTOX is denatured by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colorless to slightly yellow solution free of particulate matter. The reconstituted solution should be visually inspected for clarity and absence of particulate prior to use. When reconstituted, BOTOX may be stored in a refrigerator (2°C - 8°C) for up to 24 hours prior to use.

From a microbiological point of view, the product should be used immediately. If not used immediately, use in aseptic storage and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

This product is for single use only and any unused solution should be discarded.

Procedure to follow for safe disposal of vials, syringes and materials used:

For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any unused vials, syringes, and accessories should be incinerated or, under controlled conditions, rendered non-infectious by the autoclaving process (121°C, 15 psi for 15 minutes).

Identification of the product:

In order to verify receipt of actual BOTOX product from Allergan, look for a holographic film on the vial label. In order to see this film, examine the vial under a desk lamp or fluorescent light source.

Rotating the vial back and forth between your fingers, look for horizontal lines of rainbow color on the label and confirm that the name "Allergan" appears within the rainbow lines. (Note that the film on the label is absent in the Aesthetica or Xeomin varieties. If you do not see the rainbow lines or the name "Allergan" does not appear, do not use the product and contact your local Allergan office for additional information.)
1. **WHAT BOTOX IS AND WHAT IT IS USED FOR**

**What BOTOX is**

BOTOX is a muscle relaxant that is injected into the muscles or deep into the skin. It works by partially blocking the nerve impulse to any muscles that have been injected and reduces excessive contractions of those muscles. In the case of chronic migraines, it is thought that BOTOX blocks pain signals, which indirectly blocks the development of a migraine.

**When injected into the skin**, BOTOX works on sweat glands to reduce the amount of sweat produced.

**What BOTOX is used for**

- In adults, BOTOX is used to treat:
  - persistent muscle spasms in the eyelid and face;
  - persistent muscle spasms in the neck and shoulders;
  - persistent muscle spasms in the wrist and hand of patients who have suffered a stroke;
  - excessive sweating of the armpit that affects the activities of daily living, when other local treatments do not help.

- In adults, BOTOX is used to prevent:
  - headaches in patients with chronic migraines.

**Chronic migraines** is a disease that affects the nervous system. It is thought that BOTOX may help prevent headaches by affecting the nervous system.

**BOTOX has been shown to significantly reduce headache frequency in patients with chronic migraines.** After two treatment sessions, approximately 47% of patients had a 50% or greater reduction in headache frequency compared to baseline in the number of days with headache they experienced.

In children aged two years or older with cerebral palsy, who can walk, BOTOX is used to:

- Relieve pain caused by the persistent muscle spasm in the leg.
- Relieve the persistent muscle spasm in the leg.

2. **BEFORE YOU USE BOTOX**

**Do NOT use BOTOX**

- If you are allergic (hypersensitive) to botulinum toxin type A or any of the other ingredients of BOTOX;
- If you have any injection in the proposed site of injection.

**Take special care with BOTOX**

**Before using BOTOX**

Tell your doctor if you:

- have had any problems with injections (such as itching) in the past;
- have inflammation in the muscles or skin area where your doctor plans to inject;
- have significant weakness of existing of the muscle where your doctor plans to inject;
- have any other medical problems, including chronic diseases or chronic disorders affecting your nervous system, such as amyotrophic lateral sclerosis or motor neurone disease;
- have an unusual reaction to previous Botulinum toxin injections.

After you have been given BOTOX

- Contact your doctor and seek medical advice immediately if you experience any of the following:
  - difficulty in breathing, swallowing, or speaking;
  - fever, chills, swelling in the face, throat, eyes, nose, mouth, or ears;
  - sudden dizziness or loss of balance;
  - rash, hives, swelling, breathing difficulties, shortness of breath, or severe skin reactions (possible symptoms of severe allergic reaction).

**General precautions**

If you are given BOTOX too soon or the dose is too high, your body may start producing some antibodies, which can reduce the effect of BOTOX.

If you have not done much exercise for a long time before receiving BOTOX treatment, then after your injections you should start any activity gradually.

BOTOX contains human albumin which comes from human blood. Allergic reactions to blood products are rare. In blood donors, however, there is a rare chance that the blood could become infected with HIV.

Furthermore, BOTOX is made in a way that should remove or destroy viruses. It is unlikely that this medicine will improve the range of motion of joints where the surrounding muscle has lost its ability to stretch.

When BOTOX is used in the treatment of persistent muscle spasms in the eyelid, it could make your eyes blink less often, which may harm the surface of your eye. In order to prevent this, you may need treatment with eye drops, cleansers, soft contact lenses or even protective covering with an eye patch. Your doctor will tell you if this is required.

BOTOX does not prevent headaches in patients with episodic migraines, which occur less than 15 days a month.

**Taking other medicines**

Tell your doctor or pharmacist if you are:

- using any medicine to treat infections or muscle relaxants. Some of these medicines may increase the effect of BOTOX;
- using any medicine containing botulinum toxin (the active substance of BOTOX), as this may increase the effect of BOTOX.

Please tell your doctor or pharmacist if you are taking...
or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

The use of BOTOX is not recommended during pregnancy. If you are pregnant or become pregnant whilst being treated, your doctor will discuss with you whether you should continue with your treatment.

BOTOX is not recommended in breast-feeding women.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

BOTOX may cause dizziness, sleepiness, tiredness or problems with your vision. If you experience any of these effects, do not drive or use any machines. If you are not sure, ask your doctor for advice.

3. HOW TO USE BOTOX

BOTOX must only be injected by healthcare professionals with specific skills on how to use the medicine.

Method and route of administration

BOTOX is injected into your muscles (intramuscularly) or into the skin (intradermally). It is injected directly into the affected area of your body. Your doctor will usually inject BOTOX into several sites within each affected area.

General information about dosage

- The number of injections per muscle and the dose vary depending on the indication. Therefore, your doctor will decide how much, how often, and in which muscle(s) BOTOX will be given to you. It is recommended that your doctor uses the lowest effective dose.
- Dosages for the elderly are the same as for other adults.

The dosage of BOTOX and the duration of its effect will vary depending on the condition for which you are treated. Below are details corresponding to each condition.

For persistent muscle spasms of the eyelid and face

Doseage

In the first treatment session, your doctor may give multiple injections in the affected muscles with 1.25 to 25 Units of BOTOX into each injection site. The maximum dose for the first treatment session is 25 Units per affected area (for example, per eye). For the following treatment sessions, the total maximum dose can be increased up to 100 Units, if needed.

Duration of treatment effect

You will usually see an improvement within 3 days after the injection. The maximum effect is usually seen 1 to 2 weeks after treatment. When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 3 months.

For persistent muscle spasms of the neck and shoulders

Doseage

Your doctor may give multiple injections in the affected muscles with up to 50 Units of BOTOX into each injection site. The maximum dose for the first treatment session is 200 Units.

Duration of treatment effect

When the effect starts to wear off, you can have the treatment again if needed, normally not more often than every 12 weeks.

For persistent muscle spasms in the wrist and hand of patients who have had a stroke

Doseage

Your doctor may give multiple injections in the affected muscles. The dose and number of injections will vary depending on a number of factors, the type of muscle to be injected, the size of the muscles, severity of spasms, etc.

Duration of treatment effect

You will usually see an improvement within the first 2 weeks after the injection. The maximum effect is usually seen about 4 to 6 weeks after treatment. When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 12 weeks.

For excessive sweating of the armpits

Doseage

Your doctor will give multiple injections with a total of 50 Units of BOTOX in each armpit.

Duration of treatment effect

You will usually see an improvement within the first 6 weeks after injection. On average, the effect usually lasts 4 to 7 months after the first injection. When the effect starts to wear off, you can have the treatment again if needed.

For persistent muscle spasms in the legs of children who have cerebral palsy

Doseage

Your doctor may give multiple injections in the affected muscles. The dose will depend on the weight of your child.

Duration of treatment effect

The improvement usually appears within 2 weeks after the injection. When the effect starts to wear off, it is possible, but not more often than every 2 months.

For the prevention of headache in adults who have chronic migraine

Doseage

Your doctor may give multiple injections (between 31 and 36) in 7 muscle groups of the head, neck, and shoulders, with up to 5 Units of BOTOX intracranial injection site. Injections are divided into 4 areas in the forehead, 2 areas on the sides of your head, the back of your head, your upper neck area, and your shoulders. The injections are given to both the left and right sides of these head and neck muscles, except for one injection given to the muscle that is between your eyebrows. The total dose range is between 150 Units and 190 Units per treatment session.

Duration of treatment effect

When the effect starts to wear off, further treatment is possible, but not more often than every 12 weeks.

If you have received more BOTOX than you should

The signs of too much BOTOX may not appear for several days after the injection. Should you develop signs of BOTOX, you should see your doctor who might keep you under observation for several days. If you have received too much BOTOX, you may have some of the following symptoms and you must contact your doctor immediately. He/She will decide if you have to go to hospital:

- difficulty in breathing, swallowing, or speaking due to muscle paralysis;
- food or liquid accidentally going into your lungs which might cause pneumonia (infection of the lungs) due to muscle paralysis;
- drooping of the eyelids, double vision;
- generalised weakness.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, BOTOX can cause side effects, although not everybody gets them. In general, side effects occur within the first few days following injection and last only for a short time. In rare cases, they may last for several months or longer.

If you have any difficulty in breathing,
swallowing or speaking after receiving BOTOX, contact your doctor immediately.

If you experience redness, swelling including swelling of the face or throat, wheezing, feeling faint and shortness of breath, contact your doctor immediately.

The side effects are classified into the following categories, depending on how often they occur:

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>occur in more than 1 out of 10 people who use the medicine</td>
</tr>
<tr>
<td>Common</td>
<td>occur in less than 1 out of 10 people but more than 1 out of 100 people who use the medicine</td>
</tr>
<tr>
<td>Uncommon</td>
<td>occur in less than 1 out of 100 people but more than 1 out of 1,000 people who use the medicine</td>
</tr>
<tr>
<td>Rare</td>
<td>occur in less than 1 out of 1,000 people but more than 1 out of 10,000 people who use the medicine</td>
</tr>
<tr>
<td>Very rare</td>
<td>occur in less than 1 out of 10,000 people who use the medicine</td>
</tr>
</tbody>
</table>

Below are lists of side effects which vary depending on the part of the body where BOTOX is injected:

**Injections in the eyelid and face**

- Dropping of the eyelid.
- Swelling of the lid.
- Redness or inflammation of the cornea (transparent outer covering of the eye).
- Difficulty in completely closing the eye.
- Blepharoptosis (droop of the upper lid).
- Inflammation; dryness and sensitivity to light.

**Uncommon side effects:**

- Dizziness.
- Difficulty in seeing clearly.
- Blurred vision.
- Double vision.
- Tiredness.
- Inflammation of the cornea (transparent outer covering of the eye).
- Weakness of the face muscles.
- Drop of the muscles on one side of the face.
- Rash.
- Abnormal turning of the eyelids towards or away from the nose.

**Rare side effects:**

- Swelling of the eyelid.
- Swelling of the cornea (transparent outer covering of the eye).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the neck and shoulder**

- Difficulty in swallowing.
- Pain.
- Muscle weakness.

**Common side effects:**

- Dizziness.
- Flu syndrome.
- Sleepiness.
- Muscle cramps.
- Decreased skin sensation.
- Feeling of weakness.
- Feeling generally unwell.
- Feeling sick.
- Headache.
- Stiff or sore muscles.
- Swelling and infection inside the nose (rhinitis).
- Blocked or runny nose, cough, sore throat, hoarseness or irritation in the throat.
- Dry mouth.

**Uncommon side effects:**

- Shortness of breath.
- Double vision.
- Fever.
- Dropping of the eyelid.
- Changes in your voice.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the wrist and hand of patients who have had a stroke**

- Muscle weakness.
- Muscle cramps.
- Feeling of dizziness or spinning (vertigo).
- Lack of coordination of movements.
- Loss of memory.
- General weakness.
- Pain.
- Skin pain or inflammation.
- Decreased skin sensation.
- Numbness.
- Swelling of the extremities such as the hands and feet.
- Inflammation of the skin (dermatitis).
- Feeling generally unwell.
- Feeling sick.
- Increased sensitivity where the injections were given.
- Rash.
- Numbness around the mouth.
- Difficulty in sleeping ( insomnia).
- Irritability.

Some of these uncommon side effects may also be related to your disease.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections for excessive sweating of the axilla**

- Hot flashes.
- Increased sweating at sites other than the armpit.
- Reactions and pain where the injection was given.

**Uncommon side effects:**

- Muscle weakness.
- Feeling of weakness.
- Muscle pain.
- Pain in the extremities, such as the hands and fingers.
- Problem with the joints.
- Feeling sick.
- Sweating or pain where the injection was given.
- Irritability.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the legs of children with cerebral palsy**

- Very common side effects:
  - Viral infections.
  - Ear infections.

- Uncommon side effects:
  - Muscle weakness.
  - Problems with walking.
  - Numbness.
  - Muscle pain.
  - Urinary incontinence (not being able to control when you empty your bladder).
  - Feeling generally unwell.
  - Rash.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
Botox

108

any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

If any of the side effects gets serious, or if you notice
any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

5. HOW TO STORE BOTOX

Keep out of the reach of children.
Store in a refrigerator (2°C–8°C), or store in a freezer (at
or below 25°C).

If the solution is made up, immediate use of the
solution is recommended; however it can be stored for up
to 24 hours in a refrigerator (2°C–8°C).

Your doctor or pharmacist should not use BOTOX after the expiry date
which is based on the label after "EXP". The expiry date
refers to the last day of that month.

6. FURTHER INFORMATION

What BOTOX contains
- The active substance is Botulinum toxin type A from
  Clostridium botulinum.
- The other ingredients are human albumin and sodium chloride.

What BOTOX looks like and content of the pack

BOTOX is presented as a white powder in a transparent
glass vial. Each vial contains 100 Allergan Units of botulinum toxin
type A. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes
may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Allergan Ltd,
Marlow International,
The Parks, Marlow,
Bucks SL7 1YL,
UK.

Manufacturer: Allergan Pharmaceuticals Ireland
Castradale Road,
Westport,
County Mayo,
Ireland.

This medicinal product is authorised in the Member States of the EU
under the following name: BOTOX Austria,
Belgium, Czech Republic, Cyprus, Denmark,
Estonia, Finland, France, Germany, Greece, Hungary, Iceland,
Ireland, Italy, Luxembourg, Malta, Netherlands, Norway,
Poland, Portugal, Spain, Sweden, Slovenia,
United Kingdom

This leaflet was last approved in MMYYY.

any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

If any of the side effects gets serious, or if you notice
any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

5. HOW TO STORE BOTOX

Keep out of the reach of children.
Store in a refrigerator (2°C–8°C), or store in a freezer (at
or below 25°C).

If the solution is made up, immediate use of the
solution is recommended; however it can be stored for up
to 24 hours in a refrigerator (2°C–8°C).

Your doctor or pharmacist should not use BOTOX after the expiry date
which is based on the label after "EXP". The expiry date
refers to the last day of that month.

6. FURTHER INFORMATION

What BOTOX contains
- The active substance is Botulinum toxin type A from
  Clostridium botulinum.
- The other ingredients are human albumin and sodium chloride.

What BOTOX looks like and content of the pack

BOTOX is presented as a white powder in a transparent
glass vial. Prior to injection, the product must be dissolved
in a sterile saline solution.

Each vial contains 100 Allergan Units of botulinum toxin
type A. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes
may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Allergan Ltd,
Marlow International,
The Parks, Marlow,
Bucks SL7 1YL,
UK.

Manufacturer: Allergan Pharmaceuticals Ireland
Castradale Road,
Westport,
County Mayo,
Ireland.

This medicinal product is authorised in the Member States of the EU
under the following name: BOTOX Austria,
Belgium, Czech Republic, Cyprus, Denmark,
Estonia, Finland, France, Germany, Greece, Hungary, Iceland,
Ireland, Italy, Luxembourg, Malta, Netherlands, Norway,
Poland, Portugal, Spain, Sweden, Slovenia,
United Kingdom

This leaflet was last approved in MMYYY.

any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

If any of the side effects gets serious, or if you notice
any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

5. HOW TO STORE BOTOX

Keep out of the reach of children.
Store in a refrigerator (2°C–8°C), or store in a freezer (at
or below 25°C).

If the solution is made up, immediate use of the
solution is recommended; however it can be stored for up
to 24 hours in a refrigerator (2°C–8°C).

Your doctor or pharmacist should not use BOTOX after the expiry date
which is based on the label after "EXP". The expiry date
refers to the last day of that month.

6. FURTHER INFORMATION

What BOTOX contains
- The active substance is Botulinum toxin type A from
  Clostridium botulinum.
- The other ingredients are human albumin and sodium chloride.

What BOTOX looks like and content of the pack

BOTOX is presented as a white powder in a transparent
glass vial. Prior to injection, the product must be dissolved
in a sterile saline solution.

Each vial contains 100 Allergan Units of botulinum toxin
type A. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes
may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Allergan Ltd,
Marlow International,
The Parks, Marlow,
Bucks SL7 1YL,
UK.

Manufacturer: Allergan Pharmaceuticals Ireland
Castradale Road,
Westport,
County Mayo,
Ireland.

This medicinal product is authorised in the Member States of the EU
under the following name: BOTOX Austria,
Belgium, Czech Republic, Cyprus, Denmark,
Estonia, Finland, France, Germany, Greece, Hungary, Iceland,
Ireland, Italy, Luxembourg, Malta, Netherlands, Norway,
Poland, Portugal, Spain, Sweden, Slovenia,
United Kingdom

This leaflet was last approved in MMYYY.

any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

If any of the side effects gets serious, or if you notice
any side effects not listed in this leaflet, please tell
your doctor or pharmacist.

5. HOW TO STORE BOTOX

Keep out of the reach of children.
Store in a refrigerator (2°C–8°C), or store in a freezer (at
or below 25°C).

If the solution is made up, immediate use of the
solution is recommended; however it can be stored for up
to 24 hours in a refrigerator (2°C–8°C).

Your doctor or pharmacist should not use BOTOX after the expiry date
which is based on the label after "EXP". The expiry date
refers to the last day of that month.

6. FURTHER INFORMATION

What BOTOX contains
- The active substance is Botulinum toxin type A from
  Clostridium botulinum.
- The other ingredients are human albumin and sodium chloride.

What BOTOX looks like and content of the pack

BOTOX is presented as a white powder in a transparent
glass vial. Prior to injection, the product must be dissolved
in a sterile saline solution.

Each vial contains 100 Allergan Units of botulinum toxin
type A. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes
may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Allergan Ltd,
Marlow International,
The Parks, Marlow,
Bucks SL7 1YL,
UK.

Manufacturer: Allergan Pharmaceuticals Ireland
Castradale Road,
Westport,
County Mayo,
Ireland.

This medicinal product is authorised in the Member States of the EU
under the following name: BOTOX Austria,
Belgium, Czech Republic, Cyprus, Denmark,
Estonia, Finland, France, Germany, Greece, Hungary, Iceland,
Ireland, Italy, Luxembourg, Malta, Netherlands, Norway,
Poland, Portugal, Spain, Sweden, Slovenia,
United Kingdom

This leaflet was last approved in MMYYY.
The following information is intended for medical or healthcare professionals only:

Please refer to the Summary of Product Characteristics for complete prescribing information for BOTOX.

For all indications:
- Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with syncope, pneumonia, and/or significant disability.

Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including swallowing difficulties are at increased risk of these side effects. The botulinum toxin product should be used under specialist supervision in these patients and should not be used if the benefit of treatment is not outweigh the risk. Patients with a history of syncope and aspiration should be treated with extreme caution.

Reconstitution of the medicinal product:
- It is good practice to perform reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage.
- Reconstitute BOTOX only with sterile preservative-free normal saline (0.9% sodium chloride for injection). Draw up an appropriate amount of diluent (see dilution table below) into a syringe:

<table>
<thead>
<tr>
<th>Amount of diluent added (0.9% Sodium chloride injection)</th>
<th>Resulting dose (Units per 0.1 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>30 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>60 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>120 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>240 Units</td>
</tr>
<tr>
<td>8 ml</td>
<td>480 Units</td>
</tr>
</tbody>
</table>

Since BOTOX is opalescent by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Gently swirl the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear, colorless to slightly yellow solution free of particulate matter. The reconstituted solution should be visually inspected for clarity and absence of particulates prior to use. When reconstituted, BOTOX may be stored in a refrigerator (2°C - 8°C) for up to 24 hours prior to use.

This product is for single use only and any unused solution should be discarded.

Procedure to follow for safe disposal of vials, syringes and materials used:
- For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any unused vials, syringes and spillages etc. should be discarded, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%) for 5 minutes.

Identification of the product:
- In order to verify receipt of actual BOTOX product from Allergan, look for a holographic film on the vial label. In order to see the film, examine the vial under a desk lamp or fluorescent light source.
- Rotating the vial back and forth between your fingers, look for horizontal lines of rainbow color on the label and confirm that the name “Allergan” appears within the rainbow lines. (Note that the film on the label is absent in the Expiry/Lot Number area.) If you do not see the rainbow lines or the name “Allergan” does not appear, do not use the product and contact your local Allergan office for additional information.
2. BEFORE YOU USE BOTOX

Do NOT use BOTOX
• If you are allergic (hypersensitive) to botulinum toxin type A or any of the other ingredients of BOTOX;
• If you have an infection at the proposed site of injection.

Take special care with BOTOX

Before using BOTOX
Tell your doctor if you:
• have had any problems with injections (such as fading) in the past;
• have inflammation in the muscles or skin area where your doctor plans to inject;
• have significant weakness of existing muscle(s) which your doctor plans to inject;
• have any other muscle problems or chronic disease affecting your muscles (such as myasthenia gravis or Eaton-Lambert Syndrome);
• have other diseases affecting your nervous system (such as amyotrophic lateral sclerosis or motor neuronopathy);
• have any diseases called closed-angle glaucoma (high pressure in the eye) or were told you are at risk of developing this type of glaucoma;
• have had any surgery that may have in some way changed the muscle to be injected.

After you have been given BOTOX
Contact your doctor and seek medical attention immediately if you experience any of the following:
• difficulty in breathing, swallowing, or speaking;
• breast, swelling including swelling of the face or throat, wheezing, feeling faint or shortness of breath (possible symptoms of severe allergic reaction).

General precautions
If you are given BOTOX too soon or the dose is too high, your body may start producing some antibodies, which can reduce the effect of BOTOX.

If you have not done much exercise for a long time before receiving BOTOX treatment, then after your injections you should start exercising gradually.

BOTOX contains human albumin which comes from human blood. As with any medical product which is created from human blood, there is a possibility of catching an infection. To reduce this risk, blood donors are chosen very carefully. Furthermore, BOTOX is made in a way that should remove or destroy viruses.

It is unlikely that this medicine will improve the range of vision of patients where the surrounding muscle has lost its ability to move.

When BOTOX is used in the treatment of persistent muscle spasms in the eyelid, it could make your eyes blink less often, which may harm the surface of your eyes. In order to protect your eyes you should need to use artificial tears. You may also need to use drops, contact lenses or even protective coverings which close the eye. Your doctor will tell you if this is required.

BOTOX does not prevent headaches in patients with episodic migraine, which occur less than 15 days a month.

Taking other medicines
Tell your doctor or pharmacist if:
• you are taking any medications (used to treat infections) of muscle relaxants. Some of these medicines may increase the effect of BOTOX;
• you have recently been injected with a medicine containing botulinum toxin (the active substance of BOTOX), as this may increase the effect of BOTOX too much.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
Pregnancy and breast-feeding
The use of BOTOX is not recommended during pregnancy.
If you are pregnant or become pregnant whilst being treated, your doctor will discuss with you whether you should continue with your treatment.
BOTOX is not recommended in breast-feeding women.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
BOTOX may cause dizziness, sleepiness, tiredness or problem with your vision. If you experience any of these effects, do not drive or use any machines. If you are not sure, ask your doctor for advice.

3. HOW TO USE BOTOX
BOTOX must only be injected by healthcare professionals with specific skills on how to use the medicine.

Method and route of administration
BOTOX is injected into your muscles (intramuscularly) or into the skin (intradermally). It is injected directly into the affected area of your body; your doctor will usually inject BOTOX into several sites within each affected area.

General information about dosage
- The number of injections per muscle and the dose vary depending on the indications. Therefore, your doctor will decide how much, how often, and in which muscle(s) BOTOX will be given to you. It is recommended that your doctor use the lowest effective dose.
- Dosages for the elderly are the same as for other adults.

The dosage of BOTOX and the duration of its effect will vary depending on the condition for which you are treated. Below are details corresponding to each condition:

For persistent muscle spasms of the eyelid and face

Doseage
In the first treatment session, your doctor may give multiple injections in the affected muscles with 1.25 to 2.5 Units of BOTOX into each injection site.
The maximum dose for the first treatment session is 25 Units per affected area (for example per eye). For the following treatment sessions, the total maximum dose can be increased up to 100 Units, if needed.

Duration of treatment effect
You will usually see an improvement within 3 days after the injection.

The maximum effect is usually seen 1 to 2 weeks after treatment. When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 3 months.

For persistent muscle spasms of the neck and shoulders

Doseage
Your doctor may give multiple injections in the affected muscles with up to 50 Units of BOTOX into each injection site.
The maximum dose for the first treatment session is 200 Units.

Duration of treatment effect
When the effect starts to wear off, you can have the treatment again if needed, normally not more often than every 12 weeks.

For persistent muscle spasms in the wrist and hand of patients who have had a stroke

Doseage
Your doctor may give multiple injections in the affected muscles. The dose and number of injections will vary depending on a number of factors, including your needs, the muscles to be injected, the size of the muscles, severity of spasms, etc.

Duration of treatment effect
You will usually see an improvement within the first 2 weeks after the injection.
The maximum effect is usually seen about 4 to 6 weeks after treatment. When the effect starts to wear off, you can have the treatment again if needed, but not more often than every 12 weeks.

For excessive sweating of the armpits

Doseage
Your doctor will give multiple injections with a total of 50 Units of BOTOX in each armpit.

Duration of treatment effect
You will usually see an improvement within the first week after injection. On average the effect usually lasts 4-7 months after the first injection.

When the effect starts to wear off, you can have the treatment again if needed.

For persistent muscle spasms in the legs of children who have cerebral palsy

Doseage
The doctor may give multiple injections in the affected muscles. The dose will depend on the weight of your child.

Duration of treatment effect
The improvement usually appears within the first 2 weeks after the injection. When the effect starts to wear off, after 6 months treatment is possible, but not more often than every 2 months.

For the prevention of headaches in adults who have chronic migraine

Doseage
Your doctor may give you multiple injections (between 31 and 36) in 7 muscular groups of the face, head, neck and shoulders, with up to 50 Units BOTOX into each injection site. Injections are divided across muscles in your forehead, your temples on the side of your head, the back of your head, your upper neck area, and your shoulders. The injection site is on both the left and right side of these head and neck muscles, except for one injection given to the muscle that is between your eyebrows.
The total dose range is between 315 Units and 1950 Units per treatment session.

Duration of treatment effect
When the effect starts to wear off, further treatment is possible, but not more often than every 12 weeks.

If you have received more BOTOX than you should

The signs of too much BOTOX may not appear for several days after the injection. Should you swallow BOTOX or have it accidentally injected, you should see your doctor who might keep you under observation for several days. If you have received too much BOTOX, you may have any of the following symptoms and you must contact your doctor immediately. Health will decide if you have to go to hospital:
- difficulty in breathing, swallowing or speaking due to muscle paralysis;
- hoarseness or difficulty in speaking due to swelling into your larynx which might cause pneumonia (infection of the larynx) due to muscle paralysis;
- drooping of the eyelids, double vision;
- generalised weakness.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, BOTOX can cause side effects, although not everybody gets them. In general side effects occur within the first few days following injection and last for a short time. In rare cases, they may last for several months or longer.

If you have any difficulty in breathing, swallowing or speaking after receiving BOTOX, contact your doctor immediately.
<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occur in more than 1 out of 10 people who use the medicine</td>
<td></td>
</tr>
<tr>
<td>Occur in less than 1 out of 100 people who use the medicine</td>
<td></td>
</tr>
<tr>
<td>Occur in less than 1 out of 1,000 people who use the medicine</td>
<td></td>
</tr>
</tbody>
</table>

**Injections in the eyelid and face**

**Very common side effect:**
- Drooping of the eyelid.

**Common side effects:**
- Swelling of the eye.
- Mild inflammation of the cornea (transparent outer covering of the eye).
- Difficulty in completely closing the eye.
- Overflow of tears.
- Watery eye.

**Uncommon side effects:**
- Dizziness.
- Difficulty in seeing clearly.

**Rare side effect:**
- Swelling of the eyelid.

**Very rare side effect:**
- Ulcer of the cornea (transparent outer covering of the eye).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the neck and shoulder**

**Very common side effects:**
- Muscle weakness.
- Pain.

**Common side effects:**
- Diplopia (double vision).
- Headache.
- Muscle cramps.
- Increased sweating in the hands and feet.
- Increased sweating in the armpits.
- Increased sweating of the extremities (hands and feet).
- Increased sweating of the face.

**Uncommon side effects:**
- Numbness.
- Headache.
- Swelling and irritation inside the nose (rhinitis).

**Injections in the wrist and hand of patients who have had a stroke**

**Common side effects:**
- Muscle weakness.
- Muscle cramps.
- Difficulty in swallowing.

**Uncommon side effects:**
- Rash.

**Injections for excessive sweating of the armpits**

**Common side effects:**
- Not flushed.
- Increased sweating at sites other than the armpit.

**Uncommon side effects:**
- Muscle weakness.

**Injections in the legs of children with cerebral palsy**

**Very common side effects:**
- Hot flushes.

**Common side effects:**
- Headache.

**Uncommon side effects:**
- Numbness.

**Injections in the hand and shoulder of patients who have had a stroke**

**Common side effects:**
- Muscle weakness.

**Uncommon side effects:**
- Dizziness.

**Injections in the wrist and hand of patients who have had a stroke**

**Common side effects:**
- Muscle weakness.

**Uncommon side effects:**
- Rash.
Injects in the head and neck to prevent headache in patients who suffer from chronic migraine

Common side effects:
- headache, migraines;
- rash, itching;
- pain where the injection was given;
- drooping of the eyelid;
- muscle weakness;
- neck pain;
- muscle pain, cramp;
- muscle stiffness, tightness;

Uncommon side effects:
- difficulty in swallowing;
- skin pain;
- jaw pain;
- swollen eyes;

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

General information about other side effects

Side effects related to the spread of BOTOX far away from the site of injection have been reported very rarely and include:
- muscle weakness;
- difficulty in swallowing or food or liquid accidentally going into the lung that might cause pneumonia.

The difficulty in swallowing may range from mild to severe, and in some cases you may need treatment. In rare cases, people have died because of swallowing difficulties.

Side effects affecting the heart have been rarely reported:
- irregular heartbeat;
- heart attack;

Some of these people have died. However, some of these patients were already suffering from heart complaints.

Serious or immediate allergic reactions have been rarely reported, including:
- headache;
- swelling including swelling of the face or throat;
- wheezing;
- feeling faint;
- shortness of breath.

There have been very rare reports of glaucoma (high pressure in the eye).

There have been reports of:
- problems or convulsions after treatment with BOTOX, particularly in patients who have previously experienced these symptoms. These effects occurred mainly when BOTOX was used for the treatment of persistent muscle spasms in the legs of children with cerebral palsy.

As with any injection, you may suffer from injection related side effects:
- pain or bruising where the injection is given;
- a drop in blood pressure or fainting may be caused by needle-related pain and/or anxiety.

After injection of BOTOX patients have also suffered:
- fever and flu-like symptoms.

The following are described as additional side effects reported for BOTOX, in any disease, since it has been marketed:
- allergic reaction;
- chronic disease affecting the muscles (myasthenia gravis);
- blurred vision;
- fainting;
- pain/harmfulness or weakness starting from the spine;
- paralysis of the face;
- difficulty moving the arms and shoulders;
- decreased skin sensation;
- muscles pain;
- abdominal pain;
- diarrhea, vomiting, loss of appetite;
- fever;
- different types of red bumpy skin rashes;
- feeling generally unwell;
- speech problems;
- itching;
- excessive sweating;
- decreased hearing.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BOTOX

Keep out of the reach and sight of children. Store in a refrigerator (2°C – 8°C), or store in a freezer (at or below -20°C). After the solution is made up, immediate use of the solution is recommended; however it can be stored for up to 24 hours in a refrigerator (2°C – 8°C).

Your doctor should not use BOTOX after the expiry date which is stated on the label after “EXP”. The expiry date refers to the last day of that month.

6. FURTHER INFORMATION

What BOTOX contains
- The active substance is: Botulinum toxin type A from Clostridium botulinum.
- Other ingredients are human albumin and sodium chloride.

What BOTOX looks like and content of the pack
BOTOX is presented as a white powder in a transparent glass vial. Prior to injection, the product must be dissolved in a sterile saline solution. Each vial contains 200 Allergan Units of botulinum toxin type A. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Allergan Ltd., 1000 North辰 Avenue, Irvine, CA, 92662, United States of America
Manufacturer: Allergan Pharmaceuticals Ireland, Castledermot, Co. Kildare, Ireland

This medicinal product is authorised in the Member States of the EEA under the following name: BOTOX France and Ireland
This leaflet was last approved in MYYYY
The following information is intended for medical or healthcare professionals only;

Please refer to the Summary of Product Characteristics for complete prescribing information for BOTOX.

For all indications:

Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia, and/or significant death.

Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurologic disorders including swallowing difficulties are at increased risk of these side effects. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Reconstitution of the medicinal product:

It is good practice to perform vial reconstitution and syringe preparation over a plastic lined paper towel to catch any spillage.

Reconstitute BOTOX only with sterile preservative-free normal saline (0.9% sodium chloride for injection). Draw up an appropriate amount of diluent (see dilution table below) into a syringe.

<table>
<thead>
<tr>
<th>Amount of diluent added</th>
<th>Resulting dose (Units per 0.1 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>40 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>20 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>10 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>5 Units</td>
</tr>
<tr>
<td>8 ml</td>
<td>2.5 Units</td>
</tr>
</tbody>
</table>

Since BOTOX is denatured by bubbling or similar action, inject the diluent gently into the vial. Discard the air if vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear viscous solution, free of particulate matter. The reconstituted solution should be visually inspected for clarity and absence of particles prior to use. When reconstituted, BOTOX may be stored in a refrigerator (2°C - 8°C) for up to 24 hours prior to use.

This product is for single use only and any unused solution should be discarded.

Procedure to follow for safe disposal of vials, syringes and needles used:

- For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any used vials, syringes, and needles should be autoclaved, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%) for 5 minutes.

Identification of the product:

In order to verify receipt of actual BOTOX product from Allergan:

- Look for a holographic film on the vial base. In order to expose this film, examine the vial under a desk lamp or fluorescent light source.

- Rotate the vial back and forth between your fingers to look for horizontal lines of rainbow colours on the label. Confirm that the name “Allergan” appears within the rainbow lines on the label is absent in the “Expired Date Number Code”. If you do not see the rainbow lines or the name “Allergan” do not use the product and contact your local Allergan office for additional information.
Labelling

Botox

(Botulinum toxin type A)

PL 00426/0074-0105
PL 00426/0118-0025
PL 00426/0119-0007
Annex 1

Our Reference: PL 00426/0074–0117
Product: PL 00426/0074 Botox
Marketing Authorisation Holder: ALLERGAN LIMITED

Reason:
To update the SPC in line with the agreed wording of Vistabel (PL 05179/0010) with regards to the indications relating to glabellar lines. Consequential updates are made to the PIL.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 108407 and covers the following submissions PL 00426/0118–0037, PL 00426/0119–0020.

Supporting Evidence
None apart from minutes of a meeting with the MHRA discussing the strategy for a potential change in brand name. Modules 2–5 of the dossier have previously been assessed for Botox® and Vistabel®.

Evaluation
Updates were made to sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.4, 6.6 and 10 of the SmPC for Botox 50, 100 and 200 Allergan units – powder for solution for injection.

Changes were also introduced to the SmPC following a review of the Botox PSUR.

All of the approved indications are included on all three of the Botox SmPCs in order to maintain consistency of indications and the related safety information across all three presentations of Botox and to ensure that all product information is available to all patients receiving the product regardless of indication.

The Botox SmPCs currently state in Section 6.6 that each vial is for single use only. To further strengthen the SmPCs, it was agreed to add an additional statement in Section 4.2 to advise physicians that the most appropriate vial size should be selected for the indication. This will help to ensure that a 50U vial should be used for a single patient for the treatment of glabellar lines, if available.

Conclusion
After discussion with the MAH, suitable changes were made to the SmPC such that the following text was accepted for sections 4.1, 4.2, 4.4, 4.8, 5.1, 6.4, 6.6 and 10. In all sections the text is identical for each PL.

The PIL is acceptable. A single adhesive patient label sticker was also added to the Botox cartons that should be added to the individual patient notes. In addition a perforation was introduced on the carton to allow easier opening of the carton. This is acceptable.

4.1 Therapeutic indications

- the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
- the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)

BOTOX is also indicated for focal spasticity, including the treatment of:

- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older and
- wrist and hand disability due to upper limb spasticity associated with stroke in adults.

BOTOX is also indicated for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at frown (glabellar lines), in adults <65 years old, when the severity of these lines has an important psychological impact for the patient.

4.2 Posology and method of administration

Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan units are different from other botulinum toxin preparations.

This product is for single use only and any unused solution should be discarded. The most appropriate vial size should be selected for the indication.

The following information is important:

If different vial sizes of BOTOX are being used as part of one injection procedure, care should be taken to use the correct amount of diluent when reconstituting a particular number of units per 0.1 ml. The amount of diluent varies between BOTOX 50 Allergan Units, BOTOX 100 Allergan Units and BOTOX 200 Allergan Units. Each syringe should be labelled accordingly.

BOTOX must only be reconstituted with sterile sodium chloride 9 mg/ml (0.9%) solution for injection. The appropriate amount of diluent (see dilution table below) should be drawn up into a syringe.

<table>
<thead>
<tr>
<th>Dilution table for BOTOX 50, 100 and 200 Allergan Units vial size:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting dose (Units per 0.1 ml)</td>
</tr>
<tr>
<td>20 Units</td>
</tr>
<tr>
<td>10 Units</td>
</tr>
<tr>
<td>5 Units</td>
</tr>
<tr>
<td>4 Units</td>
</tr>
<tr>
<td>2.5 Units</td>
</tr>
<tr>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

BOTOX should only be given by physicians with appropriate qualifications, and expertise in the treatment and the use of the required equipment.
For instructions on use, handling and disposal of vials please refer to section 6.6.

**Elderly population**

Adequate studies on geriatric dosing have not been performed. The lowest effective dose with the longest clinically indicated interval between injections is recommended. Elderly patients with significant medical history and concomitant medications should be treated with caution.

There is limited phase 3 clinical data with BOTOX for glabellar lines in patients older than 65 years (see section 5.1). Until more studies have been performed in this age group, BOTOX is not recommended in patients older than 65 years.

**Paediatric population**

The safety and effectiveness of BOTOX in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia and primary hyperhidrosis of the axillae in children (under 12 years) have not been demonstrated.

The safety and efficacy of BOTOX in adolescents aged 12 to 17 years for the treatment of severe axillary hyperhidrosis have not been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made (see sections 4.8 and 5.1).

The safety and effectiveness of BOTOX in the treatment of glabellar lines and in the prophylaxis of chronic migraine headaches have not been demonstrated in individuals under 18 years of age. The use of BOTOX is not recommended in patients less than 18 years for these indications.

**Posology**

Generally valid optimum dose levels and number of injection sites per muscle have not been established for all indications. In these cases, individual treatment regimens should therefore be drawn up by the physician. Optimum dose levels should be determined by titration but the recommended maximum dose should not be exceeded.

**Blepharospasm**

Reconstituted BOTOX is injected using a sterile, 27-30 gauge/0.40-0.30 mm needle. Electromyographic guidance is not necessary. The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision. Avoiding injection near levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. The following diagrams indicate the possible injection sites:
In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. The initial dose should not exceed 25 Units per eye. Normally no additional benefit is conferred by treating more frequently than every three months. It is rare for the effect to be permanent.

In the management of blepharospasm total dosing should not exceed 100 Units every 12 weeks.

**Hemifacial spasm**

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

**Cervical dystonia**

Several dosing regimens have been used in clinical trials for treatment of cervical dystonia with BOTOX. Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response.

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted BOTOX ranged from 140 to 280 Units. In more recent studies, the doses have ranged from 95 to 360 Units (with an approximate mean of 240 Units). As with any drug treatment, initial dosing in a naïve patient should begin at the lowest effective dose. No more than 50 Units should be given at any one injection site. No more than 100 Units should be given to the sternomastoid. To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally. No more than 200 Units total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response. A total dose of 300 Units at any one sitting should not be exceeded.

The following doses are recommended:

<table>
<thead>
<tr>
<th>Type I</th>
<th>Sternomastoid</th>
<th>50 - 100 Units; at least 2 sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head rotated</td>
<td>Levator scapulae</td>
<td>50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td>toward side of</td>
<td>Scalene</td>
<td>25 - 50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td>shoulder</td>
<td>Splenius capitis</td>
<td>25 - 75 Units; 1 - 3 sites</td>
</tr>
<tr>
<td>elevation</td>
<td>Trapezius</td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
<tr>
<td>Type II</td>
<td>Head rotation only</td>
<td>Sternomastoid</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Type III</td>
<td>Head tilted toward side of shoulder elevation</td>
<td>Sternomastoid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levator scapulae</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trapezius</td>
</tr>
<tr>
<td>Type IV</td>
<td>Bilateral posterior cervical muscle spasm with elevation of the face</td>
<td>Splenius capitis and cervicis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, semispinalis, longissimus and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment. The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose. Muscle activation patterns can change spontaneously in cervical dystonia without a change in the clinical presentation of dystonia.

A 25, 27 or 30 gauge/0.50-0.30 mm needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance.

Multiple injection sites allow BOTOX to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. Treatment intervals of less than 10 weeks are not recommended. The duration of beneficial effect reported in clinical trials showed substantial variation (from 2 to 33 weeks) with a typical duration of approximately 12 weeks.

**Primary hyperhidrosis of the axillae**

The recommended injection volume for intradermal injection in axillary hyperhidrosis is 0.1-0.2 ml. Reconstituted BOTOX (100 Units/4 mL) is injected using a 30 gauge needle. 50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor’s iodine-starch test. Doses other than 50 Units per axilla have not been studied and therefore cannot be recommended.

Clinical improvement generally occurs within the first week after injection. Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating physician deems it necessary. Treatment response has been reported to persist for 4-7 months. Injections should not be repeated more frequently than every 16 weeks (see section 5.1).
Paediatric cerebral palsy
Reconstituted BOTOX is injected using a sterile 23-26 gauge/0.60-0.45 mm needle. It is administered as a divided dose through single injections into the medial and lateral heads of the affected gastrocnemius muscle. In hemiplegia, the initial recommended total dose is 4 Units/kg body weight in the affected limb. In diplegia, the initial recommended total dose is 6 Units/kg body weight divided between the affected limbs. The total dose should not exceed 200 Units.

Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months. It may be possible to adapt the dosage regimen to obtain an interval of at least six months between treatment sessions.

Focal upper limb spasticity associated with stroke
Reconstituted BOTOX is injected using a sterile 25, 27 or 30 gauge needle for superficial muscles, and a longer needle for deeper musculature. Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, the presence of local muscle weakness, and the patient response to previous treatment.

In the controlled clinical trials the following doses were administered:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Total Dosage; Number of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum profundus</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>15 – 60 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>10 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units; 1-2 sites</td>
</tr>
</tbody>
</table>

In controlled and open non-controlled clinical trials doses between 200 and 240 Units divided among selected muscles have been used at a given treatment session.

In controlled clinical trials patients were followed for 12 weeks after single treatment. Improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open, non-controlled continuation study, most of the patients were re-injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximal cumulative dose of 960 Units over 54 weeks. If it is deemed appropriate by the treating physician, repeat doses may be administered, when the effect of a previous injection has diminished. Re-injections should not occur before 12 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected. The lowest effective dose should be used.

Chronic Migraine
The recommended reconstituted BOTOX dose for treating chronic migraine is 155 U to 195 U administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 U)
injections to 31 and up to 39 sites. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injections sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the injection sites:

![Injection Sites Diagrams]

**BOTOX Dosing By Muscle:**

<table>
<thead>
<tr>
<th>Head/Neck Area</th>
<th>Recommended Dose</th>
<th>Total Dosage (number of sites)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalisb</td>
<td>20 U (4 sites)</td>
<td></td>
</tr>
<tr>
<td>Corrugatorb</td>
<td>10 U (2 sites)</td>
<td></td>
</tr>
<tr>
<td>Procerus</td>
<td>5 U (1 site)</td>
<td></td>
</tr>
<tr>
<td>Occipitalisb</td>
<td>30 U (6 sites) up to 40 U (up to 8 sites)</td>
<td></td>
</tr>
<tr>
<td>Temporalisb</td>
<td>40 U (8 sites) up to 50 U (up to 10 sites)</td>
<td></td>
</tr>
<tr>
<td>Trapeziusb</td>
<td>30 U (6 sites) up to 50 U (up to 10 sites)</td>
<td></td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Groupb</td>
<td>20 U (4 sites)</td>
<td></td>
</tr>
</tbody>
</table>

*Total Dose Range: 155 U to 195 U, 31 to 39 sites*

*1 IM injection site = 0.1 mL = 5 U BOTOX*

*Dose distributed bilaterally*

The recommended re-treatment schedule is every 12 weeks.

**Glabellar lines**

Reconstituted BOTOX (50 U/1.25 mL) is injected using a sterile 30 gauge needle. A volume of 0.1 mL (4 U) is administered in each of the 5 injection sites: 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 U.

Before injection, the thumb or index finger are to be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection. In order to reduce the risk of ptosis, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections in the corrugator muscle must be done in the central part of that muscle, at least 1 cm above the arch of the eyebrows.
Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the glabellar lines.

Improvement of severity of glabellar lines generally occurs within one week after treatment. The effect was demonstrated for up to 4 months after injection.

Treatment intervals should not be more frequent than every three months. In the event of treatment failure or diminished effect following repeat injections, alternative treatment methods should be employed.

In case of insufficient dose and in the absence of any undesirable effects secondary to the first treatment session, adjusting the total dose up to 40 or 50 units should be considered in a second treatment session, taking into account the analysis of the previous treatment failure (see information in All indications).

**All indications**

In case of treatment failure after the first treatment session, i.e. absence, at one month after injection, of significant clinical improvement from baseline, the following actions should be taken:

- Clinical verification, which may include electromyographic examination in a specialist setting, of the action of the toxin on the injected muscle(s);
- Analysis of the causes of failure, e.g. bad selection of muscles to be injected, insufficient dose, poor injection technique, appearance of fixed contracture, antagonist muscles too weak, formation of toxin-neutralising antibodies;
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A;
- In the absence of any undesirable effects secondary to the first treatment session, instigate a second treatment session as following: i) adjust the dose, taking into account the analysis of the earlier treatment failure; ii) use EMG; and iii) maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections alternative treatment methods should be employed.

**4.4 Special warnings and precautions for use**

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX and injection into vulnerable anatomic structures must be avoided. The recommended dosages and frequencies of administration of BOTOX should not be exceeded.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these
reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted. One case of anaphylaxis has been reported in which the patient died after being injected with BOTOX inappropriately diluted with 5 ml of 1% lidocaine. Please see “Additional information” in section 4.8 for further information.

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

Patients treated with therapeutic doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including swallowing difficulties are at increased risk of these side effects. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 ‘Cervical Dystonia’).

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest clinically indicated intervals between injections.

As with any treatment with the potential to allow previously-sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually.

Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Lambert-Eaton Syndrome; such patients may have an increased sensitivity to agents such as BOTOX, which may result in excessive muscle weakness. Patients with neuromuscular disorders may be at an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX.
As with any injection, procedure-related injury could occur. An injection could result in localized infection, pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc. Care should be taken when injecting near vulnerable anatomic structures.

**Blepharospasm**
Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles.

**Cervical dystonia**
Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 Units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the oesophageal musculature. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia may contribute to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX injection.

**Primary hyperhidrosis of the axillae**
Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

**Focal spasticity associated with paediatric cerebral palsy and spasticity of the hand and wrist in adult post-stroke patients**
BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.
Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with co-morbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.2).

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. Caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

**Chronic migraine**
No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

**Glabellar lines**
It is mandatory that BOTOX is used for one single patient treatment only during a single session. The excess of unused product must be disposed of as detailed in section 6.6. Particular precautions should be taken for product preparation and administration as well as for the inactivation and disposal of the remaining unused solution (see section 6.6).

The use of BOTOX is not recommended in individuals under 18 years and in patients older than 65 years.

**4.8 Undesirable effects**

**a) General**
Based on controlled clinical trial data patients would be expected to experience an adverse reaction after treatment with BOTOX at the rates of 35% for blepharospasm, 28% for cervical dystonia, 17% for paediatric cerebral palsy and 11% for primary hyperhidrosis of the axillae. Sixteen percent of participants in clinical trials treated with BOTOX for focal spasticity of the upper limb associated with stroke and 23% with glabellar lines experienced an adverse reaction.

In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In general, adverse reactions occur within the first few days following injection and, while generally transient, may have a duration of several months or, in rare cases, longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue.

As is expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope. Fever and flu syndrome have also been reported after injections of botulinum toxin.

**b) Adverse reactions - frequency by indication**
For each indication the frequency of adverse reactions arising from clinical experience is given. The frequency is defined as follows:
- Very Common (≥ 1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very Rare (<1/10,000).
Blepharospasm/hemifacial spasm

Nervous system disorders
Uncommon: Dizziness, facial paresis and facial palsy.

Eye Disorders
Very common: Eyelid ptosis.
Common: Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation and lacrimation increase.
Uncommon: Keratitis, ectropion, diplopia, entropion, visual disturbance and vision blurred.
Rare: Eyelid oedema.
Very rare: Corneal ulceration, corneal epithelium defect and corneal perforation.

Skin and subcutaneous tissue disorders
Common: Ecchymosis
Uncommon: Rash/dermatitis.

General disorders and administration site conditions
Common: Irritation and face oedema.
Uncommon: Fatigue.

Cervical dystonia

Infections and infestations
Common: Rhinitis and upper respiratory infection.

Nervous system disorders
Common: Dizziness, hypertonia, hypoaesthesia, somnolence and headache.

Eye Disorders
Uncommon: Diplopia and eyelid ptosis.

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea and dysphonia.

Gastrointestinal disorders
Very common: Dysphagia (see section c. “Additional information” below).
Common: Dry mouth and nausea.

Musculoskeletal and connective tissue disorders
Very common: Muscular weakness.
Common: Musculoskeletal stiffness and soreness.

General disorders and administration site conditions
Very common: Pain.
Common: Asthenia, influenza like illness and malaise.
Uncommon: Pyrexia.

Paediatric cerebral palsy

Infections and infestations
Very common: Viral infection and ear infection.

Nervous system disorders
Common: Somnolence, gait disturbance and paraesthesia.

Skin and subcutaneous tissue disorders
Common: Rash.

Musculoskeletal and connective tissue disorders
Common: Myalgia, muscular weakness and pain in extremity.

Renal and urinary disorders
Common: Urinary incontinence.

Injury, poisoning and procedural complications
Common: Fall.

General disorders and administration site conditions
Common: Malaise, injection site pain and asthenia.

Focal upper limb spasticity associated with stroke

Psychiatric disorders
Uncommon: Depression and insomnia.

Nervous system disorders
Common: Hypertonia
Uncommon: Hypoaesthesia, headache, paraesthesia, incoordination and amnesia.

Ear and labyrinth disorders
Uncommon: Vertigo.

Vascular disorders
Uncommon: Orthostatic hypotension.

Gastrointestinal disorders
Uncommon: Nausea and paraesthesia oral.

Skin and subcutaneous tissue disorders
Common: Ecchymosis and purpura.
Uncommon: Dermatitis, pruritus and rash.

Musculoskeletal and connective tissue disorders
Common: Pain in extremity and muscle weakness.
Uncommon: Arthralgia and bursitis.

General disorders and administration site conditions
Common: Injection site pain, pyrexia, influenza-like illness, injection site haemorrhage and injection site irritation.
Uncommon: Asthenia, pain, injection site hypersensitivity, malaise and oedema peripheral.

Some of the uncommon events may be disease related.
Primary hyperhidrosis of the axillae

Nervous system disorders
Common: Headache and paraesthesia.

Vascular disorders
Common: Hot flushes.

Gastrointestinal disorders
Uncommon: Nausea

Skin and subcutaneous tissue disorders
Common: Hyperhidrosis (non-axillary sweating) skin odour abnormal, pruritus, subcutaneous nodule and alopecia.

Musculoskeletal and connective tissue disorders
Common: Pain in extremity
Uncommon: Muscular weakness, myalgia and arthropathy.

General disorders and administration site conditions
Common: Injection site pain.
Uncommon: Pain, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site irritation, asthenia and injection site reactions.

In the management of primary axillary hyperhidrosis, increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

In an uncontrolled safety study of BOTOX (50 U per axilla) in paediatric patients 12 to 17 years of age (N=144), adverse reactions occurring in more than a single patient (2 patients each) comprised injection site pain and hyperhidrosis (non-axillary sweating).

Chronic Migraine

Nervous system disorders
Common: Headache*, migraine*, facial paresis

Eye disorders
Common: Eyelid ptosis
Uncommon: Eyelid oedema

Skin and subcutaneous tissue disorders
Common: Pruritus, rash
Uncommon: Pain of skin

**Musculoskeletal and connective tissue disorders**
Common: Neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness
Uncommon: Pain in jaw

**General disorders and administration site conditions**
Common: Injection site pain

**Gastrointestinal disorders**
Uncommon: Dysphagia

* In placebo-controlled trials, headache and migraine, including serious cases of intractable or worsening of headache/migraine, were reported more frequently with BOTOX (9%) than with placebo (6%). They typically occurred within the first month after the injections and their incidence declined with repeated treatments.

**Glabellar lines**
Infections and infestations
Uncommon: Infection

Psychiatric disorders
Uncommon: Anxiety

Nervous system disorders
Common: Headache
Uncommon: Paraesthesia, dizziness

Eye disorders
Common: Eyelid ptosis
Uncommon: Blepharitis, eye pain, visual disturbance

Gastrointestinal disorders
Uncommon: Nausea, oral dryness

Skin and subcutaneous tissue disorders
Common: Erythema
Uncommon: Skin tightness, oedema (face, eyelid, periorbital), photosensitivity reaction, pruritus, dry skin

Musculoskeletal and connective tissue disorders
Common: Localised muscle weakness
Uncommon: Muscle twitching

**General disorders and administration site conditions**
Common: Face pain
Uncommon: Flu syndrome, asthenia, fever

c) **Additional information**
Dysphagia ranges in severity from mild to severe, with potential for aspiration, which occasionally may require medical intervention (See section 4.4).
Side effects related to spread of toxin distant from the site of administration have been reported very rarely (exaggerated muscle weakness, dysphagia, aspiration/aspiration pneumonia, with fatal outcome in some cases) (See section 4.4).

The following other adverse events have been reported since the drug has been marketed: dysarthria; abdominal pain; vision blurred; visual disturbance; pyrexia; facial palsy; facial paresis; hypoaesthesia; malaise; myalgia; pruritus; hyperhidrosis; alopecia (including madarosis); diarrhoea; anorexia; hypoaacusis; tinnitus; vertigo; radiculopathy; syncope; myasthenia gravis; paraesthesia; erythema multiforme; dermatitis psoriasiform; vomiting and brachial plexopathy; anaphylactic reaction (angioedema, bronchospasm).

There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue oedema and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other agents known to cause similar reactions.

A case of peripheral neuropathy has been reported in a large adult male after receiving four sets of BOTOX injections, totalling 1800 Units (for neck and back spasm, and severe pain) over an 11 week period.

Angle closure glaucoma has been reported very rarely following botulinum toxin treatment for blepharospasm.

New onset or recurrent seizures have been reported, typically in patients, who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. The reports in children were reports predominantly from cerebral palsy patients treated for spasticity.

Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from Clostridium botulinum. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.

Clostridium botulinum toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.

Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse
transmission is by newly formed nerve endings and motor endplates. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

There is limited clinical trial experience of the use of BOTOX in primary axillary hyperhidrosis in adolescents between the ages of 12 and 18. A single, year long, uncontrolled, repeat dose, safety study was conducted in US pediatric patients 12 to 17 years of age (N=144) with severe primary hyperhidrosis of the axillae. Participants were primarily female (86.1%) and Caucasian (82.6%). Participants were treated with a dose of 50 U per axilla for a total dose of 100 U per patient per treatment. However, no dose finding studies have been conducted in adolescents so no recommendation on posology can be made. Efficacy and safety of BOTOX in this group have not been established.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitization, as suggested by pre-clinical and clinical pharmacodynamic studies.

Clinical Data

Chronic Migraine
Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and at least 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.

During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.

<table>
<thead>
<tr>
<th>Mean change from baseline at Week 24</th>
<th>BOTOX</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=688</td>
<td>N=696</td>
<td></td>
</tr>
<tr>
<td>Frequency of headache days</td>
<td>-8.4</td>
<td>-6.6</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47%</td>
<td>35%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Total cumulative hours of headache days</td>
<td>120</td>
<td>80</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8</td>
<td>-2.4</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

Glabellar Lines
537 patients with moderate to severe glabellar lines at maximum frown have been included in clinical studies.
BOTOX injections significantly reduced the severity of glabellar lines for up to 4 months, as measured by the investigator assessment of glabellar line severity at maximum frown and by subject’s global assessment of change in appearance of his/her glabellar lines. None of the clinical endpoints included an objective evaluation of the psychological impact. Thirty days after injection 80% (325/405) of BOTOX-treated patients were considered by investigators as treatment responders (none or mild severity at maximum frown), compared to 3% (4/132) of placebo-treated patients. At this same timepoint, 89% (362/405) of BOTOX-treated patients felt they had a moderate or better improvement, compared to 7% (9/132) of placebo-treated patients.

BOTOX injections also significantly reduced the severity of glabellar lines at rest. Of the 537 patients enrolled, 39% (210/537) had moderate to severe glabellar lines at rest (15% had no lines at rest). Of these, 74% (119/161) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 20% (10/49) of placebo-treated patients.

There is limited phase 3 clinical data with BOTOX in patients older than 65 years. Only 6.0% (32/537) of subjects were >65 years old and efficacy results obtained were lower in this population.

### 6.6 Special precautions for disposal

BOTOX is reconstituted prior to use with sterile unpreserved normal saline (0.9% sodium chloride for injection). It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of diluent (see dilution table below) is drawn up into a syringe. The exposed portion of the rubber septum of the vial is cleaned with alcohol (70%) prior to insertion of the needle. Since BOTOX is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. When reconstituted, BOTOX may be stored in a refrigerator (2-8°C) for up to 24 hours prior to use. After this period used or unused vials should be discarded.

Care should be taken to use the correct diluent volume for the presentation chosen to prevent accidental overdose.

Each vial is for single use only.

<table>
<thead>
<tr>
<th>Diluent added</th>
<th>Resulting dose in units per 0.1 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>20 Units</td>
</tr>
<tr>
<td>1 ml</td>
<td>10 Units</td>
</tr>
<tr>
<td>2 ml</td>
<td>5 Units</td>
</tr>
<tr>
<td>2.5 ml</td>
<td>4 Units</td>
</tr>
<tr>
<td>4 ml</td>
<td>2.5 Units</td>
</tr>
<tr>
<td>8 ml</td>
<td>1.25 Units</td>
</tr>
</tbody>
</table>

The 'unit' by which the potency of preparations of BOTOX is measured should be used to calculate dosages of BOTOX only and is not transferable to other preparations of botulinum toxin.

An injection volume of approximately 0.1 ml is recommended. A decrease or increase in the
BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For safe disposal, unused vials should be reconstituted with a small amount of water then autoclaved. Any used vials, syringes, and spillages etc. should be autoclaved, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%).

Any unused product or waste material should be disposed of in accordance with local requirements.

10 DATE OF REVISION OF THE TEXT

24/11/2011
ALLERGAN®

PACKAGE LEAFLET:
INFORMATION FOR THE USER

BOTOX®

59 Allergan units, Powder for solution for injection in a vial

Read all of this leaflet carefully before you start using BOTOX®

In adults less than 65 years of age, BOTOX® is used for the temporary improvement of facial lines between the brows, when the severity of these lines has an important psychological impact on the patient.

In children aged 2 years or older with cerebral palsy, who can walk, BOTOX® is used to control:

- fixed deformities caused by the persistent muscle spasms in the leg.

Use with other medicines

BOTOX® does not prevent headaches in patients with episodic migraine, which occur less than 15 days a month.

Taking other medicines

- Tell your doctor or pharmacist if you are using any of the following:
  - other medicines that may affect this medicine.

Breastfeeding

BOTOX® is not recommended for breastfeeding women.

Pregnancy

BOTOX® is not recommended for pregnant women.

Driving and using machines

BOTOX® may cause dizziness, drowsiness, tiredness or problems with your vision. If you experience any of these effects, do not drive or use any machines. If you have any concerns, ask your doctor for advice.

How to use BOTOX®

BOTOX® must only be injected by doctors with specific skills in how to use the medicine.

Method of administration

BOTOX® is injected into muscles (intramuscularly) or into the skin (subcutaneously). It is injected directly into the affected area of the body. Your doctor will usually inject BOTOX® into several sites within each affected area.

General information about dosage

- The number of injections per muscle and the dose vary depending on the indications. Therefore, your doctor will decide how much, how often, and in which muscles BOTOX® will be given to you. It is recommended that your doctor uses the lowest effective dose.

Dosage

In the first treatment session, your doctor may give multiple injections in the affected muscles with a 1 to 2.5 Units of BOTOX® into each injection site.

The maximum dose for the first treatment session is 25 Units per affected area for example per eye. For the following treatment sessions, the total maximum dose can be increased up to 100 Units, if needed.
Duration of treatment effect

You will usually see an improvement within 3 days after the injections. The maximum effect is usually seen in 1-2 weeks after treatment. When the effect starts to wear off, further treatment is possible, but not more often than once every 3 months.

For persistent muscle spasms of strucutres

The usual dose is 400 Units. You will be injected with the recommended volume of 0.1 ml per 4 units of BOTOX into each of 2-5 injection sites.

The maximum dose for the first treatment session is 200 Units.

Duration of treatment effect

When the effect starts to wear off, treatment should be repeated every 3 months. You can have the treatment repeated every 3 months without a limit on the number of treatments.

Dosage

Your doctor may give multiple injections with up to 96 Units of BOTOX into each injection site. The maximum dose for the first treatment session is 200 Units.
Below are lists of side effects which vary depending on the part of the body where BOTOX® is injected.

### Injections in the eye and face for muscle spasms

- **Very common side effects:**
  - Drooping of the eyelid.
  - Swelling of the face.
  - Pain.

- **Common side effects:**
  - Headache.
  - Blurred vision.
  - Dry eyes.
  - Abnormal tearing.

- **Uncommon side effects:**
  - Muscle weakness.
  - Localized muscle weakness.
  - Inability to swallow.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### Injections in the neck and shoulder

- **Very common side effects:**
  - Increased sensitivity to light.
  - Increased tearing.
  - Headache.

- **Common side effects:**
  - Headache.
  - Blurred vision.
  - Dry eyes.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### Injections in the wrist and hand of patients who have had previous surgery

- **Very common side effects:**
  - Joint pain.
  - Muscle weakness.
  - Reduced muscle function.

- **Common side effects:**
  - Headache.
  - Blurred vision.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### General information about other side effects

- **Side effects related to the spread of BOTOX® far away from the site of injection:**
  - Difficulty swallowing.
  - Difficulty talking.
  - Difficulty breathing.

- **Side effects affecting the heart:**
  - Increased heart rate.
  - Irregular heartbeats.
  - Chest pain.

The difficulty in swallowing may range from mild to severe cases. You may need treatment. In rare cases, people have died because of swallowing difficulties.

### Injections in the head and neck to prevent headaches

- **Very common side effects:**
  - Headache.
  - Blurred vision.
  - Dry eye.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

---

**Important:**

If you have any side effects that are not listed in this leaflet, please tell your doctor or pharmacist.
UKPAR Botox ……………………………………………………………………PL 00426/0074, PLs 00426/0118–0119

Botox 50, 100 and 200 Allergan units – powder for solution for injection
### UKPAR Botox ……………………………………………………………………PL 00426/0074, PLs 00426/0118–0119

<table>
<thead>
<tr>
<th>For persistent muscle spasms of the neck and shoulders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td>Your doctor may give multiple injections in the affected muscles, with up to 50 Units of BOTOX injected into each muscle.</td>
</tr>
<tr>
<td><strong>The maximum dose for the first treatment</strong></td>
</tr>
<tr>
<td>The maximum dose is 200 Units.</td>
</tr>
<tr>
<td><strong>Duration of treatment effect</strong></td>
</tr>
<tr>
<td>When the effect starts to wear off, further treatment is possible, but not more often than every 12 weeks.</td>
</tr>
<tr>
<td><strong>For persistent muscle spasms of patients who have had a stroke</strong></td>
</tr>
<tr>
<td>Your doctor may give multiple injections in the affected muscles. The dose and number of injections will vary depending on the location of the muscles to be injected, the size of the muscles, severity of the condition and your response to treatment.</td>
</tr>
<tr>
<td><strong>Duration of treatment effect</strong></td>
</tr>
<tr>
<td>Your doctor may see an improvement in severity of the condition within 6 weeks, though it is not uncommon for further improvement to occur after 2 weeks.</td>
</tr>
<tr>
<td>The improvement will usually last for between 3 and 6 months.</td>
</tr>
<tr>
<td><strong>For excessive sweating of the palms</strong></td>
</tr>
<tr>
<td>Your doctor will give multiple injections of BTX-B in each palm, with a total of 50 Units given in each, based on the location and severity of the condition.</td>
</tr>
<tr>
<td><strong>Duration of treatment effect</strong></td>
</tr>
<tr>
<td>Your doctor may see an improvement in severity of the condition within the first week after injection.</td>
</tr>
</tbody>
</table>

### Botox 50, 100 and 200 Allergan units – powder for solution for injection

<table>
<thead>
<tr>
<th>For the prevention of head, neck and chronic migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td>Your doctor may give multiple injections (between 5 and 20) into muscle groups of the neck and shoulder area, but not more often than every 2 weeks.</td>
</tr>
</tbody>
</table>

### 142

### Perforation

*The total dose range is between 155 Units and 195 Units per treatment session.*

### 142

*The usual dose is the recommended volume of 0.1 milliliter (4 units) of BOTOX into each injection site.*

*Improvement of severity of the condition occurred within 1 week after treatment, the maximum effect being observed 5 to 8 weeks after injection. The treatment effect has been demonstrated for up to 4 months after injection.*

*The interval between treatments must not be less than three months.*

*If you have received more BOTOX than you should have it is not uncommon for further improvement to occur after 2 weeks.*

*The signs of both BOTOX may not occur after several days after injection. You should seek medical advice if you experience significant symptoms.*

*If you have received too much BOTOX, you may have any of the following side effects and you must contact your doctor immediately:*

1. Difficulty in swallowing, speaking or breathing due to muscle paralysis
2. Nausea
3. Dry mouth
4. Voice changes
5. Dizziness

*If you have any further questions or concerns, ask your doctor or pharmacist.*

### 142

*The side effects are classified into the following categories, depending on how they occur:*

*Common:
- Dizziness
- Headache
- Fatigue

*Uncommon:
- Infection at the injection site
- Rash

*Rare:
- Anaphylaxis

*Perforation:
- Patients treated with the specific doses may experience exaggerated muscle weakness. Patients with underlying neurological disorders including muscle weakness, difficulty in chewing, swallowing, difficulty in speaking, or difficulty in walking, should be advised of the potential for increased risk of these side effects. The benefit from use of product should be weighed against the increased risk of these side effects. Treatment of strabismus with BOTOX may be associated with diplopia, ptosis, anisometropia or other vision problems.*

<table>
<thead>
<tr>
<th>Further information for medical or healthcare professionals only:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please refer to the Summary of Product Characteristics for complete prescribing information.*</td>
</tr>
</tbody>
</table>

*For all indications: Side effects related to spread of botulinum toxin to sites from where it is not intended.*

*For all indications: Side effects related to spread of botulinum toxin to sites from where it is not intended.*

*For all indications: Side effects related to spread of botulinum toxin to sites from where it is not intended.*

### 142

*It is advisable to perform head repositioning and change the position of the patient when using a saline solution to clean the injection area.*

*Reconstitution of BOTOX only with sterile, preservative-free sodium chloride injection solution. Draw up an appropriate amount of diluent (solution containing saline) for injection.*

### Injection table for BOTOX 50, 100 and 200 Allergan units size sites

<table>
<thead>
<tr>
<th>Injection size</th>
<th>Powder for dilution</th>
<th>Amount of diluent</th>
<th>Amount of powder</th>
<th>Amount of sodium chloride in mg</th>
<th>Amount of diluent in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 Units</td>
<td>0.5 mL</td>
<td>50 Units</td>
<td>50 Units</td>
<td>0.9 mg</td>
<td>50 Units</td>
</tr>
<tr>
<td>100 Units</td>
<td>1 mL</td>
<td>50 Units</td>
<td>100 Units</td>
<td>1.8 mg</td>
<td>100 Units</td>
</tr>
<tr>
<td>200 Units</td>
<td>2 mL</td>
<td>50 Units</td>
<td>200 Units</td>
<td>3.6 mg</td>
<td>200 Units</td>
</tr>
</tbody>
</table>

*If you experience any of the following side effects, contact your doctor immediately:*

1. Difficulty in swallowing, speaking or breathing due to muscle paralysis
2. Nausea
3. Dry mouth
4. Voice changes
5. Dizziness

From a biochemical perspective, the product should be used on its own, in the form of a single injection, and is not recommended for use with any other products or procedures.*

*Procedure to follow for safe disposal of vials, syringes and needles used:*

1. For safe disposal, unused vials should be reconstituted with a small amount of water and then discarded. Any unused vials, syringes, and needle used should be disposed of in accordance with local regulations.*

*Identification of the product:* In order to verify the status of BOTOX product, the Allergan logo is a holographic feature that can be seen under the lamp. Additionally, the label on the vial contains a hologram. If you do not see the hologram or the name "Allergan" does not appear, do not use the product and contact your local Allergan office for additional information.*
Below are lists of side effects which vary depending on the area of injection:

**Injections in the orbit and face for muscle spasm:**
- Dry eye.
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.
- Tingling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the neck and shoulder:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the face:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the lips:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the oral area:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the hand and arm:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the neck:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the back:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the shoulder:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the wrist:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injections in the hand:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Infections in the foot:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injection in the neck:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injection in the shoulder:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injection in the elbow:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injection in the ankle:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injection in the hip:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.

**Injection in the knee:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Common side effects:**
- Headache.
- Increased sensitivity to light.
- Numbness.
- Pain.
- Swelling.

**Uncommon side effects:**
- Foreign body sensation.
- Headache.
- Increased sensitivity to light.
- Itching.
- Numbness.
- Pain.
- Swelling.
Some of these people have died. However, some of these patients were already suffering from heart conditions.

Serious or immediate allergic reactions have been rarely reported, including:
- hives,
- swelling including swelling of the face or throat;

- wheezing;
- feeling faint;
- shortness of breath.

There have been very rare reports of:
- glaucoma (high pressure in the eye).

There have been reports of:
- seizures or convulsions after treatment with BOTOX, particularly in patients who have previously experienced these symptoms. Three deaths occurred following when:

BOTOX was used for the treatment of persistent muscle spasms in the legs of children with cerebral palsy.

As with any injection, you may suffer from injection related side effects:
- pain, bruising, bleeding or injection where the injection is given;
- numbness;
- decreased skin sensation;
- tenderness;
- swelling/puffiness;

- stiffness;
- a drop in blood pressure or fainting may be caused by needle-related pain and/or anxiety.

After injection of BOTOX patients have also suffered:
- fever and flu like symptoms.

The following list describes additional side effects reported for BOTOX in any disease, since it has been marketed:

- allergic reactions, which can be serious (swelling of the face and airways, difficulty in breathing);
- other symptoms of hypersensitivity (urticaria, rash);
- pain/numbness or weakness starting from the spine;
- dropping of the muscles on one side of the face;
- weakness of the face muscles;
- difficulty moving the arm and shoulder;
- decreased skin sensation;
- muscles pain;
- abdominal pain;
- diarrhea, vomiting, loss of appetite;
- fever;
- different types of rash/bloody skin rash (vaccination);
- feeling generally unwell;
- speech problems;
- twitching;
- excessive sweating;
- hair loss;
- loss of eyebrows;
- decreased hearing;

- noises in the ear;
- feeling of dizziness or "spinning" (vertigo);
- numbness.

If any of the side effects given serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BOTOX

Keep out of the reach and sight of children.

Store in refrigerator (2°C – 8°C) or sterile ice pack or freeze (at or below -8°C).

After the solution is made up, immediate use of the solution is recommended; however it can be stored for up to 24 hours in a refrigerator (2°C – 8°C).

Your doctor should not use BOTOX after the expiry date which is stated on the label after “EXP”. The expiry date refers to the last day of that month.

6. FURTHER INFORMATION

What BOTOX contains:
- The active substance is: Botulinum toxin type A from Clostridium botulinum.
- The other ingredients are human albumin and sodium chloride.

What BOTOX looks like and content of the pack:

BOTOX is presented as a white glass vial. Prior to injection, each vial must be dissolved in a sterile saline solution. Each vial contains 100 Allergan units. Each pack contains 1, 2, 3 or 4 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Allergan Ltd., Marboro International, The Parway, Marboro, Bucks, SL7 1YL, UK

Manufacturer:
Allergan Pharmaceuticals Ireland Castledermot, Ireland

This medicinal product is authorised in the Member States of the EEA under the following name: BOTOX Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Ireland, Iceland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, United Kingdom

This leaflet was last approved in September 2011

Botox 50, 100 and 200 Allergan units – powder for solution for injection
In adults less than 18 years of age, BOTOX® is used for the temporary improvement of vertical lines between the brow and the nose, when the severity of these lines has an important psychological impact for the patient.

In children aged 2 to 12 years of age with cerebral palsy, who can walk, BOTOX® is used to:

- 

- Foot deformity caused by the persistent muscle spasms in the feet. BOTOX® relieves the persistent muscle spasm in the feet.

2. BEFORE YOU USE BOTOX

- Do NOT use BOTOX

- if you are allergic (hypersensitive) to botulinum toxin type A or any of the other ingredients of BOTOX®;

- if you have an infection at the proposed site of injection

- Take special care with BOTOX

Before using BOTOX

Tell your doctor if you:

- 

- have had any problems with injections (such as bleeding) in the past;

- have had problems in the past with previous botulinum toxin type A injections;

- have inflammation in the muscles or skin area where your doses are to be injected;

- have significant weakness or swelling of the muscles when your doctor plans to treat;

- have had recent treatment with the treatment of paralytic prostatic muscle spasm.

1. What BOTOX is and what it is used for

BOTOX® is a muscle relaxant that is injected directly into the muscles of the face that cause facial lines and wrinkles.

BOTOX® is used for:

- Treat excessive sweating of the hands and feet;

- Prevent headaches in patients with chronic migraine;

- Treat strabismus, blepharospasm, and other movement disorders.

2. How to use BOTOX

BOTOX® is administered by injection into specific muscles in the head and neck. The injections are typically given every 3 to 4 months.

3. Possible side effects

BOTOX® may cause:

- Anterior cervical spine syndrome;

- Anaphylaxis (severe allergic reaction);

- Deep vein thrombosis;

- Infected injection site;

- Palmar hyperhidrosis;

- Pinch nerve syndrome;

- Portal vein thrombosis;

- Post-injection pain;

- Reactive arthritis;

- Soft tissue infections.

4. Further information

- BOTOX® is a medication that should not be used by anyone who is pregnant or breastfeeding;

- BOTOX® is not recommended for children or adolescents;

- BOTOX® is not recommended for patients with a history of thyroid disease.

5. Notes

- BOTOX® should not be used in the same area for 3 months following a previous injection of BOTOX®.

- The maximum dose for the first treatment session is 25 units per affected area (for example, per eye). For the following treatment sessions, the total maximum dose can be increased up to 100 units, if needed.
Botox 50, 100 and 200 Allergan units – powder for solution for injection
Below are lists of side effects which vary depending on the part of the body where BOTOX® is injected.

**Injections in the eyelid and face for muscle spasm**

**Very common side effect:**
- dryness of the eyelid.

**Common side effects:**
- swelling of the face;
- pinpoint damage of the cornea (translucent surface covering the front of the eye);
- difficulty in completely closing the eyes;
- dry eyes, eye irritation and sensitivity to light.

**Uncommon side effects:**
- change in eyesight;
- feeling of dryness or irritation;
- sensation of foreign body in the eye;
- rash;
- abnormal tearing of the eyelids, cornea or conjunctiva.

**Rare side effect:**
- swelling of the eyelid.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the neck and shoulder**

**Very common side effects:**
- difficulty swallowing;
- pain;
- muscle weakness.

**Common side effects:**
- change in vision;
- dryness;
- muscle cramps;
- feeling of weakness;
- feeling generally unwell;
- feeling sick;
- increased sensitivity to light;
- itchy sensation;
- lump under the skin;
- numbness around the mouth;
- sensitivity to light;
- swelling and irritation inside the nose (mucosa);
- blood in or near nose, cough, sore throat, hoarse or inflamed in the throat;
- dry mouth.

**Uncommon side effects:**
- shortness of breath;
- double vision;
- fever;
- dryness of the eyelid;
- changes in your voice.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the wrist and hand of patients who have had a wrist tenosynovectomy**

**Common side effects:**
- muscle pain;
- increased muscle tension;
- feeling of dislocation or displacement in the wrist;
- pain in the hand and fingers.

**Uncommon side effects:**
- rash;
- feeling of weakness.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with BOTOX®. If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck to prevent headache in patients who suffer from chronic migraines**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- dryness, eye irritation and sensitivity to light.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the back of the head (buried needle technique)**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for tension (rectus) or movement disorders**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- dryness, eye irritation and sensitivity to light.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for blepharospasm**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for spasticity**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for strabismus**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for spasticity**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for dystonia**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for spasticity**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for tremors**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for facial nerve palsy**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for blepharospasm**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for strabismus**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for spasticity**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for dystonia**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for spasticity**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for tremors**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for facial nerve palsy**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for blepharospasm**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for strabismus**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for spasticity**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for dystonia**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injection in the head and neck for spasticity**

**Common side effects:**
- headache;
- muscle weakness;
- muscle pain;
- vision disturbances.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
Serious or immediate allergic reactions have been rarely reported, including:
- hives;
- swelling including swelling of the face or throat;
- wheezing;
- feeling faint;

There have been very rare reports of:
- glaucoma (high pressure in the eye);
- there have been reports of:
- seizures or convulsions after treatment with BOTOX, particularly in patients who have previously experienced these symptoms. These effects occurred mainly when BOTOX was used for the treatment of persistent muscle spasms in the legs of children with cerebral palsy.

As with any injection, you may suffer from injection related side effects:
- pain, bruising, bleeding or infection where the injection is given;
- numbness;
- decreased skin sensation;
- tenderness;
- swelling/puffiness;
- redness;
- a drop in blood pressure or fainting may be caused by needle-related pain and/or an allergic reaction.

After injection of BOTOX patients have also suffered:
- fever and flu-like symptoms.

The following list describes additional side effects reported for BOTOX, in any disease since it has been marketed:
- allergic reactions, which can be serious (swelling of the face and airways, difficulty in breathing);
- chronic disease affecting the muscles (myasthenia gravis);
- blurred vision;
- difficulties in seeing clearly;
- tasting;
- pain/numbness/weakness starting from the spine;
- dragging of the muscles on one side of the body;
- weakness of the face muscles;
- difficulty moving the arm and shoulder;
- decreased skin sensation;
- muscles pain;
- abdominal pain;
- diaphoresis; vomiting; loss of appetite;
- fever;
- different types of red/bloody skin rashers;
- feeling generally unwell;
- speech problems;
- itching;
- excessive sweating;
- hair loss;
- loss of eyebrows;
- decreased hearing;
- noises in the ear;

- feeling of dizziness or “spinning” (vertigo);
- numbness;

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE BOTOX
Keep out of reach of children.
Store in a refrigerator (2°C–8°C), or at room temperature.

UKPAR Botox ……………………………………………………………………PL 00426/0074, PLs 00426/0118–0119

6. FURTHER INFORMATION
What BOTOX contains
- The active substance is: Botulinum toxin type A from Clostridium botulinum.
- The other ingredients are human albumin and sodium chloride.

What BOTOX looks like and content of the pack
BOTOX is presented as a white powder in a transparent glass vial. Prior to injection, the product must be dissolved in a sterile saline solution.
Each vial contains 200 Allergan Units of botulinum toxin type A.
Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes may be marketed.

Marketing Authorization Holder
Allergan Ltd.,
Marlborough, Marlboro,
Massachusetts, USA

Manufacturer:
Allergan Pharmaceuticals Ireland
Castlebar Road
Westport
County Mayo
Ireland

This medicinal product is authorised in the Member States of the EEA under the following name: BOTOX
Austria, Belgium, Czech Republic, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Slovak Republic, United Kingdom

This leaflet was last approved in September 2011

Botox 50, 100 and 200 Allergan units – powder for solution for injection 148
Botox 50, 100 and 200 Allergan units – powder for solution for injection
Botox 50, 100 and 200 Allergan units – powder for solution for injection
Annex 2

Our Reference: PL 00426/0074–0149
Product: PL 00426/0074 Botox
Marketing Authorisation Holder: ALLERGAN LIMITED

Reason:
To update sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SPC due to the addition of a new indication for the temporary improvement in the appearance of moderate to severe lateral canthal lines (crow's feet lines) in adults treated either alone or simultaneously with glabellar lines, when the severity of these lines has an important psychological impact for the patient. Consequentially, the leaflet is updated.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 14227389 and covers the following submissions PL 00426/0118–0071, PL 00426/0119–0058.

Supporting Evidence
Updated SPC fragments 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 10.
Dossier documentation: m1.0, m1.1, m1.2, m1.3, m1.4, m1.6, m1.8, m1.9, m1.10, m2.2, m2.5, m2.7, m5.2, m5.3, m5.4.

Evaluation
RMP version 6 has been submitted with this variation. This RMP has subsequently been reupdated into version 7.0 and resubmitted through a parallel variation procedure (submission 152). Therefore RMP v6.0 is not approved. Further assessment of the RMP will be undertaken through the parallel procedure.

Conclusion
The proposed changes are acceptable.

4.1 Therapeutic indications

BOTOX is indicated for:

- the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
- the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)
- the management of bladder dysfunctions in adult patients who are not adequately managed with anticholinergics
  o overactive bladder with symptoms of urinary incontinence, urgency and frequency
  o neurogenic detrusor overactivity with urinary incontinence due to subcervical spinal cord injury (traumatic or non-traumatic) or multiple sclerosis

BOTOX is also indicated for focal spasticity, including the treatment of:

- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older
and
➢ wrist and hand disability due to upper limb spasticity associated with stroke in adults.

BOTOX is also indicated for the temporary improvement in the appearance of the following facial lines, when the severity of these lines has an important psychological impact in adult patients:

➢ moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines)
➢ moderate to severe lateral canthal lines (crow’s feet lines) seen at maximum smile
➢ moderate to severe crow’s feet lines seen at maximum smile and glabellar lines seen at maximum frown when treated simultaneously.

4.2 Posology and method of administration

Posology

Refer to specific recommendations for each indication described below.

Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan units are different from other botulinum toxin preparations.

This product is for single use only and any unused solution should be discarded. The most appropriate vial size should be selected for the indication.

An injection volume of approximately 0.1 ml is recommended. A decrease or increase in the BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For instructions on reconstitution of the powder for solution for injection, handling and disposal of vials please refer to section 6.6.

Elderly patients

Overall, with the exception of overactive bladder, adequate studies on geriatric dosing have not been performed. The lowest effective dose with the longest clinically indicated interval between injections is recommended. Elderly patients with significant medical history and concomitant medications should be treated with caution (for Overactive bladder see sections 4.8 and 5.1).

There is limited phase 3 clinical data with BOTOX for glabellar lines in patients older than 65 years (see section 5.1). There is very limited data with BOTOX in patients older than 65 years treated for urinary incontinence with neurogenic detrusor overactivity.

Paediatric population
The safety and effectiveness of BOTOX in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia in children (under 12 years) have not been demonstrated.

The safety and effectiveness of BOTOX in the treatment of primary hyperhidrosis of the axillae have not been investigated in children under 12 years. The safety and efficacy of BOTOX in adolescents aged 12 to 17 years for the treatment of severe axillary hyperhidrosis have not been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made (see sections 4.8 and 5.1).

The safety and effectiveness of BOTOX in the treatment of glabellar lines seen at maximum frown and/or crow’s feet lines seen at maximum smile, in the prophylaxis of chronic migraine headaches and in the management of overactive bladder and urinary incontinence with neurogenic detrusor overactivity have not been demonstrated in individuals under 18 years of age. The use of BOTOX is not recommended in patients less than 18 years for these indications.

The safety and effectiveness of BOTOX in the treatment of upper limb spasticity associated with stroke has not been established in children and adolescents under 18 years of age.

**Method of Administration**

Refer to specific guidance for each indication described below. BOTOX should only be administered by physicians with appropriate qualifications and expertise in the treatment and the use of the required equipment.

Generally valid optimum dose levels and number of injection sites per muscle have not been established for all indications. In these cases, individual treatment regimens should therefore be drawn up by the physician. Optimum dose levels should be determined by titration but the recommended maximum dose should not be exceeded.

**Blepharospasm/hemifacial spasm**

Reconstituted BOTOX is injected using a sterile, 27-30 gauge/0.40-0.30 mm needle. Electromyographic guidance is not necessary. The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision. Avoiding injection near levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. The following diagrams indicate the possible injection sites:
In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. The initial dose should not exceed 25 Units per eye. Normally no additional benefit is conferred by treating more frequently than every three months.

In the management of blepharospasm total dosing should not exceed 100 Units every 12 weeks.

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

**Cervical dystonia**

Several dosing regimens have been used in clinical trials for treatment of cervical dystonia with BOTOX. Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response.

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted BOTOX ranged from 140 to 280 Units. In more recent studies, the doses have ranged from 95 to 360 Units (with an approximate mean of 240 Units). As with any drug treatment, initial dosing in a naïve patient should begin at the lowest effective dose. No more than 50 Units should be given at any one injection site. No more than 100 Units should be given to the sternomastoid. To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally. No more than 200 Units total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response. A total dose of 300 Units at any one sitting should not be exceeded.

The following doses are recommended:

<table>
<thead>
<tr>
<th>Type</th>
<th>Head</th>
<th>Sternomastoid</th>
<th>Levator scapulae</th>
<th>Scapulae</th>
<th>Sphenius capitis</th>
<th>Trapezius</th>
<th>Total Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Rotated towards side of shoulder elevation</td>
<td>50 - 100 Units; at least 2 sites</td>
<td>50 Units; 1 - 2 sites</td>
<td>25 - 50 Units; 1 - 2 sites</td>
<td>25 - 75 Units; 1 - 3 sites</td>
<td>25 - 100 Units; 1 - 8 sites</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Rotation only</td>
<td>25 - 100 Units; at least 2 sites if &gt;25 Units given</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Tilted towards side of shoulder elevation</td>
<td>25 - 100 Units at posterior border; at least 2 sites if &gt;25 Units given</td>
<td>25 - 100 Units; at least 2 sites</td>
<td>25 - 75 Units; at least 2 sites</td>
<td>25 - 100 Units; 1 - 8 sites</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, semispinalis, longissimus and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment. The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose. Muscle activation patterns can change spontaneously in cervical dystonia without a change in the clinical presentation of dystonia.

A 25, 27 or 30 gauge/0.50-0.30 mm needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance.

Multiple injection sites allow BOTOX to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. Treatment intervals of less than 10 weeks are not recommended. The duration of beneficial effect reported in clinical trials showed substantial variation (from 2 to 33 weeks) with a typical duration of approximately 12 weeks.

**Primary hyperhidrosis of the axillae**

The recommended injection volume for intradermal injection in axillary hyperhidrosis is 0.1-0.2 ml. Reconstituted BOTOX (100 Units/4 mL) is injected using a 30 gauge needle. 50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor’s iodine-starch test. Doses other than 50 Units per axilla cannot be recommended.

Clinical improvement generally occurs within the first week after injection. Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating physician deems it necessary. Treatment response has been reported to persist for 4-7 months. Injections should not be repeated more frequently than every 16 weeks (see section 5.1).

**Paediatric cerebral palsy**

Reconstituted BOTOX is injected using a sterile 23-26 gauge/0.60-0.45 mm needle. It is administered as a divided dose through single injections into the medial and lateral heads of the affected gastrocnemius muscle. In hemiplegia, the initial recommended total dose is 4 Units/kg body weight in the affected limb. In diplegia, the initial recommended total dose is 6 Units/kg body weight divided between the affected limbs. The total dose should not exceed 200 Units.
Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months. It may be possible to adapt the dosage regimen to obtain an interval of at least six months between treatment sessions.

**Focal upper limb spasticity associated with stroke**
Reconstituted BOTOX is injected using a sterile 25, 27 or 30 gauge needle for superficial muscles, and a longer needle for deeper musculature. Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, the presence of local muscle weakness, and the patient response to previous treatment.

In the controlled clinical trials the following doses were administered:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Total Dosage; Number of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum profundus</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>15 – 60 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>10 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units; 1-2 sites</td>
</tr>
</tbody>
</table>

In controlled and open non-controlled clinical trials doses between 200 and 240 Units divided among selected muscles have been used at a given treatment session.

In controlled clinical trials patients were followed for 12 weeks after single treatment. Improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open, non-controlled continuation study, most of the patients were re-injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximal cumulative dose of 960 Units over 54 weeks. If it is deemed appropriate by the treating physician, repeat doses may be administered, when the effect of a previous injection has diminished. Re-injections should not occur before 12 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected. The lowest effective dose should be used.

**Chronic Migraine**
The recommended reconstituted BOTOX dose for treating chronic migraine is 155 Units to 195 Units administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 Units) injections to 31 and up to 39 sites. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to
one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the injection sites:

---

BOTOX Dosing By Muscle:

<table>
<thead>
<tr>
<th>Head/Neck Area</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 Units (4 sites)</td>
</tr>
<tr>
<td>Corrugator&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 Units (2 sites)</td>
</tr>
<tr>
<td>Procerus</td>
<td>5 Units (1 site)</td>
</tr>
<tr>
<td>Occipitalis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 Units (6 sites) up to 40 Units (up to 8 sites)</td>
</tr>
<tr>
<td>Temporalis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40 Units (8 sites) up to 50 Units (up to 10 sites)</td>
</tr>
<tr>
<td>Trapezius&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 Units (6 sites) up to 50 Units (up to 10 sites)</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 Units (4 sites)</td>
</tr>
</tbody>
</table>

**Total Dose Range:**

155 Units to 195 Units
31 to 39 sites

---

<sup>a</sup>1 IM injection site = 0.1 mL = 5 Units BOTOX
<sup>b</sup>Dose distributed bilaterally

The recommended re-treatment schedule is every 12 weeks.

**Overactive bladder**

The recommended dose is 100 Units of BOTOX, as 0.5 ml (5 Units) injections across 20 sites in the detrusor muscle.

The reconstituted solution of BOTOX (100 Units/10 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 ml of the reconstituted BOTOX prior to the start of the injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 ml each (total volume 10 ml) should be spaced approximately 1 cm apart (see figure below). For the final injection, approximately 1 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection should be injected so the full dose is delivered. After the
injections are given, the saline used for bladder wall visualisation should not be drained so that the patients can demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

For the patient preparation and monitoring, see section 4.4.

Re-treatment
Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was ~24 weeks), but no sooner than 3 months from the prior bladder injection.

Urinary incontinence due to neurogenic detrusor overactivity
The recommended dose is 200 Units of BOTOX, as 1 ml (~6.7 Units) injections across 30 sites in the detrusor muscle.

The reconstituted solution of BOTOX (200 Units/30 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 ml prior to the start of the injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 ml each (total volume 30 ml) should be spaced approximately 1 cm apart (see figure above). For the final injection, approximately 1 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should be drained.

For the patient preparation and monitoring, see section 4.4.
Re-treatment
Patients should be considered for reinjection when the clinical effect of the previous injection has diminished, but no sooner than 3 months from the prior bladder injection. In phase 3 clinical studies, the median interval between the first and second administrations was 42 weeks in patients with spinal cord injury and 45 weeks in patients with multiple sclerosis.

Limited data are available beyond 2 treatments. No urodynamic data beyond 2 treatments and no histopathological data after repeated treatment are currently available.

Patients should not receive multiple treatments in the event of limited symptomatic improvement.

Glabellar lines seen at maximum frown
Reconstituted BOTOX (50 Units/1.25 mL) is injected using a sterile 30 gauge needle. A volume of 0.1 mL (4 Units) is administered in each of the 5 injection sites (see Figure 1): 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units.

Before injection, the thumb or index finger is to be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection. In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections in the corrugator muscle must be done in the central part of that muscle, a distance of at least 1 cm above the arch of the eyebrows.

Figure 1:
Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the vertical lines between the eyebrows seen at maximum frown (also known as Glabellar Lines), see section 4.4.

 Improvement of severity of vertical lines between the eyebrows seen at maximum frown (glabellar lines) generally occurs within one week after treatment. The effect was demonstrated for up to 4 months after injection.

 Treatment intervals should not be more frequent than every three months. In the event of treatment failure or diminished effect following repeat injections, alternative treatment methods should be employed.

 In case of insufficient dose initiate a second treatment session by, adjusting the total dose up to 40 or 50 units, taking into account the analysis of the previous treatment failure (see information in All indications).

 The efficacy and safety of repeat injections of BOTOX for the treatment of glabellar lines beyond 12 months has not been evaluated.

 **Crow’s Feet Lines seen at maximum smile**

 Reconstituted BOTOX (50 Units/1.25 ml) is injected using a sterile 30 gauge needle 0.1 ml (4 Units) is administered in each of the 3 injection sites per side (total of 6 injection sites) in the lateral orbicularis oculi muscle, for a total dose of 24 Units in a total volume of 0.6 ml (12 Units per side).

 In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

 Injections should be given with the needle tip bevel up and oriented away from the eye. The first injection (A) should be made approximately 1.5 to 2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow’s feet region are above and below
the lateral canthus, inject as shown in Figure 2. Alternatively, if the lines in the crow’s feet region are primarily below the lateral canthus, inject as shown in Figure 3.

Figure 2:     Figure 3:

For simultaneous treatment with glabellar lines seen at maximum frown, the dose is 24 Units for crow’s feet lines seen at maximum smile and 20 Units for glabellar lines (see Administration Instructions for Glabellar Lines, and Figure 1), for a total dose of 44 Units in a total volume of 1.1 ml.

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the lateral canthal lines seen at maximum smile (also known as Crow’s Feet Lines), see section 4.4.

Improvement of severity of crow’s feet lines seen at maximum smile, when assessed by the investigator, occurred within one week of treatment. The effect was demonstrated for a median of 4 months after injection.

Treatment intervals should not be more frequent than every 3 months.

The efficacy and safety of repeat injections of BOTOX for the treatment of crow’s feet lines beyond 12 months has not been evaluated.

All indications
In case of treatment failure after the first treatment session, i.e. absence, at one month after injection, of significant clinical improvement from baseline, the following actions should be taken:

- Clinical verification, which may include electromyographic examination in a specialist setting, of the action of the toxin on the injected muscle(s);
- Analysis of the causes of failure, e.g. bad selection of muscles to be injected, insufficient dose, poor injection technique, appearance of fixed contracture, antagonist muscles too weak, formation of toxin-neutralising antibodies;
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A;
- In the absence of any undesirable effects secondary to the first treatment session, instigate a second treatment session as following: i) adjust the dose, taking into account the analysis of the earlier treatment failure; ii) use EMG; and iii) maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections alternative treatment methods should be employed.

### 4.4 Special warnings and precautions for use

The recommended dosages and frequencies of administration of BOTOX should not be exceeded due to the potential for overdose, exaggerated muscle weakness, distant spread of toxin and the formation of neutralising antibodies. Initial dosing in treatment naïve patients should begin with the lowest recommended dose for the specific indication.

Prescribers and patients should be aware that side effects can occur despite previous injections being well tolerated. Caution should therefore be exercised on the occasion of each administration.

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exaggerated muscle weakness.

Elderly and debilitated patients should be treated with caution.

Consideration should be given to the risk-benefit implications for the individual patient before embarking on treatment with BOTOX.

Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 ‘Cervical Dystonia’).

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Lambert-Eaton Syndrome in patients with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) and in patients with underlying neurological disorders. Such patients may have an increased sensitivity to agents such as BOTOX, even at therapeutic doses, which may result in excessive muscle weakness and an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered...
to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

As with any treatment with the potential to allow previously-sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually.

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX and injection into vulnerable anatomic structures must be avoided. Pneumothorax associated with injection procedure has been reported following the administration of BOTOX near the thorax. Caution is warranted when injecting in proximity to the lung (particularly the apices) or other vulnerable anatomic structures.

Serious adverse events including fatal outcomes have been reported in patients who had received off-label injections of BOTOX directly into salivary glands, the oro-lingual-pharyngeal region, oesophagus and stomach. Some patients had pre-existing dysphagia or significant debility.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted. One case of anaphylaxis has been reported in which the patient died after being injected with BOTOX inappropriately diluted with 5 ml of 1% lidocaine.

As with any injection, procedure-related injury could occur. An injection could result in localised infection, pain, inflammation, paraesthesia, hypoesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.

Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s), ptosis or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

There have been rare reports of adverse events following administration of BOTOX involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to botulinum toxin injection has not been established. The reports in children were predominantly from cerebral palsy patients treated for spasticity.

Formation of neutralising antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some
studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest clinically indicated intervals between injections.

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

**Paediatric use**
The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 has not been established. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

**Blepharospasm**
Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles.

**Cervical dystonia**
Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 Units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the
oesophageal musculature. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia may contribute to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX injection.

**Primary hyperhidrosis of the axillae**
Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

**Focal spasticity associated with paediatric cerebral palsy and spasticity of the hand and wrist in adult post-stroke patients**
BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

There have been post-marketing reports of death (sometimes associated with aspiration pneumonia) and of possible distant spread of toxin in children with co-morbidities, predominantly cerebral palsy following treatment with botulinum toxin. See warnings under section 4.4, ‘Paediatric use’.

**Chronic migraine**
No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

**Bladder dysfunctions**
**Patient preparation and monitoring**
Prophylactic antibiotics should be administered to patients with sterile urine or asymptomatic bacteriuria in accordance with local standard practice.

The decision to discontinue anti-platelet therapy should be subject to local guidance and benefit/risk consideration for the individual patient. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate medical caution should be exercised when performing the cystoscopy. The patient should be observed for at least 30 minutes post-injection.

In patients who are not regularly practicing catheterisation, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate. Patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required.

**Overactive bladder**
Prior to injection an intravesical instillation of diluted local anaesthetic, with or without sedation, may be used, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.
Urinary incontinence due to neurogenic detrusor overactivity

BOTOX injection can be performed under general or local anaesthesia with or without sedation. If a local anaesthetic intravesical instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.

Autonomic dysreflexia associated with the procedure can occur and greater vigilance is required in patients known to be at risk.

Glabellar lines seen at maximum frown and/or Crow’s Feet lines seen at maximum smile

It is mandatory that BOTOX is used for one single patient treatment only during a single session. The excess of unused product must be disposed of as detailed in section 6.6. Particular precautions should be taken for product preparation and administration as well as for the inactivation and disposal of the remaining unused solution (see section 6.6).

The use of BOTOX is not recommended in individuals under 18 years. There is limited phase 3 clinical data with BOTOX in patients older than 65 years.

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the vertical lines between the eyebrows seen at maximum frown (also known as Glabellar Lines) or in the lateral canthal lines seen at maximum smile (also known as Crow’s Feet Lines), see section 4.2. There is a risk of eyelid ptosis following treatment, refer to Section 4.2 for administration instructions on how to minimise this risk.

4.8 Undesirable effects

a) General

In controlled clinical trials adverse events considered by the investigators to be related to BOTOX were reported in 35% of the patients with blepharospasm, 28% with cervical dystonia, 17% with paediatric cerebral palsy, 11% with primary hyperhidrosis of the axillae, 16% with focal spasticity of the upper limb associated with stroke, 26% with overactive bladder, and 32% with neurogenic detrusor overactivity. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In controlled clinical trials for glabellar lines seen at maximum frown, adverse events considered by the investigators to be related to BOTOX were reported in 23% (placebo 19%) of patients. In treatment cycle 1 of the pivotal controlled clinical trials for crow’s feet lines seen at maximum smile, such events were reported in 8% (24 Units for crow’s feet lines alone) and 6% (44 Units: 24 Units for crow’s feet lines administered simultaneously with 20 Units for glabellar lines) of patients compared to 5% for placebo.

Adverse reactions may be related to treatment, injection technique or both. In general, adverse reactions occur within the first few days following injection and, while generally transient, may have a duration of several months or, in rare cases, longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue.

As is expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have
resulted in vasovagal responses, including transient symptomatic hypotension and syncope. Fever and flu syndrome have also been reported after injections of botulinum toxin.

**b) Adverse reactions - frequency by indication**

For each indication the frequency of adverse reactions arising from clinical experience is given. The frequency is defined as follows:
- Very Common \(\geq \frac{1}{10}\)
- Common \(\geq \frac{1}{100} \text{ to } \frac{1}{10}\)
- Uncommon \(\geq \frac{1}{1,000} \text{ to } \frac{1}{100}\)
- Rare \(\geq \frac{1}{10,000} \text{ to } \frac{1}{1,000}\)
- Very Rare \(<\frac{1}{10,000}\)

**Blepharospasm/hemifacial spasm**

**Nervous system disorders**
- Uncommon: Dizziness, facial paresis and facial palsy

**Eye Disorders**
- Very common: Eyelid ptosis
- Common: Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation and lacrimation increase
- Uncommon: Keratitis, ectropion, diplopia, entropion, visual disturbance and vision blurred
- Rare: Eyelid oedema
- Very rare: Corneal ulceration, corneal epithelium defect and corneal perforation

**Skin and subcutaneous tissue disorders**
- Common: Ecchymosis
- Uncommon: Rash/dermatitis

**General disorders and administration site conditions**
- Common: Irritation and face oedema
- Uncommon: Fatigue

**Cervical dystonia**

**Infections and infestations**
- Common: Rhinitis and upper respiratory infection

**Nervous system disorders**
- Common: Dizziness, hypertonia, hypoaesthesia, somnolence and headache

**Eye Disorders**
- Uncommon: Diplopia and eyelid ptosis

**Respiratory, thoracic and mediastinal disorders**
- Uncommon: Dyspnoea and dysphonia

**Gastrointestinal disorders**
- Very common: Dysphagia (see section c. “Additional information” below)
- Common: Dry mouth and nausea

**Musculoskeletal and connective tissue disorders**
- Very common: Muscular weakness
- Common: Musculoskeletal stiffness and soreness
General disorders and administration site conditions
Very common: Pain
Common: Asthenia, influenza like illness and malaise
Uncommon: Pyrexia

Paediatric cerebral palsy

Infections and infestations
Very common: Viral infection and ear infection

Nervous system disorders
Common: Somnolence, gait disturbance and paraesthesia

Skin and subcutaneous tissue disorders
Common: Rash

Musculoskeletal and connective tissue disorders
Common: Myalgia, muscular weakness and pain in extremity

Renal and urinary disorders
Common: Urinary incontinence

Injury, poisoning and procedural complications
Common: Fall

General disorders and administration site conditions
Common: Malaise, injection site pain and asthenia

Focal upper limb spasticity associated with stroke

Psychiatric disorders
Uncommon: Depression and insomnia

Nervous system disorders
Common: Hypertonia
Uncommon: Hypoaesthesia, headache, paraesthesia, incoordination and amnesia

Ear and labyrinth disorders
Uncommon: Vertigo

Vascular disorders
Uncommon: Orthostatic hypotension

Gastrointestinal disorders
Uncommon: Nausea and paraesthesia oral

Skin and subcutaneous tissue disorders
Common: Ecchymosis and purpura
Uncommon: Dermatitis, pruritus and rash

Musculoskeletal and connective tissue disorders
Common: Pain in extremity and muscle weakness
Uncommon: Arthralgia and bursitis

**General disorders and administration site conditions**
Common: Injection site pain, pyrexia, influenza-like illness, injection site haemorrhage and injection site irritation
Uncommon: Asthenia, pain, injection site hypersensitivity, malaise and oedema peripheral

Some of the uncommon events may be disease related.

**Primary hyperhidrosis of the axillae**

**Nervous system disorders**
Common: Headache and paraesthesia

**Vascular disorders**
Common: Hot flushes

**Gastrointestinal disorders**
Uncommon: Nausea

**Skin and subcutaneous tissue disorders**
Common: Hyperhidrosis (non-axillary sweating) skin odour abnormal, pruritus, subcutaneous nodule and alopecia

**Musculoskeletal and connective tissue disorders**
Common: Pain in extremity
Uncommon: Muscular weakness, myalgia and arthropathy

**General disorders and administration site conditions**
Common: Injection site pain
Uncommon: Pain, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site irritation, asthenia and injection site reactions

In the management of primary axillary hyperhidrosis, increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

In an uncontrolled safety study of BOTOX (50 Units per axilla) in paediatric patients 12 to 17 years of age (N= 144), adverse reactions occurring in more than a single patient (2 patients each) comprised injection site pain and hyperhidrosis (non-axillary sweating).

**Chronic Migraine**
Nervous system disorders
Common: Headache*, migraine*, facial paresis

Eye disorders
Common: Eyelid ptosis
Uncommon: Eyelid oedema

Skin and subcutaneous tissue disorders
Common: Pruritus, rash
Uncommon: Pain of skin

Musculoskeletal and connective tissue disorders
Common: Neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness
Uncommon: Pain in jaw

General disorders and administration site conditions
Common: Injection site pain

Gastrointestinal disorders
Uncommon: Dysphagia

* In placebo-controlled trials, headache and migraine, including serious cases of intractable or worsening of headache/migraine, were reported more frequently with BOTOX (9%) than with placebo (6%). They typically occurred within the first month after the injections and their incidence declined with repeated treatments.

Overactive bladder

Infections and infestations
Very common: Urinary tract infection
Common: Bacteriuria

Renal and urinary disorders
Very common: Dysuria†
Common: Urinary retention, residual urine volume*, pollakiuria, leukocyturia

*elevated post-void residual urine volume (PVR) not requiring catheterisation
†procedure-related adverse reactions

In the phase 3 clinical trials urinary tract infection was reported in 25.5% of patients treated with BOTOX 100 Units and 9.6% of patients treated with placebo. Urinary retention was reported in 5.8% of patients treated with BOTOX 100 Units and in 0.4% of patients treated with placebo. Clean intermittent catheterisation was initiated in 6.5% of patients following treatment with BOTOX 100 Units versus 0.4% in the placebo group.

Overall, 42.5% of patients (n = 470) were ≥ 65 years of age and 15.1% (n = 167) were ≥ 75 years of age. No overall difference in the safety profile following BOTOX treatment was observed between patients ≥ 65 years compared to patients < 65 years in these studies, with the exception of urinary tract infection where the incidence was higher in elderly patients in both the placebo and BOTOX groups compared to the younger patients.
No change was observed in the overall safety profile with repeat dosing.

*Urinary incontinence due to neurogenic detrusor overactivity*

**Infections and infestations**

Very common: Urinary tract infection

**Psychiatric disorders**

Common: Insomnia†

**Gastrointestinal disorders**

Common: Constipation†

**Musculoskeletal and connective tissue disorders**

Common: Muscular weakness†, muscle spasm

**Renal and urinary disorders**

Very common: Urinary retention

Common: Haematuria*, bladder diverticulum

**General disorders and administration site conditions**

Common: Fatigue†, gait disturbance†

**Injury, poisoning and procedural complications**

Common: Autonomic dysreflexia*, fall†

* procedure-related adverse reactions
† only in multiple sclerosis

In the phase 3 clinical trials, urinary tract infection was reported in 49% of patients treated with BOTOX 200 Units and in 36% of patients treated with placebo (in multiple sclerosis patients: 53% vs. 29%, respectively; in spinal cord injury patients: 45% vs. 42%, respectively). Urinary retention was reported in 17% of patients treated with BOTOX 200 Units and in 3% of patients treated with placebo (in multiple sclerosis patients: 29% vs. 4%, respectively; in spinal cord injury patients: 5% vs. 1%, respectively). Among patients who were not catheterising at baseline prior to treatment, catheterisation was initiated in 39% following treatment with BOTOX 200 Units versus 17% on placebo. The risk of urinary retention increased in patients older than 65 years.

No change in the type and frequency of adverse reactions was observed following 2 treatments.

**Glabellar lines**

**Infections and infestations**

Uncommon: Infection

**Psychiatric disorders**

Uncommon: Anxiety

**Nervous system disorders**

Common: Headache
Uncommon: Paraesthesia, dizziness

Eye disorders
Common: Eyelid ptosis
Uncommon: Blepharitis, eye pain, visual disturbance

Gastrointestinal disorders
Uncommon: Nausea, oral dryness

Skin and subcutaneous tissue disorders
Common: Erythema
Uncommon: Skin tightness, oedema (face, eyelid, periorbital), photosensitivity reaction, pruritus, dry skin

Musculoskeletal and connective tissue disorders
Common: Localised muscle weakness
Uncommon: Muscle twitching

General disorders and administration site conditions
Common: Face pain
Uncommon: Flu syndrome, asthenia, fever

Crow’s Feet Lines

The following adverse drug reactions were reported in the double-blind, placebo-controlled clinical studies following injection of BOTOX 24 Units for crow’s feet lines alone:

Eye disorders
Common: Eyelid oedema

General disorders and administration site conditions
Common: Injection site haemorrhage*, injection site haematoma*
Uncommon: Injection site pain*, injection site paraesthesia

*procedure-related adverse reactions

Crow’s Feet Lines and Glabellar Lines

The following adverse drug reactions were reported in double-blind, placebo-controlled clinical studies following injection of BOTOX 44 Units (simultaneous treatment of crow’s feet lines and glabellar lines):

General disorders and administration site conditions
Common: Injection site haematoma*
Uncommon: Injection site haemorrhage*, injection site pain*

*procedure-related adverse reactions

No change was observed in the overall safety profile following repeat dosing.

c) Additional information
The following list includes adverse drug reactions or other medically relevant adverse events that have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects);

Cardiac disorders
Arrhythmia, myocardial infarction

Ear and labyrinth disorders
Hypoacusis, tinnitus, and vertigo

Eye disorders
Angle-closure glaucoma (for treatment of blepharospasm), strabismus, vision blurred, and visual disturbance

Gastrointestinal disorders
Abdominal pain, diarrhoea, constipation, dry mouth, dysphagia, nausea, and vomiting

General disorders and administration site conditions
Denervation atrophy, malaise, and pyrexia

Immune system disorders
Anaphylaxis, angioedema, serum sickness, and urticaria

Metabolism and nutrition disorders
Anorexia

Musculoskeletal and connective tissue disorders
Muscle atrophy, and myalgia

Nervous system disorders
Brachial plexopathy, dysphonia, dysarthria, facial paresis, hypoesthesia, muscle weakness, myasthenia gravis, peripheral neuropathy, paraesthesia, radiculopathy, seizures, syncope, and facial palsy

Respiratory, thoracic and mediastinal disorders
Aspiration pneumonia (some with fatal outcome), dyspnoea, respiratory depression, and respiratory failure

Skin and subcutaneous tissue disorders
Alopecia, dermatitis psoriasiform, erythema multiforme, hyperhidrosis, madarosis, pruritus, and rash

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from Clostridium botulinum. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.
**Clostridium botulinum** toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.

Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse transmission is by newly formed nerve endings and motor end plates. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

There is limited clinical trial experience of the use of BOTOX in primary axillary hyperhidrosis in adolescents between the ages of 12 and 18. A single, year long, uncontrolled, repeat dose, safety study was conducted in US paediatric patients 12 to 17 years of age (N=144) with severe primary hyperhidrosis of the axillae. Participants were primarily female (86.1%) and Caucasian (82.6%). Participants were treated with a dose of 50 Units per axilla for a total dose of 100 Units per patient per treatment. However, no dose finding studies have been conducted in adolescents so no recommendation on posology can be made. Efficacy and safety of BOTOX in this group have not been established.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitisation, as suggested by pre-clinical and clinical pharmacodynamic studies.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition BOTOX inhibits afferent neurotransmitters and sensory pathways.

**Clinical Data**

**Chronic Migraine**

Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.

During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.

<table>
<thead>
<tr>
<th>Mean change from baseline at Week 24</th>
<th>BOTOX</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache days</td>
<td>-8.4</td>
<td>-6.6</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47%</td>
<td>35%</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Total cumulative hours of headache on headache days</td>
<td>120</td>
<td>80</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>p = 0.009</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8</td>
<td>-2.4</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

**Overactive bladder**

Two double-blind, placebo-controlled, randomised, 24-week phase 3 clinical studies were conducted in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. A total of 1105 patients (mean age of 60 years), whose symptoms had not been adequately managed with at least one anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 Units of BOTOX (n=557), or placebo (n=548), after having discontinued anticholinergics for more than one week.

Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies:
<table>
<thead>
<tr>
<th>Daily Frequency of Urinary Incontinence Episodes</th>
<th>BOTOX 100 Units (N=557)</th>
<th>Placebo (N=548)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Baseline</td>
<td>5.49</td>
<td>5.39</td>
<td></td>
</tr>
<tr>
<td>Mean Change(^{\dagger}) at Week 2</td>
<td>-2.66</td>
<td>-1.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean Change(^{\dagger}) at Week 6</td>
<td>-2.97</td>
<td>-1.13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean Change(^{\dagger}) at Week 12(^{\ast})</td>
<td>-2.74</td>
<td>-0.95</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

| Proportion with Positive Treatment Response using Treatment Benefit Scale (%) |
| Week 2                                    | 64.4                   | 34.7           | < 0.001 |
| Week 6                                    | 68.1                   | 32.8           | < 0.001 |
| Week 12\(^{\ast}\)                       | 61.8                   | 28.0           | < 0.001 |

| Daily Frequency of Micturition Episodes |
| Mean Baseline                            | 11.99                  | 11.48          |         |
| Mean Change\(^{\dagger}\) at Week 12\(^{\ast}\) | -2.19                  | -0.82          | < 0.001 |

| Daily Frequency of Urgency Episodes |
| Mean Baseline                         | 8.82                   | 8.31           |         |
| Mean Change\(^{\dagger}\) at Week 12\(^{\ast}\) | -3.08                  | -1.12          | < 0.001 |

| Incontinence Quality of Life Total Score |
| Mean Baseline                           | 34.1                   | 34.7           |         |
| Mean Change\(^{\dagger}\) at Week 12\(^{\ast}\) | +21.3                  | +5.4           | < 0.001 |

| King’s Health Questionnaire: Role Limitation |
| Mean Baseline                               | 65.4                   | 61.2           |         |
| Mean Change\(^{\dagger}\) at Week 12\(^{\ast}\) | -24.3                  | -3.9           | < 0.001 |

| King’s Health Questionnaire: Social Limitation |
| Mean Baseline                                 | 44.8                   | 42.4           |         |
| Mean Change\(^{\dagger}\) at Week 12\(^{\ast}\) | -16.1                  | -2.5           | < 0.001 |

| Percentage of patients achieving full continence at Week 12 (dry patients over a 3-day diary) |
| 27.1%                                      | 8.4%                   | < 0.001       |

* Percentage of patients who achieved at least a 75% and 50% reduction from baseline in urinary incontinence episodes were 46.0% and 60.5% in the BOTOX group compared to 17.7% and 31.0% in the placebo group, respectively.

\(^{\dagger}\) Least Squares (LS) mean changes are presented

\(^{\ast}\) Co-primary endpoints

\(^{\ast}\) Secondary endpoints

\(^{\dagger}\) Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

The median duration of response following BOTOX treatment, based on patient request for re-treatment, was 166 days (~24 weeks).

A total of 839 patients were evaluated in a long-term open-label extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments. The mean reductions from baseline in daily frequency of urinary incontinence were -3.07 (N=341), -3.49
(N=292), and -3.49 (N=204) episodes at week 12 after the first, second, and third BOTOX 100 Unit treatments, respectively. The corresponding proportions of patients with a positive treatment response on the Treatment Benefit Scale were 63.6% (N=346), 76.9% (N=295), and 77.3% (N=207), respectively.

In the pivotal studies, none of the 615 patients with analysed serum specimens developed neutralising antibodies after 1 – 3 treatments.

**Urinary incontinence due to neurogenic detrusor overactivity**

Two double-blind, placebo-controlled, randomised phase 3 clinical studies were conducted in a total of 691 patients with spinal cord injury or multiple sclerosis, who were not adequately managed with at least one anticholinergic agent and were either spontaneously voiding or using catheterisation. These patients were randomised to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

**Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies:**

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units (N=227)</th>
<th>Placebo (N=241)</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary Incontinence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.4</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 2</td>
<td>-16.8</td>
<td>-9.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change† at Week 6a</td>
<td>-20.0</td>
<td>-10.5</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change† at Week 12</td>
<td>-19.8</td>
<td>-9.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>250.2</td>
<td>253.5</td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 6b</td>
<td>+140.4</td>
<td>+6.9</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH20)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>51.5</td>
<td>47.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change† at Week 6b</td>
<td>-27.1</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td><strong>Incontinence Quality of Life Total Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>35.4</td>
<td>35.3</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change† at Week 6b</td>
<td>+23.6</td>
<td>+8.9</td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 12</td>
<td>+26.9</td>
<td>+7.1</td>
<td></td>
</tr>
<tr>
<td>Percentage of patients achieving full continence at Week 6 (dry patients over a 7 day diary)*</td>
<td>37%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

*The percentage of patients achieving at least a 75% reduction from baseline, in incontinence episodes, was 63% for the BOTOX 200 Unit group and 24% for the placebo group. The percentages achieving at least a 50% reduction from baseline were 76% and 39% respectively.

† LS mean changes are presented

a Primary endpoint

b Secondary endpoints

c I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

d In the pivotal studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

The median duration of response (time to < 50% reduction in incontinence episodes) was 42 weeks in the 200 Unit dose group.

For all efficacy endpoints in the pivotal phase 3 studies, patients experienced consistent response with re-treatment (N=116).
None of the 475 patients with analysed serum specimens developed neutralising antibodies after 1-2 treatments.

In the multiple sclerosis (MS) patients enrolled in the pivotal studies, the MS exacerbation annualised rate (i.e., number of MS exacerbation events per patient year) was 0.23 in the 200 Unit dose group and 0.20 in the placebo group. With repeated BOTOX treatments, including data from a long term study, the MS exacerbation annualised rate was 0.19 during each of the first two BOTOX treatment cycles.

Glabellar Lines
357 patients with moderate to severe vertical lines between the eyebrows (glabellar lines) seen at maximum frown have been included in clinical studies.

BOTOX injections significantly reduced the severity of glabellar lines seen at maximum frown for up to 4 months, as measured by the investigator assessment of glabellar line severity at maximum frown and by subject’s global assessment of change in appearance of his/her vertical lines between the eyebrows (glabellar lines) seen at maximum frown. None of the clinical endpoints included an objective evaluation of the psychological impact. Thirty days after injection, 80% (325/405) of BOTOX-treated patients were considered by investigators as treatment responders (none or mild severity at maximum frown), compared to 3% (4/132) of placebo-treated patients. At this same timepoint, 89% (362/405) of BOTOX-treated patients felt they had a moderate or better improvement, compared to 7% (9/132) of placebo-treated patients.

BOTOX injections also significantly reduced the severity of glabellar lines at rest. Of the 357 patients enrolled, 39% (210/537) had moderate to severe glabellar lines at rest (15% had no lines at rest). Of these, 74% (119/161) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 20% (10/49) of placebo-treated patients.

There is limited phase 3 clinical data with BOTOX in patients older than 65 years. Only 6.0% (32/537) of subjects were >65 years old and efficacy results obtained were lower in this population.

Crow’s Feet Lines
1362 patients with moderate to severe crow’s feet lines seen at maximum smile, either alone (N=445, Study 191622-098) or also with moderate to severe glabellar lines seen at maximum frown (N=917, Study 191622-099), were enrolled.

BOTOX injections significantly reduced the severity of crow’s feet lines seen at maximum smile compared to placebo at all timepoints (p <0.001) for up to 5 months. This was measured by the proportion of patients achieving a crow’s feet lines severity rating of none or mild at maximum smile in both pivotal studies; until day 150 (end of study) in Study 191622-098 and day 120 (end of first treatment cycle) in Study 191622-099. For both investigator and subject assessments, the proportion of subjects achieving none or mild crow’s feet lines severity seen at maximum smile was greater in patients with moderate crow’s feet lines seen at maximum smile at baseline, compared to patients with severe crow’s feet lines seen at maximum smile at baseline. Table 1 summarises results at day 30, the timepoint of the primary efficacy endpoint.

In Study 191622-104 (extension to Study 191622-099), 101 patients previously randomised to placebo were enrolled to receive their first treatment at the 44 Units dose. Patients treated
with BOTOX had a statistically significant benefit in the primary efficacy endpoint compared to placebo at day 30 following their first active treatment. The response rate was similar to the 44 Units group at day 30 following first treatment in Study 191622-099. A total of 123 patients received 4 cycles of 44 Units BOTOX for combined crow’s feet and glabellar lines treatment.

Table 1. Day 30: Investigator and Patient Assessment of Crow’s Feet Lines Seen at Maximum Smile - Responder Rates (% of Patients Achieving Crow’s Feet Lines Severity Rating of None or Mild)

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Dose (crow’s feet lines)</th>
<th>Dose (crow’s feet lines)</th>
<th>Investigator Assessment</th>
<th>Patient Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>191622-098</td>
<td>24 Units</td>
<td>44 Units (24 Units crow’s feet lines; 20 Units glabellar lines)</td>
<td>66.7%* (148/222)</td>
<td>58.1%* (129/222)</td>
</tr>
<tr>
<td>191622-099</td>
<td>24 Units</td>
<td>44 Units (24 Units crow’s feet lines)</td>
<td>54.9%* (168/306)</td>
<td>45.8%* (140/306)</td>
</tr>
<tr>
<td>191622-099</td>
<td>24 Units</td>
<td>44 Units (24 Units crow’s feet lines)</td>
<td>59.0%* (180/305)</td>
<td>48.5%* (148/305)</td>
</tr>
<tr>
<td>191622-099</td>
<td>24 Units</td>
<td>44 Units (24 Units crow’s feet lines)</td>
<td>54.9%* (168/306)</td>
<td>45.8%* (140/306)</td>
</tr>
<tr>
<td>191622-099</td>
<td>24 Units</td>
<td>44 Units (24 Units crow’s feet lines)</td>
<td>59.0%* (180/305)</td>
<td>48.5%* (148/305)</td>
</tr>
</tbody>
</table>

*p < 0.001 (BOTOX vs placebo)

Improvements from baseline in subject-assessment of the appearance of crow’s feet lines seen at maximum smile were seen for BOTOX (24 Units and 44 Units) compared to placebo, at day 30 and at all timepoints following each treatment cycle in both pivotal studies (p<0.001).

Treatment with BOTOX 24 Units also significantly reduced the severity of crow’s feet lines at rest. Of the 528 patients treated, 63% (330/528) had moderate to severe crow’s feet lines at rest at baseline. Of these, 58% (192/330) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 11% (39/352) of placebo-treated patients.

Improvements in subject’s self-assessment of age and attractiveness were also seen for BOTOX (24 Units and 44 Units) compared to placebo using the Facial Line Outcomes (FLO-11) questionnaire, at the primary timepoint of day 30 (p<0.001) and at all subsequent timepoints in both pivotal studies.

In the pivotal studies, 3.9% (53/1362) of patients were older than 65 years of age. Patients in this age group had a treatment response as assessed by the investigator, of 36% (at day 30) for BOTOX (24 Units and 44 Units). When analysed by age groups of ≤50 years and >50 years, both populations demonstrated statistically significant improvements compared to placebo. Treatment response for BOTOX 24 Units, as assessed by the investigator, was lower in the group of subjects >50 years of age than those ≤50 years of age (42.0% and 71.2%, respectively).

Overall BOTOX treatment response for crow’s feet lines seen at maximum smile is lower (60%) than that observed with treatment for glabellar lines seen at maximum frown (80%).
916 patients (517 patients at 24 Units and 399 patients at 44 Units) treated with BOTOX had specimens analysed for antibody formation. No patients developed the presence of neutralising antibodies.
**Botox 50, 100 and 200 Allergan units — powder for solution for injection**

<table>
<thead>
<tr>
<th>Section</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. WHAT BOTOX IS AND WHAT IT IS USED FOR</strong></td>
<td>Botox is a neurotoxin solution that is injected into muscles to reduce the activity of those muscles. It is used to treat conditions such as migraines, muscle spasms, and other disorders.</td>
</tr>
</tbody>
</table>

**What is Botox?**

Botox is a neurotoxin solution that is injected into muscles to reduce the activity of those muscles. It is used to treat conditions such as migraines, muscle spasms, and other disorders. It works by blocking the release of a chemical that causes muscle contractions, thereby reducing the activity of the muscle it is injected into.

**How is Botox used for?**

Botox is used for various medical conditions, including:

- **Migraines:** To reduce the frequency and severity of migraines.
- **Muscle spasms:** To treat spasticity caused by disorders such as cerebral palsy.
- **Excessive sweating:** To reduce underarm sweating.
- **Other conditions:** Botox may also be used to treat conditions such as blepharospasm, eyelid twitching, and strabismus.

**Before you use Botox**

- **Consult your doctor:** Before using Botox, you should consult your doctor to ensure it is the right treatment for your condition.
- **Tell your doctor:** You should tell your doctor about any other medications you are taking, any allergies you have, and any medical conditions you have.
- **Ask your doctor:** Your doctor may perform a physical examination and ask about your medical history before giving you Botox.

**How to use Botox**

Botox is typically administered by injection. The injection site is usually on the head, neck, or shoulder area. The injection is usually given by a healthcare professional, such as a doctor or nurse.

**What is the expected effect of Botox?**

The expected effect of Botox is to reduce the activity of the muscles it is injected into. This can result in the improvement of certain symptoms, such as headache frequency, muscle spasm, or excessive sweating.

**Duration of effect**

The duration of effect of Botox can vary depending on the condition being treated. In general, the effects of Botox last for 3 to 6 months.

**What is the cost of Botox?**

The cost of Botox can vary depending on the treatment area and the number of units injected. In general, Botox is a costly treatment, but it can provide significant relief for certain conditions.

**Side effects**

The most common side effects of Botox include:

- **Reddening at the injection site**
- **Swelling or bruising**
- **Headache**
- **Nausea or vomiting**

**Precautions**

Before using Botox, you should tell your doctor about any medical conditions you have, any medications you are taking, and any allergies you have. You should also inform your doctor if you have a history of bleeding disorders or if you have had any previous allergic reactions to Botox.
The safety and effectiveness of BOTOX in the treatment of chronic migraines have not been studied in children (under 18 years).

The safety and effectiveness of BOTOX in the treatment of vertical lines between the eyes and/or fan-shaped lines from the corner of the eyes in individuals under 18 years of age have not been established and such use is not recommended.

The safety and effectiveness of BOTOX in the treatment of excessive sweating of the hands and/or feet, armpits, and underarms have not been established in children under 18 years of age.

There is limited experience of using BOTOX in the treatment of vertical and/or fan-shaped lines in patients older than 85 years.

For persistent muscle spasms of the eyelid and face: dosage

In the first treatment session, your doctor may give multiple injections in the affected muscles with 1.25 to 2.5 Units of BOTOX at each injection site. The maximum dose for the first treatment session is 250 Units of BOTOX in 10 injection sites. Following the first treatment session, the total treatment dose can be increased up to 500 Units if needed.

Duration of treatment effect

The maximum effect usually occurs in 1 to 2 weeks after the injection. When the effect starts to wear off, you may consider a further treatment.

For persistent muscle spasms of the neck and shoulders: dosage

Your doctor may give multiple injections in the affected muscles with up to 50 Units of BOTOX at each injection site. The maximum dose for the first treatment session is 200 Units of BOTOX in 10 injection sites. Following the first treatment session, the total treatment dose can be increased up to 500 Units if needed.

Duration of treatment effect

The maximum effect usually occurs in 1 to 2 weeks after the injection. When the effect starts to wear off, you may consider a further treatment.

For excessive sweating of the armpits:

Your doctor may give multiple injections in a total of 50 Units of BOTOX at each injection site. The maximum dose for the first treatment session is 100 Units of BOTOX in 10 injection sites. Following the first treatment session, the total treatment dose can be increased up to 200 Units if needed.

Duration of treatment effect

The maximum effect usually occurs in 1 to 2 weeks after the injection. When the effect starts to wear off, you may consider a further treatment.

For persistent muscle spasms in the legs of children who have cerebral palsy:

Your doctor may give multiple injections in the affected muscles. The dosage will depend upon the size of your child.

Duration of treatment effect

The improvement usually appears within the first 2 weeks after the injection. When the effect starts to wear off, further treatment is possible but not more often than every 12 weeks.

For the prevention of headache in adults who have chronic migraine:

Your doctor may give multiple injections (between 25 and 90) in 2 muscle groups of the face, head, neck and shoulders, with up to 5 Units of BOTOX into each injection site. Injections are administered across muscles in your forehead, your temples on the side of your head, the back of your upper neck, and your shoulders. The injections are given to the left and right side of these head and neck muscles. Within 7 days after injection, you may notice an area given to the muscle that is between your eyebrows.

The total dose range is between 125 Units and 195 Units per treatment session.

Duration of treatment effect

When the effect starts to wear off, further treatment is possible but not more often than every 12 weeks.

For overactive bladder with leakage of urine: dosage

Your doctor will give multiple injections into the bladder wall. The total dose is up to 100 Units of BOTOX.

Your doctor will give you antibiotics around the time of the injection to help prevent urinary tract infection. The injection will be administered by a procedure called cystoscopy. An instrument with a light at the end will be inserted into your bladder through the opening by which you let out the urine (the urethra). The needle will be inserted into the bladder wall the injections into the bladder wall will be made. Please ask your doctor to explain further details of the procedure to you.

You may be given a total anesthetic before the injection so that your bladder will be filled with anesthetic solution for a while and then drained. You will be observed for at least 30 minutes after the injection because if you can use some0nemale's health.

If you were using a catheter (as soft, hollow tube that is inserted into your bladder to help empty urine from the bladder) before treatment with BOTOX, you should be seen by your doctor at least 1 week after treatment.

Your doctor may also give you a urinary catheter (as soft, hollow tube that is inserted into your urethra to help empty urine from the bladder). BOTOX treatment will not be used to relieve an infection or a catheter is required to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.

You must contact your doctor for a urine sample because your only available for use in the treatment of an infection or to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.

You must contact your doctor for a urine sample because your only available for use in the treatment of an infection or to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.

Your doctor will give you antibiotics around the time of the injection to help prevent urinary tract infection. The injection will be administered by a procedure called cystoscopy. An instrument with a light at the end will be inserted into your bladder through the opening by which you let out the urine (the urethra). The needle will be inserted into the bladder wall the injections into the bladder wall will be made. Please ask your doctor to explain further details of the procedure to you.

You may be given a total anesthetic before the injection so that your bladder will be filled with anesthetic solution for a while and then drained. You will be observed for at least 30 minutes after the injection because if you can use some0nEMALE's health.

If you were using a catheter (as soft, hollow tube that is inserted into your bladder to help empty urine from the bladder) before treatment with BOTOX, you should be seen by your doctor at least 1 week after treatment.

Your doctor may also give you a urinary catheter (as soft, hollow tube that is inserted into your urethra to help empty urine from the bladder). BOTOX treatment will not be used to relieve an infection or a catheter is required to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.

Your doctor will give you antibiotics around the time of the injection to help prevent urinary tract infection. The injection will be administered by a procedure called cystoscopy. An instrument with a light at the end will be inserted into your bladder through the opening by which you let out the urine (the urethra). The needle will be inserted into the bladder wall the injections into the bladder wall will be made. Please ask your doctor to explain further details of the procedure to you.

You may be given a total anesthetic before the injection so that your bladder will be filled with anesthetic solution for a while and then drained. You will be observed for at least 30 minutes after the injection because if you can use some0nEMALE's health.

If you were using a catheter (as soft, hollow tube that is inserted into your bladder to help empty urine from the bladder) before treatment with BOTOX, you should be seen by your doctor at least 1 week after treatment.

Your doctor may also give you a urinary catheter (as soft, hollow tube that is inserted into your urethra to help empty urine from the bladder). BOTOX treatment will not be used to relieve an infection or a catheter is required to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.

Your doctor will give you antibiotics around the time of the injection to help prevent urinary tract infection. The injection will be administered by a procedure called cystoscopy. An instrument with a light at the end will be inserted into your bladder through the opening by which you let out the urine (the urethra). The needle will be inserted into the bladder wall the injections into the bladder wall will be made. Please ask your doctor to explain further details of the procedure to you.

You may be given a total anesthetic before the injection so that your bladder will be filled with anesthetic solution for a while and then drained. You will be observed for at least 30 minutes after the injection because if you can use some0nEMALE's health.

If you were using a catheter (as soft, hollow tube that is inserted into your bladder to help empty urine from the bladder) before treatment with BOTOX, you should be seen by your doctor at least 1 week after treatment.

Your doctor may also give you a urinary catheter (as soft, hollow tube that is inserted into your urethra to help empty urine from the bladder). BOTOX treatment will not be used to relieve an infection or a catheter is required to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.

Your doctor will give you antibiotics around the time of the injection to help prevent urinary tract infection. The injection will be administered by a procedure called cystoscopy. An instrument with a light at the end will be inserted into your bladder through the opening by which you let out the urine (the urethra). The needle will be inserted into the bladder wall the injections into the bladder wall will be made. Please ask your doctor to explain further details of the procedure to you.

You may be given a total anesthetic before the injection so that your bladder will be filled with anesthetic solution for a while and then drained. You will be observed for at least 30 minutes after the injection because if you can use some0nEMALE's health.

If you were using a catheter (as soft, hollow tube that is inserted into your bladder to help empty urine from the bladder) before treatment with BOTOX, you should be seen by your doctor at least 1 week after treatment.

Your doctor may also give you a urinary catheter (as soft, hollow tube that is inserted into your urethra to help empty urine from the bladder). BOTOX treatment will not be used to relieve an infection or a catheter is required to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.

Your doctor will give you antibiotics around the time of the injection to help prevent urinary tract infection. The injection will be administered by a procedure called cystoscopy. An instrument with a light at the end will be inserted into your bladder through the opening by which you let out the urine (the urethra). The needle will be inserted into the bladder wall the injections into the bladder wall will be made. Please ask your doctor to explain further details of the procedure to you.

You may be given a total anesthetic before the injection so that your bladder will be filled with anesthetic solution for a while and then drained. You will be observed for at least 30 minutes after the injection because if you can use some0nEMALE's health.

If you were using a catheter (as soft, hollow tube that is inserted into your bladder to help empty urine from the bladder) before treatment with BOTOX, you should be seen by your doctor at least 1 week after treatment.

Your doctor may also give you a urinary catheter (as soft, hollow tube that is inserted into your urethra to help empty urine from the bladder). BOTOX treatment will not be used to relieve an infection or a catheter is required to empty your bladder. Your doctor will decide if and when you need to return for the same treatment.
4. POSSIBLE SIDE EFFECTS

<table>
<thead>
<tr>
<th>Possible Side Effects</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Dizziness</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Difficult to eat</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Difficulty in swallowing</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Headaches</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Infections in the neck and shoulder</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Nervousness</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Dizziness</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Dry skin</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Difficulty in breathing</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Chest pain</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Fast heartbeat</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Trouble in sleeping</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>common</td>
<td>uncommon</td>
<td>rare</td>
<td>very rare</td>
</tr>
</tbody>
</table>

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Injections in the legs of children with cerebral palsy

- Nervousness
- Muscle weakness
- Difficulty in breathing
- Chest pain
- Fast heartbeat
- Trouble in sleeping
- Muscle weakness

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the forehead for vertical lines**

- **Common side effects are:**
  - headache
  - drooping eyelid
  - skin redness
  - increased muscle weakness
  - numbness
  - dryness
  - eye pain
  - visual disturbance
  - muscle twitching
  - eye closure difficulty

- **Uncommon side effects are:**
  - increased pain or tenderness
  - increased muscle weakness
  - dryness
  - eye pain
  - visual disturbance
  - muscle twitching
  - eye closure difficulty

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the fan-shaped lines from the corner of the eyes**

- **Common side effects are:**
  - sagging of the eyelid
  - eye pain
  - vision changes
  - eye twitching
  - eye pain
  - visual disturbance

- **Uncommon side effects are:**
  - increased pain or tenderness
  - increased muscle weakness
  - dryness
  - eye pain
  - visual disturbance
  - muscle twitching
  - eye closure difficulty

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Injections in the fan-shaped lines from the corner of the eyes, when treated at the same time as injections in the forehead for vertical lines**

- **Common side effects are:**
  - injection site bleeding
  - injection site pain

- **Uncommon side effects are:**
  - injection site bleeding
  - injection site pain

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**General information about other side effects**

Side effects related to the spread of BOTOX far away from the site of injection have been reported very rarely and include:

- muscle weakness
- muscle weakness
- muscle weakness
- muscle weakness
- muscle weakness
- muscle weakness
- muscle weakness
- muscle weakness
- muscle weakness
- muscle weakness

**Difficulties in swallowing**

Food or liquid accidentally going into the lungs which in some cases may lead to pneumonia.

**The difficulty in swallowing may range from mild to severe and in some cases you may need treatment. In rare cases, people have died because of swallowing difficulties.**

**Side effects affecting the heart have been rarely reported:**

- irregular heartbeat
- heart attack

Some of these people were healthy. However, some of these patients were already suffering from serious or immediate allergic reactions have been rarely reported.

- nausea
- breathing difficulty following the injection or throat or chest

**6. FURTHER INFORMATION**

**What BOTOX contains:**

- The active substance is: Botulinum toxin type A from Clostridium botulinum.
- The other ingredients are: sodium chloride and disodium edetate.

**What BOTOX looks like and contains:**

- BOTOX is supplied as a white powder in vials. Prior to injection, the product must be reconstituted in the vial contents.
- Each vial contains 50, 100 or 200 units of Botulinum toxin type A.
- Each pack contains 1, 2, 3 or 6 vials. Pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

- Allergan plc, Dublin 4, Ireland
- **PL 00426/0074, PLIs 00426/0118–0119**
**The following information is intended for medical or healthcare professionals only:**

Please refer to the Summary of Product Characteristics for complete prescribing information for BOTOX.

**Foral indications:**
Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported since 1990. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exagerrated muscle weakness.

**Pneumonitis associated with injection procedure has been reported following administration of BOTOX near the hronks. Caution is advised when injecting in proximity to the lung, particularly the apices.**

Serious adverse events including fatal outcomes have been reported in patients who have received off-label injections of BOTOX directly into the subcutaneous tissue, preauricular, submental, the oropharyngeal region, oesophagus and/or stomach. Some patients had pre-existing dysphagia or significant debility.

**Reconstitution of the medicinal product:**
It is good practice to perform viral reconstitution and syringe preparation over plastic-based paper towels to catch any spillage.

Reconstitute BOTOX only with sterile unpreserved normal saline (0.9% sodium chloride for injection). Draw up an appropriate amount of diluent (see dilution table or instructions below) into a syringe.

**Dilution table for BOTOX 50, 100 and 200 Allergan units vials:**

<table>
<thead>
<tr>
<th>Resulting dose (Units per 0.1 ml)</th>
<th>Amount of diluent (sodium chloride 9 mg/ml (60% solution for injection) added in a 50 unit vial)</th>
<th>Amount of diluent (sodium chloride 9 mg/ml (60% solution for injection) added in a 100 unit vial)</th>
<th>Amount of diluent (sodium chloride 9 mg/ml (60% solution for injection) added in a 200 unit vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 Units</td>
<td>0.25 ml</td>
<td>0.5 ml</td>
<td>N/A</td>
</tr>
<tr>
<td>10 Units</td>
<td>0.5 ml</td>
<td>1 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>5 Units</td>
<td>1 ml</td>
<td>2 ml</td>
<td>4 ml</td>
</tr>
<tr>
<td>4 Units</td>
<td>1.25 ml</td>
<td>2.5 ml</td>
<td>5 ml</td>
</tr>
<tr>
<td>2.5 Units</td>
<td>2 ml</td>
<td>4 ml</td>
<td>8 ml</td>
</tr>
<tr>
<td>1.25 Units</td>
<td>4 ml</td>
<td>8 ml</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Three BOTOX is denatured by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colorless to slightly yellow solution free of particulate matter. The reconstituted solution should be visually inspected for clarity and absence of particles prior to use. When reconstituted in the vial, BOTOX may be stored in a refrigerator (2°C – 8°C) for up to 24 hours prior to use.

From a microbiological point of view, the product should be used immediately if not used immediately, its-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

**Dilution instructions for treatment of urinary incontinence due to overactive bladder:**
It is recommended that a 100 Unit or two 50 Unit vials are used for convenience of reconstitution.

Or, reconstitute a 100 Unit vial of BOTOX with 10 ml of 0.9% non-preserved saline solution and mix gently. Draw the saline from the vial into a 10 ml syringe. Complete the reconstitution by adding 6 ml of 0.9% non-preserved saline solution into the 10 ml syringe and mix gently. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Or, reconstitute two 50 Unit vials of BOTOX each with 5 ml of 0.9% non-preserved saline solution and mix gently. Draw the saline from each vial into a single 10 ml syringe. This will result in a single 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

**Procedure to follow for safe disposal of vials, syringes and materials used:**
For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any used vials, syringes, and spillages etc should be autoclaved, or the diluent BOTOX inactivated using dilute hypochlorite solution (0.9%) for 5 minutes.

**Identification of the product:**
In order to verify receipt of actual BOTOX product from Allergan, look for a holographic film on the vial label. In order to see the film, examine the vial under a desk lamp or fluorescent light source. Rotating the vial back and forth between your fingers, look for no linear lines of rainbow colour on the label and confirm that the name “Allergan” appears within the rainbow lines. Note that the film on the label is absent in the Expolot Lot Number area. If you do not see the rainbow lines or the name “Allergan” does not appear, do not use the product and contact your local Allergan office for additional information.

**ALLERGAN®**

Botox 50, 100 and 200 Allergan units – powder for solution for injection
Annex 3

Our Reference: PL 00426/0074–0148
Product: PL 00426/0074 BOTOX
Marketing Authorisation Holder: ALLERGAN LIMITED

Reason:
To add an indication for focal spasticity, including the treatment of “ankle disability due to lower limb spasticity associated with stroke in adults” to the product licence. As a consequence, section 4.1 (therapeutic indications) of the SPC has been updated.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 141513 and covers the following submissions PL 00426/0118–0070, PL 00426/0119–0056.

Supporting Evidence
Updated SPC fragments 4.1, 4.2, 4.4, 4.8, 5.1, 10.
Dossier documentation: m1.0, m1.1, m1.2, m1.3, m1.4, m1.6, m1.8, m1.9, m1.10, m2.2, m2.5, m2.7, m5.2, m5.3, m5.4.

Evaluation
Scope of the variation
The scope of this type II variation is the extension to a new indication for BOTOX, the treatment of “ankle disability due to lower limb spasticity associated with stroke in adults”.

Other changes to the SmPC related to this variation concern section 4.2 (Posology and method of administration), section 4.4 (Special warnings and precautions for use), section 4.8 (Undesirable effects), and 5.1 (Pharmacodynamic properties).
The PIL has been revised accordingly.

PIP
BOTOX® was first approved in Europe in 1992. It is not protected by a Supplementary Protection Certificate (SPC) or a patent which qualifies for the granting of the SPC. As such, the product does not fall within the scope of Article 8 of the Paediatric Regulation.

BOTOX is already approved in children for focal spasticity (dynamic equinus foot deformity) related to cerebral palsy. Two clinical studies are ongoing in the US in this indication in compliance with FDA’s Pediatric Research Equity Act (PREA) requirements (Studies 191622-111, 191622-112).

SCIENTIFIC DISCUSSION

Background information
Spasticity is a chronic manifestation of an upper motor neuron lesion involving the motor cortex and efferent pathways. The lesion can be a result of acute injuries to the central nervous system (CNS), such as stroke, sudden head trauma, spinal cord injury, or chronic neurological disorders such as cerebral palsy and multiple sclerosis. Spasticity can present in the lower limb (eg, foot with equinus deformity of the ankle or abnormal postures of the knee, hip, and toe) and/or upper limb (fingers, wrist, elbow, and shoulder deformities).

Population prevalence along with rates and degree of spasticity vary by the underlying etiology; however, stroke is the most common source of spasticity in adults. It has been estimated in four separate studies among European populations that up to 40% of post-stroke patients will develop some degree of spasticity. Approximately 80% of post-stroke spasticity patients have involvement of any lower limb muscle and approximately 66% of post-stroke patients with spasticity have involvement of the ankle joint muscles, which is the most commonly affected muscle group in the lower limb.
In the lower limb, spasticity leads to decreased mobility and compromised balance from clinical patterns of dysfunction due to the equinus foot deformity, stiff knee, excessive hip flexion, and adducted thighs. The combination of poor balance and low ability to perform motor functions leads to impaired gait function that necessitates ambulatory assistance and dependence with motor functional activities. Pain is also a significant symptomatic issue that commonly occurs concurrently with spasticity. In the lower limb, persistent extension of extremities is associated with pain during the stance phase of gait in addition to pain while walking. In addition to the clinical impact, spasticity as a whole has been found to negatively affect self-perceived function and health-related quality of life in post-stroke patients. One study revealed a low baseline self-perception of physical functioning in a population of spastic patients. Pain associated with increased muscle tone has also been found to have a significant detrimental effect on quality of life.

**Current Treatment Options**

Spasticity is rarely managed optimally by a single therapeutic modality, and treatment can include a combination of:

- pharmacologic antispastic systemic agents, including baclofen (oral and intrathecal pump), dantrolene sodium (oral), diazepam (oral), and tizanidine (oral);
- local neuromuscular blocks, using local anesthetics (eg, lidocaine, bupivicaine, and etidiocaine) or chemoneurometics (ethyl alcohol, phenol);
- surgical interventions, including orthopedic (eg, hip replacement, contracture release, tendon lengthening, and tendon transfer) and neurosurgical procedures;
- physical therapy, orthotics.

A focal treatment with a favorable safety profile and targeted efficacy would represent a significant advance over currently available options for patients with lower limb spasticity. The benefit for such a focal treatment has already been demonstrated for post-stroke spasticity associated with the upper limb (wrist and hand), as well as for the lower limb in the pediatric population with cerebral palsy (dynamic equinus foot deformity), both of which are currently approved indications of BOTOX in many European countries.

The 2010 International Consensus Statement for lower limb disorders of movement and muscle tone in adults assigned a Grade A (according to American Academy of Neurology evidence classification) to the evidence of the effectiveness of botulinum toxin A to: “Reduce lower limb spasticity in adults with acquired brain injury, increase passive range of motion in the lower limb in adults with spasticity, reduce pain associated with lower limb spasticity in adults, reduce the need for bracing in adults with lower limb spasticity” (Olver et al, 2010).

**Clinical efficacy**

A total of eight studies have been conducted to evaluate BOTOX for the treatment of adult lower limb spasticity: six phase 2 studies, one phase 3 study, and one health economic study, as shown hereafter.

All studies were conducted in compliance with Good Clinical Practice (GCP) regulations and guidelines. The studies involved 700 unique patients with lower limb spasticity, 625 of whom were treated with BOTOX at a mean dose of 295.5 U in the lower limb; some of these patients also received concurrent treatment in the upper limb.
Tabulated summary of the studies

<table>
<thead>
<tr>
<th>Study ID (Region)</th>
<th>Design</th>
<th>Treatment Groups (No. of Patients)</th>
<th>Muscles Injected</th>
<th>No. of Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 2 Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| BTOX-138/139-8051 (US) | Multicenter, double-blind, randomized (exploratory study) | BOTOX \( \sim 4 \, \text{U/kg} \pm 1 \, \text{U/kg} \) \( N = 33 \)  
BOTOX \( \sim 2 \, \text{U/kg} \pm 1 \, \text{U/kg} \) \( N = 36 \)  
placebo \( N = 27 \) | Medial and lateral gastrocnemius ± anterior or posterior tibialis | Up to 2<sup>a</sup> |
| 191622-501 (Europe) | Multicenter, double-blind, randomized (exploratory study) | BOTOX \( \sim 4 \, \text{U/kg} \pm 1 \, \text{U/kg} \) \( N = 45 \)  
BOTOX \( \sim 2 \, \text{U/kg} \pm 1 \, \text{U/kg} \) \( N = 45 \)  
placebo \( N = 41 \) | Medial and lateral gastrocnemius ± anterior or posterior tibialis | 1 |
| 191622-502 (Europe) | Multicenter, double-blind, extension, randomized<sup>b</sup> (exploratory study) | BOTOX \( \sim 4 \, \text{U/kg} \pm 1 \, \text{U/kg} \) \( N = 48 \)  
BOTOX \( \sim 2 \, \text{U/kg} \pm 1 \, \text{U/kg} \) \( N = 43 \) | Medial and lateral gastrocnemius ± anterior or posterior tibialis | 1 |
| BTOX-702-8051 (Australia) | Part I: multicenter, double-blind, randomized  
Part II: multicenter, open-label (supportive study) | Part I: BOTOX 300 U \( N = 28 \)  
BOTOX 200 U \( N = 28 \)  
placebo 300/200 \( N = 15/14 \)  
Part II: BOTOX/BOTOX<sup>c</sup> \( N = 44 \)  
placebo/BOTOX<sup>c</sup> \( N = 26 \) | Posterior tibialis, soleus, and either flexor digitorum longus or medial gastrocnemius | Part I: 1  
Part II: 1 |
| 191622-030 (US) | Multicenter, double-blind, randomized (exploratory study) | BOTOX 360 U \( N = 37 \)  
BOTOX 240 U \( N = 36 \)  
placebo \( N = 36 \) | Up to 6 muscles of upper and/or lower limb<sup>d</sup> | Up to 2 |
| 191622-911 (Japan) | Multicenter, open-label, step-wise (exploratory study) | BOTOX 75 U ± 25 U \( N = 7 \)  
BOTOX 150 U ± 50 U \( N = 7 \)  
BOTOX 225 U ± 75 U \( N = 6 \) | Gastrocnemius and soleus ± posterior tibialis if talipes varus | 1 |
| **Phase 3 Study** |
| BTX108512 (Japan) | Part I: multicenter, double-blind, randomized  
Part II: multicenter, open-label (primary efficacy study) | Part I: BOTOX 300 U \( N = 58 \)  
placebo \( N = 62 \)  
Part II: BOTOX 300 U/300 U \( N = 52 \)  
placebo/BOTOX 300 U \( N = 60 \) | Medial and lateral gastrocnemius, soleus and posterior tibialis | Part I: 1  
Part II: up to 3 |
**Study ID (Region)** | **Design** | **Treatment Groups (No. of Patients)** | **Muscles Injected** | **No. of Treatments**  
--- | --- | --- | --- | ---  
AGN/HO/SPA/001-191622 (Europe & Canada) | Part I: multicenter, double-blind, randomized  
Part II: multicenter, open-label (supportive study) | Part I: BOTOX® plus standard care (N = 139) placebo plus standard care (N = 135)  
Part II: BOTOX®/BOTOX® plus standard care (N = 113) placebo/BOTOX® plus standard care (N = 112) | Muscles of upper and/or lower limb | Part I: up to 2  
Part II: up to 4

~ = approximately, ± = optional dose and muscle (see Error! Reference source not found. for details)

a Patients could receive a second injection at either week 12 or 18 (same as initial injection) and those with a varus component of foot position could receive a supplementary injection (approximately 1.0 U/kg) into the anterior or posterior tibialis.

b Patients who received placebo in Study 191622-501 were randomized to high or low dose BOTOX in Study 191622-502. Patients who received BOTOX in Study 191622-501 received the same dose in Study 191622-502.

c In Part II, patients received either BOTOX 200 U or 300 U, as determined by the investigator.

d Study 191622-030 included patients with lower and/or upper limb spasticity; of the 109 patients enrolled, 46 patients received injections in the lower limb.

e The dose used in individual patients was determined by the treating physicians based on their experience and normal practice to maximize functional response to treatment. The protocol suggested a minimum per-muscle dose.

f Study AGN/HO/SPA/001-191622 included patients with lower and/or upper limb spasticity; of the 274 patients enrolled, 194 patients received injections in the lower limb.

### III.2.1 Phase II trials

Exploratory phase 2 studies in adult lower limb spasticity evaluated the effects of injecting different lower limb muscles as summarized in the following table. In the initial phase 2 studies, only the gastrocnemius muscle was routinely injected. Later studies evaluated the effects of injecting other ankle plantar flexors, which are known to contribute to spasticity of the ankle joint. The results of these studies contributed to the current understanding that, in addition to injections in the gastrocnemius, injections in the tibialis posterior and soleus muscles are associated with optimal intervention for the treatment of patients with lower limb spasticity. These additional muscles were treated in the successful phase 3 primary efficacy Study BTX108512.
### Botox 50, 100 and 200 Allergan units – powder for solution for injection

#### BTOX-138/139-8051 (first US exploratory study)
The only muscles injected during the first cycle were the medial and lateral heads of the gastrocnemius. The second treatment cycle allowed additional injections in the tibialis muscle at the physician’s discretion. Although statistically significant improvements were not observed for the primary measures of spasticity during either treatment cycle, numerical trends indicating enhanced effect for the patient global assessment and gait pattern were observed after the second treatment cycle, in which injections in the tibialis muscle were allowed. This suggested the potential clinical benefit of including the tibialis muscle in the treatment paradigm.

#### Study 191622-501 (double-blind, randomized, placebo controlled) and its extension Study 191622-502 (double-blind, randomized)
These studies also included injections in the gastrocnemius but additional injections were allowed either to the anterior or posterior tibialis at the physician’s discretion for both the first and the second treatments. In Study 191622-501, numerical, but not statistically significant, improvements in spasticity based on the expanded Ashworth scale (EAS) favoured BOTOX at all time points. The EAS includes half-grade increments between each of the categories, with the intent to improve sensitivity in the grading of spasticity. Statistically significant benefits of BOTOX compared to placebo were observed for the physician global assessment (PGA) in the “high” dose group (~ 4 U/kg, which equated to a total dose of 160 to 400 U) at week 4 (p = 0.017). In Study 191622-502, statistically significant (p < 0.001) decreases from baseline in mean EAS scores were found at each follow-up visit for both the “low” (~ 2 U/kg) and “high” (~ 4 U/kg) BOTOX dose groups. Approximately 35% of the patients in study 191622-501 and 50% in Study 191622-502 received injections in both the gastrocnemius and the tibialis. In these subgroups, the clinical benefit of BOTOX over placebo tended to be greater than in patients who received only gastrocnemius injections. This corroborated the findings from Study BTOX-138/139-8051, and confirmed the importance of injecting the tibialis muscle in addition to the gastrocnemius.

#### Study BTOX-702-8051 (concurrent study conducted in Australia and considered supportive)
Injections of BOTOX into the tibialis posterior, soleus, and either the gastrocnemius or flexor digitorum longus were utilized. This is the first study that included injections in the soleus muscle. Treatment of this muscle constellation resulted in an improvement in spasticity as rated by the physician, a reduction in spasm frequency, a reduction in pain when present, and increased range of motion of the ankle as measured by

#### Table: Muscle Injection Details

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Exploratory Studies</th>
<th>Supportive Studies</th>
<th>Primary Efficacy Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BTOX 138/139-8051¹</td>
<td>AGN101-001/191622²</td>
<td>BTOX-702-8051¹</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>-2 U/kg</td>
<td>75 U</td>
<td>75 U</td>
</tr>
<tr>
<td>(medial head)</td>
<td>-1 U/kg</td>
<td>50 U</td>
<td>50 U</td>
</tr>
<tr>
<td>Gastrocnemius</td>
<td>-2 U/kg</td>
<td>75 U</td>
<td>75 U</td>
</tr>
<tr>
<td>(lateral head)</td>
<td>-1 U/kg</td>
<td>50 U</td>
<td>50 U</td>
</tr>
<tr>
<td>Tibialis</td>
<td>-1 U/kg (only at 2nd injection)</td>
<td>75 U</td>
<td>75 U</td>
</tr>
<tr>
<td>(anterior or posterior)</td>
<td>-1 U/kg (if spasticity of tibialis)</td>
<td>75 U</td>
<td>75 U</td>
</tr>
<tr>
<td>Solas</td>
<td>--</td>
<td>50-100 U</td>
<td>75 U</td>
</tr>
<tr>
<td>Flexor digitorum longus/brachis</td>
<td>--</td>
<td>50-100 U</td>
<td>75 U</td>
</tr>
<tr>
<td>Flexor hallucis longus/brachis</td>
<td>--</td>
<td>25-75 U</td>
<td>75 U</td>
</tr>
<tr>
<td>Total per protocol dose</td>
<td>160-490 U</td>
<td>200-490 U</td>
<td>n/a</td>
</tr>
</tbody>
</table>

¹ For calculation of doses, patient body weights were grouped in 10 kg increments. Actual doses ranged from 1.8 U/kg to 2.2 U/kg in the ~2 U/kg group, from 3.8 U/kg to 4.4 U/kg in the ~4 U/kg group, and from 9.2 kg to 1.1 U/kg for the ~1 U/kg dose to the tibialis. ² Actual doses ranged from 1.8 U/kg to 3.3 U/kg (low dose group) and 3.6 U/kg to 5.6 U/kg (high dose group). ³ Study 191622-430 included patients with lower and/or upper limb spasticity; of the 109 patients enrolled, 46 patients received injections in the lower limb. ⁴ Study AGN101-001/191622 included patients with lower and/or upper limb spasticity; of the 274 patients enrolled, 204 patients received injections in the lower limb. Muscle doses per muscle as suggested by the protocol are listed above. ⁵ Muscles injected were either the flexor digitorum longus or medial gastrocnemius. ⁶ The minimum recommended BOTOX dose for the ankle plantar flexors was 280 U.
goniometry. In patients with more severe spasticity (ie, AS score of 3 at baseline), a statistically significant reduction in spasticity compared to placebo was observed at week 8 (p = 0.0111). A second injection of BOTOX (at least 12 weeks after the first injection) further decreased muscle tone, reduced spasm frequency, and improved the overall assessment by the physician of patient response to treatment. These results suggested that injections into the tibialis posterior and soleus muscles, in addition to the gastrocnemius or flexor digitorum longus, are associated with enhanced clinical effect, which is not unexpected as these ankle plantar flexors all contribute to the spasticity of the ankle joint.

Study 191622-030 (US exploratory)
It was designed to evaluate the pulmonary function safety of repeat doses of BOTOX for the treatment of post-stroke focal spasticity. Up to 6 muscles of the upper and lower limb were injected at the discretion of the physician. There were too few patients with any specific muscle complex injected to allow conclusions regarding muscle selection.

Study 191622-911 (Japan exploratory)
It was designed to investigate the tolerability and safety of BOTOX in Japanese patients with spastic gait due to post-stroke hemiplegia. Patients received injections in the medial and lateral gastrocnemius, soleus, and posterior tibialis. This 20-patient, open-label study demonstrated improvements in spasticity symptoms following treatment with BOTOX.

Dose Selection

Exploratory phase 2 studies in adult lower limb spasticity evaluated the effects of a wide range of BOTOX doses. In the initial exploratory phase 2 Studies BTOX-138/139-8051, 191622-501, and 191622-502, patients were dosed on a U/kg basis. This resulted in a wide range of actual doses, and considerable overlap between the “low” dose group (80 to 240 U) and “high” dose group (160 to 400 U). Neither BOTOX group was shown to be significantly more effective than placebo in decreasing lower limb spasticity in adults. Exploratory analyses using the actual dose received, however, indicated a trend toward increased benefit in the subgroup of patients receiving at least 300 U compared to the overall high-dose group and placebo group in Study 191622-501. This suggested the need for a fixed-dose paradigm to limit the range of actual doses administered and thus the variability in response.

Therefore, in the subsequent supportive phase 2 Study BTOX-702-8051, patients received a fixed total dose of 200 or 300 U. Although the study was not designed or powered to statistically compare these two BOTOX dose groups, improvements in AS scores were consistently numerically greater with the 300 U dose compared to the 200 U dose. In patients with an AS score of 3 at baseline, there was a statistically significant difference between BOTOX 300 U and placebo at week 8 (p = 0.0469), while the lower 200 U dose did not clearly differentiate from placebo.

Due to the localized activity of BOTOX, both the muscle selection and dose per muscle are important factors in optimizing treatment benefit. In patients with spasticity of the plantar flexors, it is important to administer BOTOX to all 3 main muscles contributing to the spasticity of the ankle joint: gastrocnemius, tibialis, and soleus. The doses per muscle for the pivotal trial BTX108512 were calculated to distribute the fixed total dose of 300 U among the optimized muscle complex. This muscle selection is also consistent with a recently published international consensus statement regarding the use of botulinum toxin for the treatment of spasticity of equinus and inverted foot in patients with lower limb spasticity (Olver et al, 2010).
Patient Selection

In addition to varying dosing paradigms, the exploratory phase 2 studies evaluated patients with varying degrees of severity at baseline and the efficacy of BOTOX was not always clearly demonstrated. Patients with more severe baseline spasticity are more likely to require treatment for spasticity and to benefit from such treatment. More marked improvements in AS were demonstrated in patients with more severe baseline spasticity (ie, AS score of 3 at baseline) in Study BTOX-702-8051, therefore the pivotal trial was designed to include patients with a minimum score of 3 (considerable increase in muscle tone – passive movement difficult) on the modified Ashworth Scale (MAS).

Measures of Muscle Tone

Since its first publication, the AS has undergone several modifications, with each sharing the same principle but using different scale ranges and definitions. In 1987, the addition of the 1+ intermediate score, with its definition and a change to the definitions used for scores of 1, 2, and 4 (definition for a score of 3 remained the same) were proposed. These definitional changes and the addition of the 1+ grade (making the AS into the 6-point MAS) were made to increase the sensitivity of the measure and facilitate scoring.

<table>
<thead>
<tr>
<th>Ashworth Scale (Ashworth, 1964)</th>
<th>Modified Ashworth Scale (Bohannon and Smith, 1987)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Definition</td>
</tr>
<tr>
<td>0</td>
<td>No increase in (muscle) tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in (muscle) tone giving a catch (and release) when the limb was moved in flexion or extension</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in (muscle) tone but limb easily flexed (or moves easily)</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in tone, passive movement difficult</td>
</tr>
<tr>
<td>4</td>
<td>Limb rigid in flexion or extension</td>
</tr>
</tbody>
</table>

The initial exploratory phase 2 Studies BTOX-138/139-8051, 191622-501, and 191622-502 used the EAS, which added half-grade increments between each of the categories with the intent to improve sensitivity in
the grading of spasticity when the tone was assessed as intermediate between 2 units on the scale. However, the EAS has not been formally validated.

The change from baseline in the AS at a single post-treatment primary time point was used in the upper limb studies and lower limb phase 2 studies. Individual time points are clearly important and relevant to demonstrate the onset and time course of treatment benefit. Also, considering the differences of individual peak efficacy and duration of the pharmacodynamic effect of BOTOX, the use of area under the curve (AUC) as a summary index provides a more comprehensive temporal evaluation of efficacy than assessment at a single time point. AUC integrates repeated assessments during the trial into summary measures by taking into account the onset and time course of the drug effect. Compared to end-of-study visit analyses within each treatment group, Pham et al, 1999 found that the AUC summary reported smaller effects with reduced errors in the estimates. The AUC is a particularly relevant method of analysis when evaluating the efficacy of a single BOTOX treatment, which has a prolonged duration of effect on muscle activity.

The phase 3 pivotal trial BTX108512 used the AUC of the MAS ankle score change from baseline over the 12-week, double-blind period as the primary endpoint. Secondary endpoints included the MAS ankle score changes from baseline at each visit. The proportion of responders (defined as patients who achieved a reduction from baseline of $\geq 1$ in MAS ankle score) was also calculated at each visit.

**Global Measures of Response to Treatment**

Global measures of response to treatment were included in the exploratory and supportive phase 2 studies. Subjective global assessments by patients and physicians are widely used and accepted scales that assess the overall clinical benefit of treatment across a wide variety of disorders, including spasticity (Neurotoxin Spasticity Consensus Group, 2006). Such assessments are used in product development as a confirmatory bridge from the disease-oriented primary outcome variable to a measurement of a patient’s meaningful benefit. The phase 3 pivotal trial BTX108512 included physician and patient global impression as secondary endpoints to complement the more objective MAS measure of muscle tone.

*Based on the results of six Phase II studies, a pivotal Phase III trial was designed. Once the paradigm of a fixed dose - as for other BOTOX indications – had been chosen and the relevant muscles selected, an attempt was made to compare two doses, 200 U and 300 U, although the trial was not powered for this, a numerical trend favoured the higher dose. The 300 U dose ultimately chosen for the pivotal Phase III trial appears consistent with the doses injected in the upper limb (200 – 240 U), where the muscles are less voluminous. Therefore, the rationale for the 300 U dose is acceptable.*

**III.2.2 Pivotal Phase III study (BTX108512)**

**Title:**
A Multicenter Study to Evaluate the Efficacy and Safety in Patients with Post-Stroke Lower Limb Spasticity Receiving a Double-Blind, Placebo-Controlled GSK1358820 Treatment Followed by an Open-Label GSK1358820 Treatment

*(Note that the sponsor of this study was GlaxoSmithKline K.K.)*

**Investigator(s):**
A total of 20 investigators (in 19 medical institutions) in Japan

*These were mainly neurosurgery departments and rehabilitation centres.*

**Study period:**
Initiation date: May 22, 2007 (Date of consent obtained from the first subject)
Completion date: December 24, 2008 (Date of the visit/observation for last subject completed)

**A. Methods**

**Design**
The study consisted of two parts:
- Part 1 (DB phase): A multicenter, placebo-controlled, randomized, double-blind, parallel-group design;
Part 2 (OL phase): A multicenter, uncontrolled, open-label design.

A screening (SCR) phase was set up before the start of Part 1 (DB phase). The SCR phase was started from 2 to 4 weeks before the start of the DB phase (Visit 2) and lasted for at least 2 weeks.

The study period was from the time of obtaining informed consent to the completion of OL phase or the time of withdrawal, consisting of the SCR phase up to 4 weeks and the treatment period of 48 weeks (12-week DB phase and 36-week OL phase) for a maximum of 52 weeks.

This study was designed based on advice and comments from the Japanese regulatory Authorities (PMDA).

*Only the first treatment cycle was comparative.*

**Objective**

**Primary**
To confirm the superior efficacy of a single treatment of BTX 300 U over placebo in patients with equinus deformity (plantar flexion of the ankle) associated with post-stroke lower limb spasticity using the Modified Ashworth Scale (MAS) ankle score.

**Secondary**
1. To evaluate the efficacy of single and repeated treatments of BTX 300 U using the MAS ankle score, Physician’s Rating Scale (PRS), speed of gait, and Clinical Global Impression (CGI) of functional disability.
2. To evaluate the safety of repeated treatments of BTX throughout the treatment period (double-blind and open-label phases).
3. To evaluate the global impression of therapeutic benefit of BTX to rehabilitation at the end of the study if any change was made to permitted concomitant rehabilitation therapy during the open-label phase.

**Selection criteria**

**Main inclusion criteria:** male or female patients with equinus deformity (plantar flexion of the ankle) who met all of the following criteria at the start of DB phase (Visit 2): at least 6 months post stroke, MAS ankle score of $\geq 3$, between 20 and 80 years old (either sex), and body weight of at least 50 kg.

**Main exclusion criteria:** bilateral hemiplegia or quadriplegia, fixed contractures of the ankle (absence of range of motion), profound atrophy of the muscles to be injected, or previous botulinum toxin therapy.

The selection criteria of the study population are appropriate.

**Treatment**

BOTOX: Each vial contained the following ingredients and was reconstituted before use (reconstituted with 8 mL of Saline JP):
- BOTOX 100 Unit (U)
- Human serum albumin 0.5 mg
- Sodium chloride 0.9 mg

Placebo (Control): Each vial (indistinguishable from the test drug) contained the following ingredients and was reconstituted before use (reconstituted with 8 mL of Saline JP):
- Sodium chloride 0.9 mg

Vials were imported from/manufactured by: Allergan Pharmaceuticals Ireland.

BTX or placebo was administered by intramuscular injection into 3 sites of each the gastrocnemius, soleus and tibialis posterior muscles (see previous diagram). A volume of 2 mL (25 U or 0) was injected into each site.

A single treatment of BTX or placebo was given in the DB phase, and up to three repeated treatments of BTX were given in the OL phase.
During the DB phase, the investigator/subinvestigator used an electromyography (EMG) or nerve stimulator, and an EMG needle to assist in proper muscle localization for injection. During the OL phase, the investigator/subinvestigator could use either of them.

The subjects were re-injected whenever they met all of the following reinjection criteria:
1. MAS ankle score of ≥2 at pre-treatment.
2. At least 12 weeks (84 days) since the last injection.
3. Body weight of ≥50 kg.

**Efficacy endpoints**

**Primary endpoint**
Area under the curve (AUC) for the change from baseline in MAS ankle score to the end of the DB phase.

**Secondary endpoints**
Throughout the treatment period (DB and OL phases), the following changes from baseline:
- MAS ankle score
- Physician Rating Scale (PRS) score evaluated from a videotape of the subject walking 10 m
- Speed of gait measured by the time to walk 10 meters
- Clinical Global Impression (CGI) of functional disability using a numerical scale by the investigator, the subject and the physiotherapist
- If any change was made to permissible concomitant rehabilitation therapy during the OL phase: global impression of therapeutic benefit of BTX to rehabilitation

Efficacy variables were assessed at Week 0 (baseline), 1, 4, 6, 8, 12 (DB) and every 4 weeks up to Week 48 (OL).

*Overall, the choice of endpoints is considered appropriate. The major issue with the use of AUC as the primary endpoint is the handling of missing data. Furthermore, no information was provided as to what effect size would be clinically meaningful.*

**Statistical analysis**
The following two analysis populations were used for efficacy analyses.

- Full Analysis Set (FAS):
  The FAS population consisted of all subjects randomized with the exception of those who did not receive any injection of the investigational product and those with no assessment of post-treatment MAS ankle score.

- Per Protocol Set (PPS):
  The PPS population consisted of all subjects in the FAS population who had no major protocol deviation during the DB phase.

The FAS was the primary population for efficacy analyses in this study. The PPS was also analyzed to confirm the robustness of the results from the primary analysis of AUC for the change from baseline of MAS ankle score.

Missing values
As the primary efficacy analysis, the FAS analysis of the change from baseline of MAS ankle score was performed on an observed dataset where data were evaluated only for the time point when it was collected. For analyses on the observed data set, AUC was calculated by eliminating the missing value and using the values prior to and following the time point of missing data.

The secondary analysis was performed on an imputed dataset where missing data in the DB phase were substituted. A missing value of a subject was substituted with the overall mean MAS ankle score (BTX and placebo groups combined) calculated from the available data for that time point.

However, for subjects withdrawn from the study in the DB phase, missing values at any Visits after the final assessment were not substituted. AUC was calculated using the data obtained up to the Visit of the final assessment.

Data on the other endpoints in the DB phase and all endpoints in the OL phase were analyzed on the observed dataset. The PPS analysis of AUC for the change from baseline in MAS ankle score was performed on the observed dataset.

Statistical tests
The mean difference of the AUC between the BTX and placebo groups was analyzed by t-test. As this does not account for differences in baseline measurement between patients the MAH had to perform an ANCOVA (analysis of covariance) in which baseline MAS is included as a covariate. This was performed on the observed and imputed datasets. Furthermore, a more appropriate imputation method was applied, where values missing between visits were imputed using the average for that time point for placebo patients.

Secondary endpoints
MAS
- MAS ankle score at each evaluation time point and change from baseline (difference between treatment arms analyzed by Wilcoxon test) in the FAS (observed and imputed datasets)
- Summary statistics of AUC by centre, age and gender
- Summary statistics of responders defined as a) subjects who did not meet the reinjection criteria on the MAS (i.e. MAS ankle score of <2 at any post-treatment evaluation time point) and b) subjects whose MAS ankle score was decreased ≥1 from baseline (change of ≤-1) at any post-treatment time point (post-hoc definition); the duration of response was the period (weeks) from the time of becoming responder to the first time of becoming a non-responder.

Others
PRS, speed of gait and CGI at each evaluation time point and change from baseline (difference between treatment arms analyzed by Wilcoxon test).

GCP compliance
The MAH provided a statement that the study was conducted in accordance with the Ethical Standards described in Directive 2001/20/EC. An internal audit was performed in two centres.
The two centres audited were the centre with the most important recruitment (24 patients) and another centre with a high recruitment (11 patients). The selection of the centres audited is considered acceptable.
B. Results

B.1 Patient disposition

The reasons for withdrawal of seven subjects during the DB phase were “adverse event” (three subjects in BTX-300U group), “subject’s request” (three subjects in BTX-300U group), and “protocol deviation” (one subject in placebo group).

The reasons for withdrawal of one subject who completed the DB phase but did not enter the OL phase and 15 subjects who withdrew during the OL phase were “subject’s request” (eight subjects), “adverse event” (seven subjects) and “other (meeting the exclusion criterion)” (one subject).
The withdrawal rate was substantially higher in the BOTOX treatment arm (10% vs. 2%), due to adverse events and subject’s requests, which are likely treatment-related. Furthermore, according to listing 11, there was an imbalance between the numbers of patients with missing MAS data: one patient (2%) in the placebo arm (withdrawn) vs. nine patients (16%) in the BTX arm (six withdrawn and three others).

**B2 Analysis sets**

All randomized patients were included in the primary analysis (FAS).

<table>
<thead>
<tr>
<th></th>
<th>BTX-300U</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects randomized</td>
<td>58</td>
<td>62</td>
<td>120</td>
</tr>
<tr>
<td>SP</td>
<td>58 (100%)</td>
<td>62 (100%)</td>
<td>120 (100%)</td>
</tr>
<tr>
<td>FAS</td>
<td>58 (100%)</td>
<td>62 (100%)</td>
<td>120 (100%)</td>
</tr>
<tr>
<td>PPS</td>
<td>55 (95%)</td>
<td>55 (89%)</td>
<td>110 (92%)</td>
</tr>
</tbody>
</table>

The reasons for exclusion from the PPS are provided below.

<table>
<thead>
<tr>
<th></th>
<th>BTX</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects randomized</td>
<td>58</td>
<td>62</td>
<td>120</td>
</tr>
<tr>
<td>Meeting exclusion criteria</td>
<td>0</td>
<td>2 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Treatment incompliance</td>
<td>0</td>
<td>1 (2%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Use of prohibited concomitant medication</td>
<td>1 (2%)</td>
<td>2 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Change in permitted non-drug therapies (rehabilitation)</td>
<td>3 (5%)</td>
<td>3 (5%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Change in inpatient/outpatient status</td>
<td>2 (3%)</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

The rate of major protocol deviations is considered acceptable. The PPS analysis set represents a high proportion of the randomised population.

**B3 Baseline characteristics**

More male subjects were enrolled than female subjects in both groups: the proportion of male subjects was 86% in the BTX-300U group and 74% in the placebo group and the mean time since stroke was 81 and 72 months in the BTX-300U and placebo groups, respectively (Table 1).
The baseline characteristics were well balanced across treatment arms, except for a higher proportion of male patients treated with BOTOX. The median time since stroke was similar in both arms (≈ 4.5 years). The population age spanned over a broad range (32 to 78 years), but as expected for a post-stroke indication, 50% of the population was over 63 years. The baseline MAS ankle score was comparable in both treatment arms; about 25% of the patients were scored “4”, i.e. with a rigid limb, and 75% scored “3”, i.e. with considerable increase in muscle tone and difficult passive movement.

**B4 Efficacy results**

**B.4.1 Primary endpoint**

When the AUC for the change from baseline in MAS ankle score during the DB phase (up to Week 12) was calculated, a mean difference of -3.428 between the BTX-300U and placebo groups was statistically significant, confirming the superiority of BTX-300U over placebo (95% CI: -5.841, -1.016, p=0.006 [t-test], Table 2). The analyses of the primary endpoint using the imputed data and the PPS demonstrated a statistically significant difference between the groups, consistent with the above result.

The primary efficacy analysis of Study BTX108512 was also performed using an ANCOVA model with treatment as a factor and baseline Modified Ashworth Scale (MAS) score of ankle as a covariate. The analyses were done based on both the observed and imputed datasets with the methodology recommended by the assessor. The results are consistent with the original analyses.
The distribution of area under the curves (AUCs) has been provided and is shown below for the imputed data. The AUC ranges from -25.5 to 0 for all patients, and the medians are -9.5 and -2.0 for BOTOX and placebo, respectively.

The MAH provided the requested sensitivity analyses, which showed very similar results to the initial analyses, with statistically significant differences overall (AUC) and from week 4 to 8. The conclusion regarding the primary efficacy results is robust to the method of analysis.

As expected, the distribution of the response was far from Gaussian with a fair proportion of non-responders, almost twice as high with placebo (42%) than with BOTOX (24%), and two patients on placebo had the highest response amongst the total population. Therefore, the difference between the median responses (9.5 vs. 2.0 for BOTOX and placebo, respectively) is considered more representative of the overall treatment effect. Still, the clinical relevance of a treatment effect of about 3 points is difficult to appreciate and has been discussed by the MAH (see section III.2.6).

B.4.2 Secondary endpoints

MAS ankle score

DB phase
The MAS ankle score was decreased more in the BTX-300U group compared with placebo, with statistically significant differences from placebo at Weeks 4, 6 and 8 (each p<0.001) (Table 3).
The change from baseline in MAS of the ankle at each time point was also re-analysed based on both the observed and imputed datasets. The results of these analyses are consistent with the original analyses.

When the proportion of responders (subjects who achieved a ≥1 reduction from baseline in MAS ankle score) was calculated at each post-treatment evaluation time point, the proportion of responders in the BTX-300U group reached a maximum of 67% at Week 6 vs. 35% in the placebo group (p < 0.001) (Table 4).

The period from the time of injection to the first time of becoming a non-responder (return of MAS ankle score to the baseline value) after becoming a responder was calculated as the “duration of response”. As a result, the median durations of response were 12 weeks in the BTX-300U group, and 4 weeks in the placebo group.

When the change from baseline in MAS ankle score was calculated for each repeat treatment cycle of BTX-300U, the MAS ankle score was decreased from baseline in all treatment cycles and the magnitude of its decrease was comparable for all treatment cycles (Table 5).
During the open-label phase when all patients received active treatment, the MAS ankle score was decreased from baseline following all repeat injections of BOTOX 300 U (given approximately every 3 months). The magnitude of the decrease was even more marked during the open-label phase compared to the double-blind phase (Figure 1).

Figure 1 Mean (SEM) for change from baseline of MAS ankle score (FAS)

A significant effect of BOTOX at Weeks 4, 6, and 8 is consistent with the known time course of the pharmacological activity of BOTOX and as observed for the treatment of upper limb spasticity. However, it barely reached a 1-point improvement on average and how this translated into a functional benefit remains to be addressed. In addition, the clinical relevance of an effect size of about 0.5 points has not been justified.

The results of the pre-defined responder analysis were not provided; according to the Assessor, the rate was 31% in the BOTOX arm vs. 16% in the placebo. Likewise, the duration of the response was not calculated as defined in the protocol; however, this is acceptable and in line with previous evaluations of BOTOX in other indications. The MAH recalculated the responder rates based on the number of patients with an assessment at each visit and performed a statistical comparison (see Table 4).

Based on listing 11, the proportion of patients without any improvement of MAS at any time was 42% (26/62) for placebo and 24% (14/58) for BOTOX, still a notable failure rate, at least after the first injection.

In the subgroup analyses (data not shown), the treatment effect was consistent - in favour of BOTOX - across the main centres (with at least five subjects in one treatment arm) except for one. The effect of BOTOX was observed in both genders and appeared slightly more pronounced in patients less than 60 years old compared to older patients, which could be expected.

PRS score
When the change from baseline in PRS score at each post-treatment evaluation time point was compared between the groups, there were slight increases in PRS score in the BTX-300U group but similar changes were seen in the placebo group, with no significant difference at any time point.
**Speed of gait**

When the change from baseline in the time (sec) required walking 10 m at each post-treatment evaluation time point was compared between the groups, the time was decreased from baseline at Week 4 onward in the BTX-300U group, but similar changes were seen in the placebo group, with no significant difference at any time point.

**CGI score**

The CGI score assessed by the investigator was increased in the BTX-300U group, with significant differences from placebo at Weeks 4, 6 and 8 (p: 0.016 to 0.048 [Wilcoxon test]) as shown in Table 6 and Figure 2. However, in the subject and physiotherapist/occupational therapist assessments, no significant difference between the groups was noted at any evaluation time point.

In the OL phase, an improvement from baseline in CGI score was noted in all repeat treatment cycles of BTX-300U in both the 300U to 300U group and the placebo to 300U group regardless of the assessor.

<table>
<thead>
<tr>
<th>Table 6 Change from baseline in CGI score (DB phase; FAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Group</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Investigator</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change from baseline</td>
</tr>
<tr>
<td>Week 1</td>
</tr>
<tr>
<td>Week 4</td>
</tr>
<tr>
<td>Week 6</td>
</tr>
<tr>
<td>Week 8</td>
</tr>
<tr>
<td>Week 12</td>
</tr>
<tr>
<td><strong>Subject</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change from baseline</td>
</tr>
<tr>
<td>Week 1</td>
</tr>
<tr>
<td>Week 4</td>
</tr>
<tr>
<td>Week 6</td>
</tr>
<tr>
<td>Week 8</td>
</tr>
<tr>
<td>Week 12</td>
</tr>
<tr>
<td><strong>Physiotherapist/occupational therapist</strong></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Change from baseline</td>
</tr>
<tr>
<td>Week 1</td>
</tr>
<tr>
<td>Week 4</td>
</tr>
<tr>
<td>Week 6</td>
</tr>
<tr>
<td>Week 8</td>
</tr>
<tr>
<td>Week 12</td>
</tr>
</tbody>
</table>
Secondary endpoints did not provide significant support to the results of the primary endpoint. Only investigator’s impression of functional disability was able to distinguish between BOTOX and placebo. In a posthoc analysis, the measure of muscle tone was correlated with the investigator’s global assessment. According to the MAH, these correlations demonstrate that decreases in the MAS scores are recognized by physicians as being beneficial to the patient and that the improvements in muscle tone (as assessed by the MAS) were thus clinically relevant and meaningful. However, it is more likely that the investigator assessment of functional disability was essentially driven by the MAS score. Indeed, it is understandable that the patient has different expectation and hence different appreciation of his/her functional disability although a posthoc analysis showed that responders had better CGI than non-responders regardless of the treatment. Notwithstanding, it is very surprising that the physiotherapist did not perceive the difference in contrast to the investigator. The physiotherapist’s opinion is considered critical to judge the patient’s functional ability.

During the DB phase, 47% patients in the placebo arm and 52% in the BOTOX arm had concomitant rehabilitation therapy. In the OL phase, a change in rehabilitation therapy was more frequent in patients only treated with BOTOX than in those first treated with placebo (27% vs. 18%, respectively); BOTOX was assessed by the physiotherapist as having therapeutic benefit to the rehabilitation in most of these cases (91%), in particular in all 13 patients treated with BOTOX since the beginning of the trial. This type of result is considered promising.

With respect to the limited change in gait observed in the study, it is acknowledged that the study population had old strokes and very impaired walking capacity at baseline, which made it very difficult to achieve an improvement in such a short period of time after a single treatment administration.

In conclusion, the pivotal trial met its primary objective by showing a statistically significant difference in the ankle muscle tone assessment but the clinical relevance of the effect size has to be justified (see section III.2.6). Furthermore, except for the investigator’s opinion, which is likely related to the muscle tone assessment, no secondary endpoints, including physiotherapist’s impression and patient-reported outcomes, added supportive evidence to this result.
III.2.3 Supportive Phase IIb Study BTOX-702-8051

Study BTOX-702-8051 was a phase 2b, randomized, double-blind, placebo-controlled study followed by an open-label extension evaluating the efficacy and safety of BOTOX in the treatment of lower limb spasticity during stroke rehabilitation. Seven centres in Australia enrolled 85 patients in the double-blind phase (Part I), and 70 patients continued on to the open-label phase (Part II). In Part I, patients were randomized in a 2:2:1:1 ratio to receive a single treatment of BOTOX 200 U (10 mL), BOTOX 300 U (15 mL), placebo (10 mL, designated placebo for 200 U group), or placebo (15 mL, designated placebo for 300 U group). In Part II, patients received a second injection of either BOTOX 200 U or BOTOX 300 U as determined by the investigator. Muscles injected were the posterior tibialis, soleus, and either the flexor digitorum longus or medial gastrocnemius. Patients were followed for 16 weeks in the double-blind phase and 12 weeks in the open-label extension. The primary efficacy endpoint was the change from baseline in AS score of the ankle plantar flexors at week 4 in the pooled BOTOX group (200 and 300 U) compared to the pooled placebo group.

For the primary efficacy endpoint, there was no statistically significant difference in the reduction of the AS score between the combined BOTOX dose groups versus the combined placebo groups: adjusted mean change from baseline at week 4 of -0.36 for BOTOX and -0.30 for placebo; p = 0.7227.

However, for patients with an AS score of 3 at baseline, there was a trend in favour of the combined BOTOX dose groups over the combined placebo groups at week 4, and a statistically significant difference was observed at week 8 (Table 7). Similar results were observed with observed data.

### Table 7 Change from baseline in AS (Ankle Plantar Flexors) in patients with BL score of 3 (ITT, imputed data)

<table>
<thead>
<tr>
<th>Visit</th>
<th>N</th>
<th>Bottox 200 (ITT=28)</th>
<th>Bottox 300 (ITT=29)</th>
<th>Placebo 200 (ITT=19)</th>
<th>Placebo 300 (ITT=17)</th>
<th>Overall (ITT=95)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vist 3</td>
<td>16</td>
<td>1 (7.1%)</td>
<td>2 (12.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Vist 4</td>
<td>16</td>
<td>1 (7.1%)</td>
<td>2 (12.5%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (6.5%)</td>
<td></td>
</tr>
</tbody>
</table>

[a] Ashworth Scale: 0=mild, 1=moderate, 2=severe, 3=very severe.
[b] P-values obtained using the Type III SS for the PROC GLM model with factors for drug and dose.

### Posthoc Analyses

Posthoc analyses comparing each BOTOX dose group to the pooled placebo group are summarized for all patients and for the subgroup of patients who had an AS ankle score of $\geq 3$ at baseline in Table 8. In the overall population, treatment with BOTOX 300 U provided a greater magnitude of reduction in the AS ankle score compared to treatment with BOTOX 200 U. There was a statistically significant difference between the reduction in the AS ankle score in the BOTOX 300 U group compared with the pooled placebo group at

Botox 50, 100 and 200 Allergan units – powder for solution for injection
week 8 (p = 0.038) in all patients and in the subgroup with an AS ankle score of ≥ 3 at baseline (p = 0.002), as well as a statistically significant difference in the mean AUC up to week 12 (p = 0.016).

Table 8  Mean (median) change from BL of AS Ankle Score (Double-blind Phase)

<table>
<thead>
<tr>
<th>Visit</th>
<th>All-Patients Population</th>
<th>Patients with Baseline AS ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX 300 U (N = 28)</td>
<td>BOTOX 300 U (N = 16)</td>
</tr>
<tr>
<td></td>
<td>BOTOX 200 U (N = 28)</td>
<td>BOTOX 200 U (N = 15)</td>
</tr>
<tr>
<td></td>
<td>Pooled Placebo (N = 29)</td>
<td>Pooled Placebo (N = 17)</td>
</tr>
<tr>
<td></td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>300 U/200 U</td>
<td>300 U/200 U</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.5 (3.0) 2.6 (3.0) 2.6 (3.0) 0.805/0.962</td>
<td>3.0 (3.0) 3.1 (3.0) 3.1 (3.0) 0.363/0.964</td>
</tr>
<tr>
<td>Week 4</td>
<td>-0.4 (0.0) -0.4 (0.0) -0.4 (0.0) 0.875/0.658</td>
<td>-0.7 (-1.0) -0.6 (-0.5) -0.3 (0.0) 0.091/0.217</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.5 (0.0) -0.2 (0.0) -0.1 (0.0) <strong>0.038/0.953</strong></td>
<td>-0.8 (-1.0) -0.4 (0.0) -0.1 (0.0) <strong>0.002/0.166</strong></td>
</tr>
<tr>
<td>Week 12</td>
<td>-0.5 (0.0) -0.2 (0.0) -0.3 (0.0) 0.291/0.775</td>
<td>-0.7 (-1.0) -0.4 (0.0) -0.4 (0.0) <strong>0.204/0.999</strong></td>
</tr>
<tr>
<td>Week 16</td>
<td>-0.4 (0.0) -0.3 (0.0) -0.3 (0.0) 0.419/0.781</td>
<td>-0.7 (0.0) -0.6 (0.0) -0.4 (0.0) 0.285/0.418</td>
</tr>
<tr>
<td>AUC up to</td>
<td>-3.86 (0.0) -2.10 (0.0) -2.36 (0.0) 0.315/0.846</td>
<td>-6.25 (-7.0) -3.40 (-4.0) -2.00 (0.0) <strong>0.016/0.297</strong></td>
</tr>
<tr>
<td>week 12</td>
<td>- (0.0) - (0.0) - (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

* P-values based on Wilcoxon rank-sum test for each time point and 2-sample t-test for AUC comparing BOTOX 300 U or 200 U to pooled placebo.

Figure 3  Mean (SEM) change from BL of AS Ankle Score in patients with AS score ≥3

Among patients with an AS score of ≥ 3 at baseline, the proportion of responders (defined as patients who achieved a ≥ 1 reduction from baseline in the AS ankle score) was consistently higher with 300 U compared with 200 U of BOTOX, with a significantly greater proportion in the BOTOX 300 U group compared to the pooled placebo group at week 8 (66.7% vs. 12.5%; p = 0.002).
Goniometric assessment of the dorsiflexor active angle at week 8 also showed a statistically significant (p = 0.035) improvement of 4.9 degrees in the BOTOX 300 U group compared to a decline of -4.2 degrees in the pooled placebo group in the analysis of the overall population. Similarly, in the analysis of the subgroup of patients with an AS ankle score of ≥ 3 at baseline, a significant improvement of 5.5 degrees in the BOTOX 300 U group compared with a decline of -2.1 degrees in the pooled placebo group was observed at week 8 (p = 0.012).

No significant difference was detected between the BOTOX and placebo groups in the timed 10 m walk (except at week 16; p = 0.044), walking endurance distance, or walking distance in 2 minutes assessed by the physiotherapist. No notable difference between the BOTOX and placebo groups was detected in assessments of mobility and walking (Part C) in the Lindmark’s Modified Fugl-Meyer Assessment (motor recovery). However, in a video review (of sitting posture, sitting-to-standing, and walking), an independent physiotherapist rated the video of the patients at week 4 in the BOTOX group as better than at baseline after the first injection (p = 0.0169) and also after the second injection (p = 0.0026; observed data). Patients in the placebo and the placebo-BOTOX groups were not rated as being significantly different to baseline at either time point.

Patients responded to two different global questions. For the general question of “Overall, how would you rate yourself today,” no clear differentiation between the BOTOX and placebo groups was observed. However, in response to the more targeted question “Was this injection beneficial?”, a clear differentiation was observed both in the overall study population and in the subset of patients who had a baseline Ashworth Scale (AS) score comparable to that in Study BTX108512, ie, ≥ 3 (Figure 4). This direct question is considered more relevant as the patient can clearly relate it to their actual treatment for ankle spasticity.

**Figure 4** Proportion of patients responding ‘Yes’ to question “Was this injection beneficial?” (a) Overall population; (b) Subset of patients with baseline Ashworth Scale Score ≥ 3

![Figure 4](image)

*A trend for a more pronounced effect on muscle tone measured by AS at the higher dose of 300 U is acknowledged. However, the statistical significance at week 8 appears mainly driven by a low placebo effect occurring by chance just at this time point (inconsistent with the previous and subsequent time points – see figure 3).

Nevertheless, this effect is supported by goniometric assessment of the dorsiflexor active angle and also with assisted pressure. An increase in ranges of motion of 5° translates into an improvement in gait as foot clearance during walking is sensitive to small angular changes of ± 2 degrees at the ankle. Such increase can mean the difference between dragging the foot on the ground during forward movement and clearing the foot of the ground, and is therefore considered clinically meaningful. Furthermore, improvement in ambulation (10 m walk) was observed only in patients treated with BOTOX. The MAH has provided the following explanation regarding the discrepancies between the posthoc analyses provided in the Summary of Efficacy and the analyses in the CSR of the goniometric assessment.
The differences in the analyses of the SCE and CSR for Study BTOX-702-8051 are summarised below.

<table>
<thead>
<tr>
<th>Summary of Clinical Efficacy</th>
<th>Clinical Study Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline definition</td>
<td>last non-missing measurement in visit 1 or 2</td>
</tr>
<tr>
<td>Treatment of comparison</td>
<td>BOTOX 300 U versus pooled placebo</td>
</tr>
<tr>
<td>Subgroup</td>
<td>BOTOX 300 U plus ≥ 3 in Ashworth scale score versus pooled placebo</td>
</tr>
<tr>
<td>Analyses model</td>
<td>1-way ANOVA with treatment as factor</td>
</tr>
</tbody>
</table>

ANOVA = analysis of variance

Both analyses demonstrated a similar result, namely that the goniometric assessment of the dorsiflexor active angle at week 8 showed a statistically significant improvement in the BOTOX 300 U (or pooled BOTOX) group compared with the pooled placebo group in the overall population. In order to provide information on a comparable population to study BTX108512, the analysis in the SCE was further performed in the subset of patients who had a baseline Ashworth score of ≥ 3 (not performed in CSR). This analysis also demonstrated a statistically significant improvement in the 300 U BOTOX group compared with the placebo group at week 8.

As for other secondary endpoints, the physician assessment of functional disability appeared consistent with the AS results, although not statistically significant; this correlation is expected. Unexpectedly, the patient assessment of improvement was rated better with the 200 U dose than with the 300 U, to the point that the difference vs. placebo was statistically significant at Week 8 and 16 (data not shown). However, when patients were asked directly “Was the injection beneficial?” as part of the Patient Assessment Scale, statistically significant differences between the 300 U and placebo groups were observed at most time points, especially in the subgroup of patients with an AS ankle score of ≥ 3 at baseline.

In conclusion, these data in a small patient sample do support those of the pivotal trial with regard to spasticity variables, including range of motion (dorsiflexor angle) and ambulation.

III.2.4 Supportive Study AGN/HO/SPA/001-191622

This study (BOTOX Economic Spasticity Trial [BEST]) was a randomized, double-blind, placebo-controlled study followed by an open-label extension of BOTOX combined with standard of care. It was designed to evaluate patient outcomes and costs of managing adults with spasticity and associated focal spasticity. Twenty-nine centres in Europe and three centres in Canada enrolled 274 patients in the double-blind phase (Part I), and 225 patients continued on to the open-label phase (Part II). Patients were randomized in a 1:1 ratio to receive BOTOX with standard of care or placebo with standard of care in Part I. The level of standard of care took into account each patient’s individual needs. Patients could receive up to two treatment cycles during Part I, separated by a minimum of 12 weeks. In Part II, patients received up to four injections of BOTOX.
The protocol allowed both upper and lower limbs to be treated at the physician’s discretion, and recommended minimum per-muscle doses. The minimum recommended BOTOX dose for the ankle plantar flexors was 280 U.

Of the 274 patients randomized, at baseline one patient did not receive treatment, 70 patients received injections only in the lower limb, 79 patients received injections only in the upper limb, and 124 patients received injections in both limbs. The subgroup of interest in this study consisted of the patients with lower limb spasticity who received BOTOX or placebo injected into the gastrocnemius (medial and lateral heads), soleus, and tibialis posterior muscles (N = 78) as this closely matches the injection paradigm for the phase 3 primary efficacy study. Patients were followed up to 52 weeks after their baseline visit (22 to 34 weeks of double-blind treatment followed by an open-label phase).

The primary efficacy endpoint was the percent of patients in the overall intent-to-treat (ITT) population (N = 273) who achieved their principal active functional goal, which was predefined at baseline, as rated by the physician. Goal attainment was measured post-treatment using a 6-point Likert scale from -3 (worse than start) to +2 (much more than expected; improvements clearly exceed the defined therapeutic goal), with a score of $\geq 0$ indicating that the patient attained his/her defined therapeutic goal. Achievement of the patient’s goal was defined as a score of $\geq 0$ at 10 weeks after the second injection (or at the week 24 visit if no second injection was given or at time of withdrawal).

For the primary endpoint in the overall ITT population, a numerically higher percentage of BOTOX-treated patients (41.5%) achieved their principal active functional goal compared to placebo (36.4%); however, the difference between the treatment groups was not statistically significant ($p = 0.511$). It should be noted that the time point for assessment of the primary endpoint (ie, at week 10 after the second treatment or week 24 if no second treatment was received) was after the anticipated peak effect of BOTOX treatment (typically observed week 4-8 post-treatment).

Attainment of the secondary functional goal (which could be passive or active), as rated by the physician, also showed that a higher percentage of BOTOX-treated patients achieved their secondary functional goal at 10 weeks after the second injection (or at the week 24 visit if no second injection was given) compared to placebo-treated patients; however, the difference was not statistically significant (51.6% versus 40.7%; $p = 0.079$). When the secondary functional goals were analyzed in the overall ITT population by whether they were active or passive, a statistically significantly higher percentage of BOTOX-treated patients achieved their passive secondary goals at 10 weeks after the second injection (or week 24 if no second injection was given) compared to placebo-treated patients (60.6% versus 38.6%; $p = 0.016$). There were no treatment differences for attainment of active secondary functional goals ($p=0.896$).

Results from the posthoc analyses of the physician rating of goal attainment in the subgroup of interest are summarized. Among this subgroup, 97.3% (72/74) selected a principal active lower limb goal at baseline related to gait/ambulation (ie, ambulation or climbing stairs). Of the 28 patients who selected an active secondary lower limb goal, all but one selected a goal related to gait/ambulation. In those patients who selected a passive secondary goal, the most frequent related to the sensory aspects of spasticity: 38% (16/42) selected goals related to pain, spasms, and other sensory-related symptoms.

For the principal functional goal (active and primarily related to ambulation), as well as the secondary functional goal (passive or active, although these were primarily related to relief of symptoms), attainment scores were likewise statistically significantly higher in the BOTOX group compared to the placebo group (Table 9). Likewise, goal attainment scores (for both principal and secondary functional goals) as assessed by the patient were statistically significantly higher with BOTOX compared to placebo treatment at week 10. The proportion of patients achieving their primary and secondary functional goals was higher in the BOTOX group (53% and 69%, respectively) compared to the placebo group (37% and 31%, respectively) (Table 10).
<table>
<thead>
<tr>
<th>Table 9</th>
<th>Goal Attainment Scores by the Physician (DB phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 10 Post Second Injection or Week 24</td>
<td>Patients with Injections in the Gastrocnemius, Soleus, Posterior Tibialis</td>
</tr>
<tr>
<td></td>
<td>BOTOX</td>
</tr>
<tr>
<td>Mean (median) goal achievement score</td>
<td>N = 34</td>
</tr>
<tr>
<td>Principal functional goal (active)</td>
<td>-0.5 (-1.0)</td>
</tr>
<tr>
<td>Number (%) of patients who achieved functional goal (score ≥ 0)</td>
<td>N = 34</td>
</tr>
<tr>
<td>Principal functional goal (active)</td>
<td>16 (47.1)</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
<td>N = 29</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
<td>20 (69.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 10</th>
<th>Goal Attainment Scores by the Patient (DB phase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 10 Post Second Injection or Week 24</td>
<td>Patients with Injections in the Gastrocnemius, Soleus, Posterior Tibialis</td>
</tr>
<tr>
<td></td>
<td>BOTOX</td>
</tr>
<tr>
<td>Mean (median) goal achievement score</td>
<td>N = 34</td>
</tr>
<tr>
<td>Principal functional goal (active)c</td>
<td>-0.2 (0.0)</td>
</tr>
<tr>
<td>Number (%) of patients who achieved functional goal (score ≥ 0)</td>
<td>N = 34</td>
</tr>
<tr>
<td>Principal functional goal (active)</td>
<td>18 (52.9)</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
<td>N = 29</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
<td>20 (69.0)</td>
</tr>
</tbody>
</table>

Goal attainment scale rated by the physician -3 (worse than start), -2 (equal to start), -1 (less than expected), 0 (expected goal), +1 (somewhat more than expected), or +2 (much more than expected)

d P-value is based on Wilcoxon rank-sum test
f P-value based on Pearson’s chi square test or Fisher’s exact test

According to consensus papers (Neurotoxin Spasticity Consensus Group (2008), Olver (2010)), patients in whom improvement in passive range of motion would be expected to provide functional benefit and/or facilitate care, would be considered the best candidates for BOTOX. Patients may be treated if improvement can be realistically expected in areas affecting function or participation, such as gait speed, independence in transfers, hygiene or dressing ability, or reduction of pain or contracture. Initiatives should be directed towards examining the effectiveness of BOTOX treatment to assist with achievement of functional and participation goals, e.g. using the Goal Attainment Scale and other validated patient-centred scales.

Such data from a subgroup of 78 patients treated in the relevant muscles have been provided; out of those patients, 74 had the lower limb as their principal functional goal and 71 as their secondary functional goal. In spite of a substantial placebo effect, with about one third of placebo patients attaining their goal, a
A significant difference was observed for the proportion of BOTOX patients attaining their secondary goal (about 70%). The physician’s and patient’s evaluation appeared very similar.

In conclusion, these data generated in a double-blind placebo-controlled trial provide evidence of actual benefit to patients while enabling them to achieve individual outcomes with a focus on improvements in function and participation which are relevant to the patient or their carers.

III.2.5 Analyses across the three relevant studies

Patient disposition
Over 90% of patients completed the double-blind phase of the 3 studies as shown below.

<table>
<thead>
<tr>
<th></th>
<th>BTX108512 (N = 120)</th>
<th>BTOX-702-8051 (N = 85)</th>
<th>AGN/HO/SPA/001-191622 (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed double-blind phase</td>
<td>113 (94.2%)</td>
<td>77 (90.6%)</td>
<td>72 (92.3%)</td>
</tr>
<tr>
<td>Enrolled in open-label extension</td>
<td>112</td>
<td>70</td>
<td>62</td>
</tr>
<tr>
<td>Completed open-label phase</td>
<td>94 (83.9%)</td>
<td>62 (88.6%)</td>
<td>59 (95.2%)</td>
</tr>
</tbody>
</table>

Patient baseline characteristics
Baseline characteristics are summarised in Table 11. Of note is the wide range in time since stroke, from 2.4 to 415 months, which is in part driven by the different inclusion criteria across the 3 studies.

Table 11 Baseline characteristics across the three studies

<table>
<thead>
<tr>
<th></th>
<th>BTX108512 (N = 120)</th>
<th>BTOX-702-8051 (N = 85)</th>
<th>AGN/HO/SPA/001-191622 (N = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>62.5</td>
<td>58.4</td>
<td>60.0</td>
</tr>
<tr>
<td>range</td>
<td>32 to 78</td>
<td>21 to 81</td>
<td>33 to 82</td>
</tr>
<tr>
<td>Sex (number [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>96 (80%)</td>
<td>65 (76.5%)</td>
<td>43 (55.1%)</td>
</tr>
<tr>
<td>female</td>
<td>24 (20%)</td>
<td>20 (23.5%)</td>
<td>35 (44.9%)</td>
</tr>
<tr>
<td>Race (number [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>0 (0.0%)</td>
<td>79 (92.9%)</td>
<td>74 (94.9%)</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Asian</td>
<td>120 (100.0%)</td>
<td>2 (2.4%)</td>
<td>3 (3.8%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0.0%)</td>
<td>4 (4.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Time since stroke (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>76.3</td>
<td>40.8</td>
<td>38.0</td>
</tr>
<tr>
<td>range</td>
<td>7 to 415</td>
<td>2.4 to 236.4</td>
<td>3 to 208</td>
</tr>
<tr>
<td>Ankle muscle tone at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>3.26</td>
<td>2.55</td>
<td>2.8</td>
</tr>
<tr>
<td>range</td>
<td>3 to 4</td>
<td>1 to 4</td>
<td>0 to 4</td>
</tr>
</tbody>
</table>

Effect on muscle tone
The results of AS scores are summarised in Table 12. At the common time points of weeks 4 and 8 for Studies BTX108512 and BTOX-702-8051, improvements were closely aligned for patients with baseline AS ankle scores ≥ 3. The between-group differences were statistically significant at week 8 in each study. While the magnitude of the AUC up to week 12 was somewhat different between the 2 studies for the BOTOX treatment group, the treatment effect (BOTOX relative to placebo) was similar.

At the single common time point of week 12 across the 3 studies, mean changes from baseline ranged from -0.5 to -0.7 for BOTOX, with a higher response in patients with baseline AS scores ≥ 3. As noted previously, week 12 was after the anticipated peak effect of BOTOX, therefore differences between the treatment groups would not be expected to be as large at this time point.
The proportions of responders (patients who achieved a $\geq 1$ reduction from baseline muscle tone ankle score) are summarised in Table 13. Findings were similar across studies, with consistently higher response rates shown for patients receiving BOTOX compared to those receiving placebo.

At the common time points of weeks 4 and 8 for Studies BTX108512 and BTOX-702-8051, BOTOX response rates were similar among patients with baseline AS scores $\geq 3$. The between-group differences were statistically significant at week 8 in each study.

At the single common time point of week 12 among the 3 studies, responder rates ranged from 40.0% to 60.9% for the BOTOX group compared to 23.5% to 34.4% for the placebo group. In patients with baseline AS ankle scores $\geq 3$, both supportive studies showed a stronger BOTOX response in comparison to placebo than was observed in Study BTX108512.

Table 13 Responder rates for AS Ankle Score across the three studies

The proportions of responders (patients who achieved a $\geq 1$ reduction from baseline muscle tone ankle score) are summarised in Table 13. Findings were similar across studies, with consistently higher response rates shown for patients receiving BOTOX compared to those receiving placebo.

At the common time points of weeks 4 and 8 for Studies BTX108512 and BTOX-702-8051, BOTOX response rates were similar among patients with baseline AS scores $\geq 3$. The between-group differences were statistically significant at week 8 in each study.

At the single common time point of week 12 among the 3 studies, responder rates ranged from 40.0% to 60.9% for the BOTOX group compared to 23.5% to 34.4% for the placebo group. In patients with baseline AS ankle scores $\geq 3$, both supportive studies showed a stronger BOTOX response in comparison to placebo than was observed in Study BTX108512.

Table 13 Responder rates for AS Ankle Score across the three studies
**Gait/ambulation**

BOTOX appeared to have little effect on the speed of gait in either the supportive Study BTOX-702-8051 or the phase III primary efficacy Study BTX108512 in the overall analyses, which may have been due to individual differences in walking ability. Thus, posthoc analyses considered baseline walking speed, with patients grouped into six categories based on those developed by Perry et al, 1995.

In the supportive Study BTOX-702-8051, there was a tendency toward a dose-related improvement in walking speed following BOTOX treatment, as reflected in the percent of patients who improved by at least 1 walking speed category during the follow-up period. As summarised in Table 14, 76.2% of patients treated with BOTOX 300 U improved by at least one category vs. only 47.4% in those treated with placebo. Similar results were observed in the analysis of the subgroup of patients with an AS ankle score of ≥ 3 at baseline, which was unexpected as more severely impaired patients may not show as much improvement in walking.

**Table 14 Improvement in walking speed (Study BTOX-702-8051, Double-blind Phase)**

<table>
<thead>
<tr>
<th>Number (%) of patients by baseline walking speed</th>
<th>BOTOX 300 U (N = 28)</th>
<th>BOTOX 200 U (N = 28)</th>
<th>Pooled Placebo 300 U /200 U (N = 29)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.1 m/sec</td>
<td>1 (3.6)</td>
<td>1 (3.6)</td>
<td>2 (6.9)</td>
<td></td>
</tr>
<tr>
<td>&gt; 0.1 to ≤ 0.23 m/sec</td>
<td>6 (21.4)</td>
<td>3 (10.7)</td>
<td>6 (20.7)</td>
<td></td>
</tr>
<tr>
<td>&gt; 0.23 to ≤ 0.4 m/sec</td>
<td>5 (17.9)</td>
<td>5 (17.9)</td>
<td>6 (20.7)</td>
<td></td>
</tr>
<tr>
<td>&gt; 0.4 to ≤ 0.58 m/sec</td>
<td>3 (10.7)</td>
<td>5 (17.9)</td>
<td>4 (13.8)</td>
<td></td>
</tr>
<tr>
<td>&gt; 0.58 to ≤ 0.8 m/sec</td>
<td>6 (21.4)</td>
<td>4 (14.3)</td>
<td>1 (3.4)</td>
<td></td>
</tr>
<tr>
<td>&gt; 0.8 m/secb</td>
<td>5 (17.9)</td>
<td>8 (28.6)</td>
<td>6 (20.7)</td>
<td></td>
</tr>
</tbody>
</table>

| Number (%) of patients overall who improved by ≥ 1 category at weeks 4, 8, 12, or 16 | 16/21 (76.2) | 9/16 (56.3) | 9/19 (47.4) | 0.060/0.600 |

Placebo groups matched to BOTOX 300 U and BOTOX 200 U were pooled.
a P-values based on Pearson’s chi-square test comparing BOTOX to pooled placebo.
b These patients were excluded from the improvement analysis because they could not improve their speed category.

In contrast, patients in Study BTX108512 did not show any tendency toward improved walking speed following BOTOX treatment. This may be due to the patients having had a longer time elapse since their stroke (mean of 76.3 months [more than 6 years] as compared to 3.4 years in Study BTOX-702-8051), resulting in a long-established spastic gait and likely accompanying neuronal reorganization. Additionally, the majority of patients in Study BTX108512 had very impaired walking capabilities at baseline: 70.8% (85/120) were limited to physiologic or household ambulation (gait speed ≤ 0.4 m/sec, ie, > 25 seconds to walk 10 metres and that may have limited their ability to improve. In contrast, only 41.2% (35/85) in Study BTOX-702-8051 exhibited this level of impairment at baseline.

In these posthoc analyses of walking speed, the placebo effect appeared quite substantial in both studies as almost half the patients were improved at some stage. After BOTOX, a similar proportion of patients was improved in the pivotal study (i.e. no difference vs. placebo at all), while in the Phase II study, a higher proportion of patients was improved. The arguments expressed by the MAH about the different patient profile in the two studies are acknowledged.

**Pain and sensory-related outcomes**

These were only studied in the two supportive efficacy studies. Patients consistently reported improvements on scales or individual questions measuring cramps, spasms, and pain following BOTOX injections. These results suggest that BOTOX effectively improves the patient experience or perception of spasticity.
Study BTOX-702-8051

Spasm frequency was evaluated using the 5-point Spasm Frequency Scale at baseline and post-treatment. At baseline, the majority of patients reported experiencing 1 or more spasms/week. At each follow-up time point, between 41% and 50% of patients treated with BOTOX 300 U reported at least a 1-point improvement in spasm frequency, in contrast to 17% to 27% of patients treated with placebo.

The percentages provided by the MAH are based on the total number of patients not those having spasms at baseline. More patients in the placebo group did not have spasms at baseline, thus, the difference between the treatment and placebo groups was actually smaller.

At each post-treatment time point, between 30.8% and 41.7% of patients treated with BOTOX 300 U reported improvement in spontaneous cramps, in contrast to 11.1% to 16.7% of patients treated with placebo (overall population); these proportions varied between 33.3% and 57.1% versus 12.5% and 28.6%, respectively, in the subset of patients with baseline AS scale ≥ 3.

Pain intensity was evaluated on a 0 to 100 visual analogue scale in response to the question “How intense is your pain at this moment?” which was a component of the Patient Assessment Scale (a 9-item questionnaire). A trend toward decreased mean pain intensity was observed in both the BOTOX 300 U and 200 U groups. Mean pain intensity values for the placebo group were more variable, with some time points showing an increase in pain intensity post treatment. However, only a minority of patients reported that they had pain at baseline (11 patients in the BOTOX 300 U group, 10 patients in the BOTOX 200 U group, and 6 patients in the placebo group).

Patients were asked “Have you noticed any change in ease of passive stretching since the injection?” as part of the Patient Assessment Scale. Responses were rated from -3 = markedly worse to +3 = markedly better. At all follow-up time points, between 35.7% and 53.8% of patients overall treated with BOTOX 300 U indicated at least a 1-point improvement in the ease of passive stretching. In contrast, only between 15.4% and 25.9% of patients treated with placebo reported at least a 1-point improvement in the ease of passive stretching at each time point. A similar trend was observed for the BOTOX 300 U group compared to the pooled placebo group in the posthoc subgroup analysis of patients with an AS ankle score of ≥ 3 at baseline (Figure 5).

Figure 5 Proportion of patients with ≥ 1-point improvement in ease of passive stretching
Subset with baseline Ashworth Scale Score ≥ 3

Study AGN/HO/SPA/001-191622

Pain intensity in response to limb stretch was assessed on an 11-point numeric rating scale ranging from 0 (no pain) to 10 (pain as bad as can be imagined); a reduction in the mean pain scale value was observed in the BOTOX group compared to the placebo group at week 12 after the first injection (by which time a BOTOX effect may be waning) and at 10 weeks after the second injection. The differences were not statistically significant. However, a higher proportion of patients had ≥ 50% reduction from baseline in the
pain score after BOTOX treatment compared to placebo: 37.5% versus 26.9%, respectively (p = 0.423), after the first treatment, and 62.5% versus 28.6% (p = 0.039) after the second treatment. Having at least a 30% reduction in pain has been established as a minimal clinically important change (Farrar et al, 2001). Thus the pain reduction associated with passive stretch observed following BOTOX treatment in this study is considered clinically meaningful.

The self-administered SF-12v2 (hereafter referred to as SF-12) health survey includes a question on pain interference with work (including both work outside the home and housework) evaluated on a 5-point scale. At baseline, 67.5% of patients in the BOTOX group and 60.5% in the placebo group reported pain interference with work at baseline. After the first and second injections, 42.9% and 45.8% of patients treated with BOTOX reported improvement of at least 1 point compared to 23.5% and 14.8% of patients treated with placebo, respectively (p = 0.015 after the second injection). Similarly, in the subgroup of patients with ankle AS score of ≥ 3, a significantly greater proportion of BOTOX patients reported at least a 1-point improvement on the pain interference scale compared with the placebo group after the second injection (56.3% versus 13.3%; p = 0.013).

Pain/sensory-related outcomes are important for the patient as reflected by their choice as passive secondary goals in Study AGN/HO/SPA/001-191622. Stretching is also an important component of self-care and physical therapy for patients with spasticity, helping to maintain range of motion and prevent muscle shortening and joint contractures.

These parameters were only evaluated in the two supportive studies. Although not often statistically significant, favourable trends were generally observed, especially for the higher BOTOX dose; of particular relevance is the ease/pain at passive stretching, which was significantly improved in both studies with BOTOX 300 U, and also the pain interference with work, which was significantly improved after the second injection of 300 U in Study AGN/HO/SPA/001-191622.

III.2.6 Justification of the effect size observed in the pivotal trial

Although the MAS has been used in clinical trials for a considerable length of time, a minimally important difference (MID) with respect to the clinical relevance of a change in MAS or MAS AUC has not been established for any major joint. Therefore, patient-related outcome measures that demonstrate the impact on the patient have been utilized to establish the clinical relevance of the observed change in ankle muscle tone in Allergan’s clinical studies. There are a number of key elements that need to be considered when determining the clinical relevance of reduction in muscle tone in a stroke population which exhibits a wide spectrum of impairments and disabilities. These considerations include tailoring/personalizing the outcome to the patient, having measures that are targeted to detect outcomes relevant to the focal treatment of spastic muscles, and taking into account of the patient’s baseline condition which may affect their ability to show functional benefit.

In contrast to the pivotal Study BTX108512, Studies BTOX-702-8051 and AGN/HO/SPA/001-191622 included a wide range of patient-related measures, including functional goal attainment, pain, and outcomes such as spasms and cramps. Clear patient benefits have been identified in these studies which were associated with similar decreases in muscle tone to those observed in Study BTX108512, including:

- difference in patient-reported CGI (even if not significant) (Study BTOX108512); of note, CGI was significantly correlated with changes in MAS
- significant difference in the patient response to the question “Was this injection beneficial?” (Study BTOX-702-8051)
- change in rehabilitation therapies (Study BTOX108512)
- significant improvement in the ability to passively stretch the affected limb (Study BTOX-702-8051) and in the pain associated with passive stretch (Study AGN/HO/SPA/001-191622)
- significant impact of pain reduction on work (Study AGN/HO/SPA/001-191622)
- improvement in spasm frequency (recalculated in patients with spasms at baseline) and in spontaneous cramps (Study BTOX-702-8051)
significant improvement in the dorsiflexor active angle (Study BTOX-702-8051)

significant differences in achievement of individualised functional goals in Study AGN/HO/SPA/001-191622

In spite of the extensive use of the Ashworth Scale, the minimal difference that is clinically relevant has not been established, which hampers the interpretation of the primary efficacy results. Therefore, the secondary efficacy variables (see next section) are essential in this evaluation. The improvement in passive stretch and in the dorsiflexor active angle as well as the reduction in cramps and pain appear particularly relevant as these changes may impact rehabilitation therapies and the patient’s ability to walk and work.

An improvement in gait and walking in patients with spasticity may be best measured by individualising the nature of improvement as post-stroke patients present with a broad spectrum of different gait and walking impairments. In the study that used this approach, significant differences in the proportions of patients achieving their gait/walking goals were observed, in spite of a high level (about one third) of placebo responders.

III.2.7 Applicability of Japanese Study BTX108512 results to EU population

Ethnic or regional factors that could potentially contribute to differences in drug response include genetic differences, diet, practice of medicine, and pattern of concomitant medication use (EMEA, 1998; Yasuda et al, 2008).

- Both the pathophysiology and clinical presentation of spasticity are the same regardless of etiology, age, sex or race. It is the alleviation of the overactivity of the affected muscles that is the target for BOTOX treatment, which is also independent of these factors.
- The presynaptic molecular machinery involved in this mechanism of action is highly conserved such that identical molecules have essentially identical interactions with the botulinum neurotoxins across a range of species that are evolutionarily highly divergent. Animal models of the neuromuscular junction studied using botulinum toxins include frogs, rats, mice, and monkeys and yield identical insights into the mechanism of action of the presynaptic molecular machinery. Given the relatively large evolutionary distance between these model systems and humans, BOTOX has the same effects on the neuromuscular junctions of the human species, regardless of ethnicity.
- Stroke and spasticity epidemiology in Japan and Europe are similar. Ischemic stroke is the most common subtype of stroke in Europe and Japan. The mortality rate from strokes is comparable in Japan, the United Kingdom, Spain, and France. The prevalence rate of post-stroke spasticity in Japan appears similar to that in Europe (20% - 40%).
- The location of the motor points, where the nerve(s) innervates the muscle, and the anatomy of the lower limb calf muscles are identical for Asians (Koreans) and Caucasians.
The risk factors for stroke identified in the Japanese population are essentially identical to those noted in western countries.

While the diet of Japanese patients is likely to differ from EU/western populations, BOTOX is injected directly into the target muscle and does not interact with any alimentary systems of the human body.

Comorbidities are similar in Japanese and western patients. In the Allergan (predominantly Caucasian) studies and the GSK Japanese study a similar patient profile was observed. Medications recorded at baseline were similar across regions. Demographics were also similar.

The high socioeconomic status, educational levels, and development in Japan and the EU enable a similar overall orientation to healthcare.

Since 2005, multiple consensus positions have been published worldwide offering physicians evidence-based guidelines on the clinical use of botulinum toxin in the treatment of spasticity associated with stroke. They reflect the current medical understanding of the treatment of stroke-related spasticity in Japan, Europe, and the US, and illustrate the similarities of treatment recommendations across these regions including the role of botulinum toxin. The consensus positions of all 3 regions recognize the use of botulinum toxin to treat decreased range of motion resulting from stroke. In addition to this specific use, the consensus positions of the European and US regions recognize a broader application to general disability from stroke-related spasticity, and the US consensus position also includes specific applications for the treatment of pain, hygiene, and function. While consensus positions of the various regions differ slightly in recognized applications, all 3 regions are in agreement that botulinum toxin provides benefit, and should be considered in the treatment of spasticity resulting from stroke.

Moreover, studies of BOTOX treatment in upper limb spasticity have shown similar responses between Japanese and Caucasian patients.

The rationale presented by the MAH for extrapolating the results of the Japanese pivotal trial to the EU patient population is endorsed.

### III.2.8 Dosing recommendations

The phase 3 primary efficacy Study BTX108512 demonstrated that BOTOX at a dose of 300 U administered to the gastrocnemius (medial and lateral heads), soleus, and tibialis posterior was effective for the treatment of patients with lower limb spasticity. Repeat treatment with BOTOX 300 U was administered when the clinical effect of the preceding treatment diminished, as long as 12 weeks had elapsed since the previous treatment.

The recommended dosing is supported by the supportive phase 2 Study BTOX-702-8051, which evaluated both 200 and 300 U doses of BOTOX, thus providing an opportunity to assess dose response. A dose response favouring 300 U was observed consistently across many parameters, both in the overall population and in the subset of patients with AS score ≥ 3 at baseline.

In the supportive Study AGN/HO/SPA/001-191622, the dose used in individual patients was determined by the treating physicians based on their experience and normal practice to maximize functional response to treatment. Efficacy was demonstrated in the subgroup of patients who received injections into the gastrocnemius (medial and lateral heads), soleus, and tibialis posterior. The minimum recommended BOTOX dose for the ankle plantar flexors was 280 U. The mean total dose injected into muscles in the lower limb was 305.1 U, with 251.1 U injected solely into the gastrocnemius, soleus, and posterior tibialis in the first double-blind, placebo-controlled treatment cycle; this dosage was comparable in the second double-blind, placebo-controlled treatment cycle.

A total dose of 300 U and the doses per muscle are also within the ranges recommended in the recently published international consensus statement regarding botulinum toxin for the treatment of spasticity of equinus and inverted foot in patients with lower limb spasticity (Olver et al, 2010). The muscle selection is likewise consistent with this consensus statement. To improve the precision of the injections into the involved muscles, it is commonly recommended that techniques such as electromyographic guidance, nerve stimulation, or ultrasound be used to facilitate localization of the affected muscles.
III.2.9 Efficacy conclusions

- Evidence of the efficacy of BOTOX at the dose of 300U in the management of patients with post-stroke lower limb (ankle) spasticity has been provided in a pivotal trial conducted in Japan. This is mainly based on the measurement of muscle tone using a validated spasticity scale (Modified Ashworth Scale, 0-4); the conclusion regarding the primary efficacy results is robust to the method of analysis.

- However, the clinical relevance of the treatment effect is difficult to appreciate. A minimally important difference with respect to the clinical relevance of a change in MAS or MAS AUC has not been established for any major joint. Therefore, patient-related outcome measures are essential to evaluate the effect of this therapy.

- Based on the MAH comprehensive justification, data from this Japanese study may be extrapolated to the EU target population. Indeed, these results are consistent with those of two supportive studies conducted in Australia, Europe and Canada.

- Overall, amongst patient with a baseline score of at least 3, the proportion of responders (patients who achieved a $\geq 1$ reduction from baseline muscle tone ankle score) ranged between 61% and 68% after BOTOX treatment vs. 29% to 39% on placebo.

- Significant and clinically meaningful improvement in range of motion (dorsiflexor angle) and ambulation was also shown in one of the supportive studies.

- Other outcomes closely related to patient benefit support the results of the primary endpoint, in particular ease/pain at passive stretching and interference of pain with work. Although improvement in walking speed appeared inconsistent across studies, the attainment scores for pre-defined functional goals (especially on ambulation and relief of symptoms) were shown to be significantly higher with BOTOX than with placebo in a Health Economics Study.

- The achievement of individual outcomes focused on improvements in function and participation which are relevant to the patient or their carers is considered essential. This is why patients should only be treated if improvement in these areas can be realistically expected. This aspect has been taken into consideration in the SmPC (section 4.4).

Clinical safety

III.3.1 Patient exposure

The safety of BOTOX in the treatment of adult post-stroke spasticity was demonstrated based on an integrated analysis of 625 BOTOX-treated patients with lower limb spasticity, some of whom also received treatment for upper limb spasticity. Many patients received multiple cycles of BOTOX treatment. The integrated database included eight completed clinical studies. Although the focus of the integrated summary of safety was on the treatment of lower limb spasticity, patients who were also concurrently treated in the upper limb were included as they provide additional safety data for a patient population in which it is not uncommon to have spasticity in both the upper and lower limbs.

The Overall Safety Population includes data from all eight clinical studies that evaluated the safety of BOTOX for the treatment of lower limb spasticity. Patients were included if they received an injection of study drug in the lower limb during a particular exposure period; some of these patients also received concurrent injections in the upper limb. This population represents the safety profile that includes the spectrum of spasticity patients studied in the BOTOX lower limb spasticity clinical development programme. In addition, the subpopulation who only received treatment in their lower limb within a given exposure period was assessed. This Lower Limb Injections Only subpopulation addresses the safety of BOTOX in patients with lower limb injections only.

Safety data were summarized for two exposure periods:


For the Overall Safety Population, the mean BOTOX dose was 285.8 U during DBPC exposure. During Any BOTOX exposure, the mean dose was 295.5 U, and the median BOTOX dose was 300 U across treatment cycles 1 to 4 during Any BOTOX exposure (Table 15). The majority (69.8%) of the 1312 individual BOTOX doses administered during Any BOTOX exposure were doses ≥ 300 U across all treatment cycles.

Table 15  BOTOX exposure (dose per treatment)

<table>
<thead>
<tr>
<th>BOTOX Dose (U)</th>
<th>Overall Safety Population (N = 625)</th>
<th>Lower Limb Only (N = 453)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>295.5</td>
<td>265.2</td>
</tr>
<tr>
<td>Median (min – max)</td>
<td>300.0 (95 – 800)</td>
<td>300.0 (95 – 740)</td>
</tr>
<tr>
<td>&lt; 100 U</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>100 – 199 U</td>
<td>88 (14.1%)</td>
<td>83 (18.3%)</td>
</tr>
<tr>
<td>200 – 299 U</td>
<td>150 (24.0%)</td>
<td>113 (24.9%)</td>
</tr>
<tr>
<td>300 – 399 U</td>
<td>298 (47.7%)</td>
<td>238 (52.5%)</td>
</tr>
<tr>
<td>≥ 400 U</td>
<td>88 (14.1%)</td>
<td>18 (4.0%)</td>
</tr>
</tbody>
</table>

* Based on a patient’s mean dose received across all cycles within the Any BOTOX exposure period.

Patient exposure by the number of BOTOX treatments received is in Table 16. For the All BOTOX dose group, 625 patients received at least one BOTOX treatment, 433 received at least two BOTOX treatments, 167 patients received at least three BOTOX treatments, and 79 patients received at least four treatments.

Table 16  BOTOX exposure (number of treatments)

<table>
<thead>
<tr>
<th>Number of BOTOX Treatments Received</th>
<th>Number of Patients by Mean Dose Received Across All the BOTOX Treatment Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX 100 U - 199 U</td>
</tr>
<tr>
<td>At least 1</td>
<td>88</td>
</tr>
<tr>
<td>At least 2</td>
<td>51</td>
</tr>
<tr>
<td>At least 3</td>
<td>2</td>
</tr>
<tr>
<td>At least 4</td>
<td>1</td>
</tr>
<tr>
<td>At least 5</td>
<td>0</td>
</tr>
</tbody>
</table>
III.3.2 Adverse events

A1. Double-blind, Placebo-controlled Exposure

Overall adverse event rates during DBPC exposure in the Overall Safety Population were 62.2% (258/415) in the All BOTOX group compared with 55.1% (146/265) in the placebo group. The most frequently reported adverse events (ie, ≥2% of patients) that occurred at a higher incidence in the All BOTOX group compared to the placebo group during DBPC exposure were fall, pain in extremity, oedema peripheral, urinary tract infection, forced expiratory volume decreased, headache, arthralgia, pulmonary function test decreased, depression, convulsion, joint sprain, and musculoskeletal pain (Table 17).

No dose-response relationship was observed for adverse events; the All BOTOX group therefore provided a representative adverse event profile. The majority of adverse events were found to be either consistent with the known mechanism of action of BOTOX or the underlying post-stroke condition of this patient population.

Table 17 Adverse Events Occurring in ≥2% of Patients (Overall Safety Population; DBPC Exposure)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>All BOTOX Doses (N = 415)</th>
<th>Placebo (N = 265)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>258 (62.2%)</td>
<td>146 (55.1%)</td>
</tr>
<tr>
<td>Fall</td>
<td>30 (7.2%)</td>
<td>13 (4.9%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>23 (5.5%)</td>
<td>23 (8.7%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>19 (4.6%)</td>
<td>10 (3.8%)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>17 (4.1%)</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>16 (3.9%)</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>Forcible expiratory volume decreased</td>
<td>14 (3.4%)</td>
<td>8 (3.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (3.4%)</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>13 (3.1%)</td>
<td>10 (3.8%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 (2.9%)</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>12 (2.9%)</td>
<td>11 (4.2%)</td>
</tr>
<tr>
<td>Pulmonary function test decreased</td>
<td>10 (2.4%)</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Depression</td>
<td>10 (2.4%)</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>Convulsion</td>
<td>10 (2.4%)</td>
<td>5 (1.9%)</td>
</tr>
<tr>
<td>Joint sprain</td>
<td>9 (2.2%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>9 (2.2%)</td>
<td>4 (1.5%)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>8 (1.9%)</td>
<td>10 (3.8%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (1.9%)</td>
<td>6 (2.3%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (1.9%)</td>
<td>7 (2.6%)</td>
</tr>
</tbody>
</table>

The adverse event of fall was reported in 7.2% of patients in the All BOTOX group and 4.9% of patients in the placebo group. Although a difference between the All BOTOX and placebo groups was observed, falls are not uncommon in the elderly and post-stroke spasticity patients, and medical review of each case did not indicate an effect of BOTOX. In addition, no dose response was observed for the incidence of falls occurring in 8.8%, 9.6%, 4.9%, and 8.2% of patients in the 100 to 199, 200 to 299, 300 to 399, and ≥400 U BOTOX dose groups, respectively. Regarding the potential consequence of a fall, ie, the adverse event of fractures, a similar incidence was reported between the All BOTOX group (1.7%) and placebo group (1.5%). As per the adverse event of fall, no dose response was observed for fractures, which occurred in 4.4%, 0.9%, 1.1%, and 2.0% of patients in the 100 to 199, 200 to 299, 300 to 399, and ≥400 U BOTOX dose groups, respectively. Medical review of each case reporting a fall or fracture demonstrated that while some of the patients reporting falls also reported fracture(s) as adverse events, most had concomitant illnesses (eg, osteoarthritis, osteoporosis, hip or joint pain, hip replacement) that would predispose them to falls and/or
fractures. The even distribution of fractures across the All BOTOX and placebo groups illustrates that, in general, the elderly post-stroke population is at risk for fractures.

Peripheral oedema occurred in 4.1% of patients in the All BOTOX group (2.9%, 4.4%, 4.3%, and 4.1% of patients in the BOTOX 100 to 199 U, 200 to 299 U, 300 to 399 U, and ≥ 400 U groups, respectively). This event occurred in 1.5% of placebo-treated patients. The majority of patients reported unilateral oedema in their injected limb. Of the 17 BOTOX-treated patients who reported peripheral oedema, eight reported the event as mild in severity, seven as moderate, and one as severe.

A2. Any BOTOX exposure

During Any BOTOX exposure, the overall incidence of adverse events in the 625 patients receiving BOTOX in the Overall Safety Population (regardless of treatment cycle) was 68.0% (425/625) for BOTOX-treated patients. The overall incidence was similar among the BOTOX dose groups: 77.3% (68/88) in the 100 to 199 U group, 70.7% (106/150) in the 200 to 299 U group, 67.1% (200/298) in the 300 to 399 U group, and 56.8% (50/88) in the ≥ 400 U group. There was no dose-dependent increase in the overall incidence of adverse events with higher BOTOX dose groups. The most frequently reported adverse events were nasopharyngitis, fall, pain in extremity, oedema peripheral, injection site pain, UTI, back pain, epilepsy, arthralgia, headache, depression, musculoskeletal pain, contusion, convulsion, FEV1 decreased, and constipation. The most frequently reported adverse events after Any BOTOX exposure were similar to those observed for BOTOX-treated patients during DBPC exposure.

For the subpopulation of Lower Limb Injections Only, a similar adverse event profile was observed to that observed in the Overall Safety Population.

A3. Repeat BOTOX treatment

The overall incidence of adverse events was similar across all BOTOX treatment cycles: 52.5% (328/625) during BOTOX treatment cycle 1, 50.1% (217/433) during BOTOX treatment cycle 2, 51.5% (86/167) during BOTOX treatment cycle 3, and 49.4% (39/79) during BOTOX treatment cycle 4. No change was observed in the overall safety profile with repeat dosing and no unexpected new adverse events were observed in patients exposed to multiple BOTOX treatments.

III.3.3 Deaths

Four deaths were reported in the Overall Safety Population. All four patients had been treated with BOTOX (and placebo in one case). None of these deaths was considered to be related to study treatment (2 myocardial infarctions, 1 cerebral infarction, 1 atrial fibrillation and pneumonia).

III.3.4 Other serious AEs

In the Overall Safety Population, the incidence of serious adverse events during DBPC exposure was 11.1% (46/415) for the All BOTOX group and 8.7% (23/265) for the placebo group and was similar across the BOTOX dose groups. The most frequently reported serious adverse event during DBPC exposure for the All BOTOX group was convulsion, which occurred in 0.7% (3/415) of patients, and for the placebo group was epilepsy, which occurred in 1.5% (4/265) of patients. None of these serious adverse events resulted in study discontinuation and none was considered to be related to study drug. Such events likely reflect the underlying conditions observed in this post-stroke patient population.

Four of these serious adverse events were considered by the investigator to be treatment-related; three in BOTOX-treated patients (arthralgia, muscular weakness, and myalgia) and one in a placebo-treated patient (deep vein thrombosis). There were no notable differences in the types and frequencies of serious adverse events between BOTOX-treated and placebo-treated patients.

The overall incidence of serious adverse events for patients in the All BOTOX group with Any BOTOX exposure was 14.4% (90/625). There were four additional treatment-related serious adverse events during Any BOTOX exposure (muscular weakness, epilepsy, back pain, and gastrointestinal hypomotility).
Overall, the serious adverse events reported represent the co-morbidities and natural history of underlying cardiovascular and atherosclerotic disease of the post-stroke elderly population in these studies.

*It is noteworthy that the relation to treatment as assessed by the investigator was considered to be indirect in some cases (i.e. myalgia secondary to muscular weakness requiring efforts to walk, epilepsy caused by more walking, back pain due to changes in walking ability).*

**III.3.5 Adverse events leading to study discontinuation**

There was a very low incidence of discontinuations due to adverse events across all studies. For the Overall Safety Population, the discontinuation rate due to adverse events was 1.4% (6/415) of patients in the All BOTOX group and no patients in the placebo group during DBPC exposure. The incidence of discontinuation in the All BOTOX group was 2.4% (15/625) during Any BOTOX exposure. Most discontinuations due to adverse events were consistent with the underlying condition of the population studied.

**III.3.6 Adverse events of interest**

**Distant spread of toxin**

Across the eight pooled studies in lower limb spasticity, 45 unique patients (37 treated with BOTOX [21 following DBPC exposure] and eight treated with placebo only) reported possible DSOT adverse events. In the Overall Safety Population, PDSOT events were reported in 5.1% (21/415) of BOTOX-treated patients and 3.0% (8/265) of placebo-treated patients during DBPC exposure, and in 5.9% (37/625) of patients with Any BOTOX exposure. The most frequently reported PDSOT events in both the BOTOX and placebo-treated groups during DBPC exposure were constipation and muscular weakness. The incidence of constipation was 1.0% (4/415) in the All BOTOX group and 1.1% (3/265) in the placebo group and the incidence of muscular weakness was 1.4% (6/415) in the All BOTOX group and 0.4% (1/265) in the placebo group. The 2 most commonly reported adverse events during Any BOTOX exposure in the Overall Safety Population were constipation (14/625; 2.2%) and muscular weakness (9/625; 1.4%).

Constipation is not unexpected, since it is a common comorbid condition observed in post-stroke patients. There was a higher incidence of muscular weakness in the BOTOX ≥ 400 U group (4/49; 8.2%); however, these events occurred only during treatment cycle 1 and did not recur in these patients. All muscular weakness events occurred 2 to 31 days after study drug administration and were considered by the investigator to be related to study treatment. Two of these events were considered to be serious. All events of muscular weakness were determined to be local, with weakness in the injected limb(s) and consistent with the BOTOX mechanism of action, with the exception of one case for which location of weakness was not specified. The overall incidence of muscular weakness decreased with repeat treatment cycles.

Dyspnoea was reported in 1.0% (4/415) of BOTOX-treated patients and 0.4% (1/265) of placebo-treated patients during DBPC exposure, and in 0.8% (5/625) of patients with Any BOTOX exposure in the Overall Safety Population. All cases of dyspnoea were either confounded by underlying comorbid conditions or were inconsistent with the pharmacologic effect of BOTOX with respect to time to onset.

**III.3.7 Adverse Drug reactions**

ADRs were determined by evaluating adverse events that occurred with a ≥ 1% overall incidence rate and ≥ 1% difference in incidence rates between the All BOTOX and the placebo groups in the Lower Limb Injections Only subpopulation. Additionally, any noteworthy adverse events not meeting the ≥ 1% difference between the All BOTOX group and the placebo group, or those occurring at an incidence rate of < 1% in the All BOTOX group during the DBPC exposure period, were also evaluated. Medical judgment was further applied, taking into consideration the extent to which the adverse event was consistent with the pharmacology of BOTOX and the consistency of the pattern of symptoms across studies/indications, and any apparent dose-response trend. This included a review of events with incidence rates of < 1%.

Based on these criteria, the following ADRs were identified: arthralgia, peripheral oedema, musculoskeletal stiffness, and rash. These events will be included in the SmPC as common adverse reactions (Table 18).
### Table 18  Adverse drug reactions (Lower Limb Injections Only Population; DBPC Exposure)

<table>
<thead>
<tr>
<th>Adverse Event Preferred Terma</th>
<th>BOTOX 100 U – 199 U (N = 66)</th>
<th>BOTOX 200 U - 299 U (N = 89)</th>
<th>BOTOX 300 U - 399 U (N = 141)</th>
<th>BOTOX ≥ 400 U (N = 11)</th>
<th>All BOTOX Doses (N = 307)</th>
<th>Placebo (N = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>48 (72.7)</td>
<td>57 (64.0)</td>
<td>73 (51.8)</td>
<td>7 (63.6)</td>
<td>185 (60.3)</td>
<td>112 (59.3)</td>
</tr>
<tr>
<td>≥1% exposed to all BOTOX doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (6.1)</td>
<td>7 (7.9)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>11 (3.6)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>2 (3.0)</td>
<td>4 (4.5)</td>
<td>4 (2.8)</td>
<td>1 (9.1)</td>
<td>11 (3.6)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>1 (1.5)</td>
<td>1 (1.1)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>4 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (1.5)</td>
<td>1 (1.1)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>4 (1.3)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Injection procedure-related adverse events were also evaluated. Injection site pain, injection site haematoma, injection site paraesthesia, and injection site thrombosis occurred at an incidence rate in the All BOTOX group versus the placebo group of 4.2% versus 5.3%, 0.0% versus 1.1%, 0.0% versus 0.5%, and 0.0% versus 0.5%, respectively. The only event that occurred in the All BOTOX group was injection site pain; however, this event is not being proposed to be added to the SmPC because it did not occur more frequently in the All BOTOX group versus the placebo group and did not meet the ADR selection criteria described above. Furthermore, this concept is already adequately covered in Sections 4.4 and 4.8 (General) of the SPC.

The methodology used to define ADRs is acceptable. The list of ADRs is agreed. It is unclear whether the site of these ADRs was local; it was specified in the application for peripheral oedema (injected limb) and arthralgia (lower limb).

Of note, although the AE of fall was more frequent with BOTOX in the Overall Safety Population, this was not the case in the Lower Limb Only Population (5.9% vs. 5.3%).

#### III.3.8 Immunogenicity

In the two studies where neutralizing antibodies were evaluated, none of the patients with baseline or post-baseline serum samples tested positive for the presence of neutralizing antibodies.

#### III.3.9 Safety conclusions

- The safety database includes a sufficient number of patients that have received various doses of BOTOX (up to 400 U) in the lower limb but also in combination with the upper limb. The median and most frequent dose administered was 300 U, which is the recommended dose for this indication.
- Overall, 35% of the population was ≥ 65 years old with twice as many males than females, which is representative of the target population.
- The safety profile of BOTOX was as expected, with a low incidence of ADRs, essentially of local origin.
- There was no evidence of distant toxin spread in the trials and no neutralising antibodies were detected.

#### Risk Management Plan

##### Updates to the RMP

**A. Product Overview**

The list of indications includes those approved in Australia, which is not an EU CMS. Therefore, whilst this is of interest, the RMP covers EU indications and safety information; therefore information relating to use in Australia should be removed and addressed in the PSUR. As the MA in the UK is a national authorisation, all indications listed in the UK should be clearly identified.
B. Safety specifications

No additional safety issues have been identified in relation to the submitted application for lower limb spasticity in adults. However it is recognised that there is some off-label use in the paediatric population with cerebral palsy and torticollis, discussed in section SVI.6.2.1.

The DUS indicates that off-label use in this patient population is limited, with the most frequently treated indication in paediatric patients as spasticity in cerebral palsy (77%), with 4% spasticity from stroke, traumatic brain injury and spinal cord injury (2008 data). Of 264 paediatric patients in the EU, only 1.5% were treated for cervical dystonia.

A review of all adverse events cases for paediatric patients was conducted and presented in detail in PSUR #21. Of 75 reports identified, 17 were serious, two of which were fatal. Both fatal cases were confounded either by concurrent medical conditions (recent severe influenza, history of tuberculous meningitis) or by recent surgical procedure (bilateral adductor lengthening surgery).

In compliance with the FDA’s Pediatric Research Equity Act (PREA) requirements, the MAH is evaluating the safety and efficacy of Botox in paediatric patients with upper limb (Studies 191622-101, 191622-105) or lower limb spasticities secondary to cerebral palsy (Studies 191622-111, 191622-112). These studies will provide additional important safety information in paediatric patients aged 2-17 years with cerebral palsy.

This section gives a detailed review of paediatric off-label use in relation to torticollis, with use and events mainly originating from Japan where this is an off-label use. Only 4% of reports originate from the off-label use of spasticity originating from stroke. Therefore there appears to be little paediatric use with respect to the proposed indication, which may reflect the general incidence of this event in the paediatric population, and hence does not appear to be a great risk in the EU at this time. It is sufficient that paediatric use will continue to be monitored through the PSUR.

C. Summary of safety concerns

The MAH has not identified any new safety concerns for focal spasticity in the ankle. The MAH identifies the following safety concerns in the Botox RMP:
The MAH proposes to remove the potential risks of:
- Seizure
- Cardiovascular events
- Death
- Guillain-Barré Syndrome

Justification for removal of potential risks is presented in Annex 12 of the RMP. Summary reports of analyses justifying the removal of these potential risks based on risk estimates for events of seizures, cardiovascular events (using SMQs for cardiac ischaemia and cardiac arrhythmias), death and Guillain-Barré syndrome, are presented in Annex 12.

In addition, the MAH is proposing to remove renal and hepatic impairment as important missing information. Reports of patients with a history of hepatic or renal impairment were routinely evaluated since PSUR #8 (January 2004). There have not been any safety concerns regarding the use of BOTOX® in these patients. Furthermore, there is no expectation that BOTOX® has any direct or indirect effect upon hepatic or renal metabolism and/or clearance functions. Therefore, Allergan proposes to remove patients with renal or hepatic impairment as an underrepresented population with important missing information.

The potential risks of seizures, cardiovascular events, death and Guillain-Barré syndrome are currently being reviewed through annual PSURs, submitted through the work-sharing program, and are being reviewed by IE as P-RMS. The PSUR will contain the more complete data set, and hence a fuller evaluation will be possible through the assessment of the PSUR. The removal of these risks do not relate to the proposed extension to the indications. Special warnings and precaution in section 4.4 refer to these risks, which state that the relationship to Botox is unknown. This does not dismiss a potential association and potential risk Therefore until a fuller evaluation of the data is possible, these potential risks should remain therefore removal from the RMP is not approved through this procedure.

Similarly, a cumulative review of all cases of renal and hepatic impairment should be undertaken through the PSUR to enable a complete assessment of the information available for patients with renal or hepatic impairment. No clinical studies have included these patients, and no further data has been presented through
this submission. Therefore until a more complete analysis is possible through the PSUR, then renal and hepatic impairment should remain as important missing information.

D. Pharmacovigilance Plan

Part III of the RMP describes ongoing and planned additional pharmacovigilance studies. These are summarised in the table 9-26 of the RMP. In relation to the new indication, the following two studies are being undertaken as requested by the FDA:

<table>
<thead>
<tr>
<th>Study</th>
<th>Objectives</th>
<th>Safety concerns addressed</th>
<th>Status (planned, started)</th>
<th>Date for submission of interim or final reports (planned or actual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-marketing commitment study (FDA): BOTOX&lt;sup&gt;®&lt;/sup&gt;</td>
<td>To evaluate the safety and efficacy of a single treatment of 2 doses (4 U/kg and 8 U/kg) of BOTOX&lt;sup&gt;®&lt;/sup&gt; with standardised physical therapy in pediatric patients with lower limb spasticity</td>
<td>Dysthagia in cervical dystonia, Disturb spread of tonus</td>
<td>US/EU/APAC studies started</td>
<td>No interim analysis is planned</td>
</tr>
<tr>
<td>Post-marketing commitment study (FDA): BOTOX&lt;sup&gt;®&lt;/sup&gt;</td>
<td>To evaluate long-term safety of repeated doses of BOTOX&lt;sup&gt;®&lt;/sup&gt; for the treatment of pediatric lower limb spasticity</td>
<td>Dysthagia in cervical dystonia, Disturb spread of tonus</td>
<td>US/EU/APAC studies started</td>
<td>Submission: May 2016, Approval: June 2017</td>
</tr>
</tbody>
</table>

The proposed indication is for use in the adult population. The SmPC contains a statement that use in children <18 years is not recommended for upper limb spasticity and is amended as follows: “The safety and effectiveness of BOTOX in the treatment of upper & lower limb spasticity associated with stroke have not been established in children and adolescents under 18 years of age”. This is sufficient.

The above studies will mainly be examining use in patients with cerebral palsy, for which there is an approved indication. However, paediatric patients with focal spasticity following stroke are not excluded from this study and therefore, may provide some safety information in the paediatric population, although this will be limited.

It is apparent that Botox could be used off-label in patients <18 years with upper or lower limb spasticity following stroke, therefore the outcome of these studies should be reported in the RMP when available.

E. Risk minimisation measures

No further risk minimisation measures have been undertaken in respect of this new indication in the UK.

The summary of risk minimisation measures requires updating to replace the potential risks of seizure, cardiovascular events, death and Guillain-Barré syndrome. In addition renal and liver should be replaced as important missing information.

RMP conclusion

The applicant has committed to providing an updated RMP as a type II variation in order to address the above comments. This is underway.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

This application is for an extension of indication to ankle disability due to post-stroke spasticity in adults whereas BOTOX is already approved in other focal spasticity indications of the upper limb (post-stroke) and lower limb (cerebral palsy in children).

Benefits

Beneficial effects

- Evidence of the efficacy of BOTOX at the dose of 300U has been provided based on the measurement of ankle muscle tone using a validated spasticity scale (modified Ashworth scale from 0 to 4). A statistically significant difference in the mean area under the curve of the change from baseline MAS
was observed between the BOTOX 300 U and placebo arms (-8.5 versus -5.1, p = 0.006). The conclusion regarding the primary efficacy results is robust to the method of analysis

- These results are consistent with those of two supportive studies. Overall, amongst the most affected patient, i.e. those with a baseline score of 3 or 4, the proportion of responders (patients who achieved a ≥ 1 reduction from baseline muscle tone ankle score) ranged between 61% and 68% after BOTOX treatment vs. 29% to 39% on placebo. Significant and clinically meaningful improvement in range of motion (dorsiflexor angle) and ambulation was also shown in one of the supportive studies.

- Other outcomes more closely related to patient benefit support the muscle tone results, in particular ease/pain at passive stretching and interference of pain with work.

- Although improvement in walking speed appeared inconsistent across studies, the attainment scores of pre-defined functional goals (especially on ambulation) were shown to be significantly higher with BOTOX than with placebo in a Health Economics Study. The proportion of patients achieving their primary and secondary functional goals was higher in the BOTOX group (53% and 69%, respectively) compared to the placebo group (37% and 31%), respectively; the difference was significant for the secondary goal, primarily related to relief of symptoms.

- As already known, BOTOX showed a maximum effect after 6-8 weeks, which waned after approximately 12 weeks. Repeated injections appeared to increase BOTOX effects.

Uncertainty in the knowledge about the beneficial effects

- Although statistically significant, the clinical relevance of the treatment effect measured on the primary endpoint (ankle score) is difficult to evaluate. Indeed, no minimally important difference has been established for this score. Therefore, improvement in other efficacy endpoints is considered essential to evaluate the actual benefit of BOTOX treatment in a patient population with a broad spectrum of gait and walking impairments. In this respect, improvement in passive stretch and in the dorsiflexor active angle as well as reduction in cramps and pain appear particularly relevant as these changes may impact rehabilitation therapies and the patient’s ability to walk and work.

- Effects on gait were not uniformly statistically significant, suggesting that improvements with BOTOX may be more subtle and individualized and therefore not readily detectable with objective gait ratings. However, supportive data from patient-related outcomes have been provided.

Risks

Unfavourable effects

- The safety database includes a sufficient number of patients that have received various doses of BOTOX (up to 400 U) in the lower limb but also in combination with the upper limb. The median and most frequent dose administered was 300 U, which is the recommended dose for this indication.

- Overall, 35% of the population was ≥ 65 years old with twice as many males than females, which is representative of the target population.

- The safety profile of BOTOX injected in various muscles of the limbs is well known, including after repeated injections; a low incidence of ADRs, essentially of local origin, was reported.

- There was no evidence of distant toxin spread in the trials and no neutralising antibodies were detected.

Benefit-risk balance

BOTOX injections into various muscles of the lower limb for the management of post-stroke spasticity are already recommended in treatment guidelines. While the treatment effect measured with a muscle tone scale did not appear dramatic in placebo-controlled trials, patient benefit was reflected in several outcomes, including walking improvement and pain reduction. Moreover, the achievement of individual outcomes focused on improvements in function and participation which are relevant to the patient or their carers is considered essential. The safety profile of BOTOX is well known.

Based on the evidence provided by outcomes closely related to patient clinical benefit, the benefit-risk balance of BOTOX is considered positive at the 300 U dose. However, patients should only be treated if improvement in these areas can be realistically expected. The MAH has included a cautionary statement to address this point in the SmPC (section 4.4).
In conclusion, it is considered that the extension of the spasticity indications of BOTOX to the lower limb (ankle) after a stroke is approvable.

The extension of indication is approved (25-01-2014).

### 4.1 Therapeutic indications

BOTOX is indicated for:

- the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
- the prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)
- the management of bladder dysfunctions in adult patients who are not adequately managed with anticholinergics
  - overactive bladder with symptoms of urinary incontinence, urgency and frequency
  - neurogenic detrusor overactivity with urinary incontinence due to subcervical spinal cord injury (traumatic or non-traumatic), or multiple sclerosis

BOTOX is also indicated for focal spasticity, including the treatment of:

- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older
- wrist and hand disability due to upper limb spasticity associated with stroke in adults
- ankle disability due to lower limb spasticity associated with stroke in adults

BOTOX is also indicated for the temporary improvement in the appearance of the following facial lines, when the severity of these lines has an important psychological impact in adult patients:

- moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines)
- moderate to severe lateral canthal lines (crow’s feet lines) seen at maximum smile
- moderate to severe crow’s feet lines seen at maximum smile and glabellar lines seen at maximum frown when treated simultaneously.

### 4.2 Posology and method of administration

**Posology**

Refer to specific recommendations for each indication described below.

**Botulinum toxin units are not interchangeable from one product to another.** Doses recommended in Allergan units are different from other botulinum toxin preparations.

**This product is for single use only and any unused solution should be discarded.** The most appropriate vial size should be selected for the indication.

An injection volume of approximately 0.1 ml is recommended. A decrease or increase in the BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For instructions on reconstitution of the powder for solution for injection, handling and disposal of vials please refer to section 6.6.
**Elderly patients**

Overall, with the exception of overactive bladder, adequate studies on geriatric dosing have not been performed. The lowest effective dose with the longest clinically indicated interval between injections is recommended. Elderly patients with significant medical history and concomitant medications should be treated with caution (for Overactive bladder see sections 4.8 and 5.1).

There is limited phase 3 clinical data with BOTOX for glabellar lines in patients older than 65 years (see section 5.1).

There is very limited data with BOTOX in patients older than 65 years treated for urinary incontinence with neurogenic detrusor overactivity.

**Paediatric population**

The safety and effectiveness of BOTOX in the treatment of blepharospasm, hemifacial spasm, idiopathic cervical dystonia in children (under 12 years) have not been demonstrated.

The safety and effectiveness of BOTOX in the treatment of primary hyperhidrosis of the axillae have not been investigated in children under 12 years. The safety and efficacy of BOTOX in adolescents aged 12 to 17 years for the treatment of severe axillary hyperhidrosis have not been established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made (see sections 4.8 and 5.1).

The safety and effectiveness of BOTOX in the treatment of glabellar lines seen at maximum frown and/or crow’s feet lines seen at maximum smile, in the prophylaxis of chronic migraine headaches and in the management of overactive bladder and urinary incontinence with neurogenic detrusor overactivity have not been demonstrated in individuals under 18 years of age. The use of BOTOX is not recommended in patients less than 18 years for these indications.

The safety and effectiveness of BOTOX have not been established in children below the age of 2 years for cerebral palsy.

The safety and effectiveness of BOTOX in the treatment of upper and lower limb spasticity associated with stroke have not been established in children and adolescents under 18 years of age.

**Method of Administration**

**Refer to specific guidance for each indication described below.**

BOTOX should only be administered by physicians with appropriate qualifications and expertise in the treatment and the use of the required equipment.

Generally valid optimum dose levels and number of injection sites per muscle have not been established for all indications. In these cases, individual treatment regimens should therefore be drawn up by the physician. Optimum dose levels should be determined by titration but the recommended maximum dose should not be exceeded.

**Blepharospasm/hemifacial spasm**

Reconstituted BOTOX is injected using a sterile, 27-30 gauge/0.40-0.30 mm needle. Electromyographic guidance is not necessary. The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision. Avoiding injection near levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. The following diagrams indicate the possible injection sites:
In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. The initial dose should not exceed 25 Units per eye. Normally no additional benefit is conferred by treating more frequently than every three months.

In the management of blepharospasm total dosing should not exceed 100 Units every 12 weeks.

Patients with hemifacial spasm or VIIth nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

**Cervical dystonia**

Several dosing regimens have been used in clinical trials for treatment of cervical dystonia with BOTOX. Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response.

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted BOTOX ranged from 140 to 280 Units. In more recent studies, the doses have ranged from 95 to 360 Units (with an approximate mean of 240 Units). As with any drug treatment, initial dosing in a naïve patient should begin at the lowest effective dose. No more than 50 Units should be given at any one injection site. No more than 100 Units should be given to the sternomastoid. To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally. No more than 200 Units total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response. A total dose of 300 Units at any one sitting should not be exceeded.

The following doses are recommended:

<table>
<thead>
<tr>
<th>Type</th>
<th>Head position</th>
<th>Muscle(s)</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Rotated toward side of shoulder elevation</td>
<td>Sternomastoid, Levator scapulae, Scalene, Splenius capitis, Trapezius</td>
<td>50 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 75 Units; 1 - 3 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
<tr>
<td>II</td>
<td>Rotation only</td>
<td>Sternomastoid</td>
<td>25 - 100 Units; at least 2 sites if &gt;25 Units given</td>
</tr>
<tr>
<td>III</td>
<td>Tilted toward side of shoulder elevation</td>
<td>Sternomastoid, Levator scapulae, Scalene, Trapezius</td>
<td>25 - 100 Units at posterior border; at least 2 sites if &gt;25 Units given</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 75 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
<tr>
<td>IV</td>
<td>Bilateral posterior cervical muscle spasm with elevation of the face</td>
<td>Splenius capitis and cervicis</td>
<td>50 - 200 Units; 2 - 8 sites, treat bilaterally</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(This is the total dose and not the dose for each side of the neck)</td>
</tr>
</tbody>
</table>
The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, semispinalis, longissimus and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment. The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose. Muscle activation patterns can change spontaneously in cervical dystonia without a change in the clinical presentation of dystonia.

A 25, 27 or 30 gauge/0.50-0.30 mm needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature. In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance.

Multiple injection sites allow BOTOX to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. Treatment intervals of less than 10 weeks are not recommended. The duration of beneficial effect reported in clinical trials showed substantial variation (from 2 to 33 weeks) with a typical duration of approximately 12 weeks.

**Primary hyperhidrosis of the axillae**

The recommended injection volume for intradermal injection in axillary hyperhidrosis is 0.1-0.2 ml. Reconstituted BOTOX (100 Units/4 mL) is injected using a 30 gauge needle. 50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart. The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor’s iodine-starch test. Doses other than 50 Units per axilla cannot be recommended.

Clinical improvement generally occurs within the first week after injection. Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating physician deems it necessary. Treatment response has been reported to persist for 4-7 months. Injections should not be repeated more frequently than every 16 weeks (see section 5.1).

**Paediatric cerebral palsy**

Reconstituted BOTOX is injected using a sterile 23-26 gauge/0.60-0.45 mm needle. It is administered as a divided dose through single injections into the medial and lateral heads of the affected gastrocnemius muscle. In hemiplegia, the initial recommended total dose is 4 Units/kg body weight in the affected limb. In diplegia, the initial recommended total dose is 6 Units/kg body weight divided between the affected limbs. The total dose should not exceed 200 Units.

Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months. It may be possible to adapt the dosage regimen to obtain an interval of at least six months between treatment sessions.

**Focal upper and lower limb spasticity associated with stroke**

Reconstituted BOTOX is injected using a sterile 25, 27 or 30 gauge needle. Needle length should be determined based on muscle location and depth. Localisation of the involved muscles with techniques such as electromyographic guidance, nerve stimulation, or ultrasound is recommended. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

If it is deemed appropriate by the treating physician, the patient should be considered for re-injection when the clinical effect of the previous injection has diminished, but generally no sooner than 12 weeks after the previous injection.
**Upper limb spasticity**

The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, the presence of local muscle weakness, and the patient response to previous treatment.

In the controlled clinical trials the following doses were administered:

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Total Dosage; Number of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum profundus</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>15 - 60 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>10 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units; 1-2 sites</td>
</tr>
</tbody>
</table>

In controlled and open non-controlled clinical trials doses between 200 and 240 Units divided among selected muscles have been used at a given treatment session.

In controlled clinical trials patients were followed for 12 weeks after single treatment. Improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open, non-controlled continuation study, most of the patients were re-injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximal cumulative dose of 960 Units over 54 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected. The lowest effective dose should be used.

**Lower limb spasticity**

The recommended dose for treating adult lower limb spasticity involving the ankle is 300 Units divided among 3 muscles.

The following diagrams indicate the injection sites for adult lower limb spasticity:

**BOTOX Dosing by Muscle for Adult Lower Limb Spasticity:**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose Total Dosage; Number of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius</td>
<td></td>
</tr>
<tr>
<td>Medial head</td>
<td>75 Units; 3 sites</td>
</tr>
<tr>
<td>Lateral head</td>
<td>75 Units; 3 sites</td>
</tr>
<tr>
<td>Soleus</td>
<td>75 Units; 3 sites</td>
</tr>
<tr>
<td>Tibialis Posterior</td>
<td>75 Units; 3 sites</td>
</tr>
</tbody>
</table>
**Chronic migraine**
The recommended reconstituted BOTOX dose for treating chronic migraine is 155 Units to 195 Units administered intramuscularly (IM) using a 30-gauge, 0.5 inch needle as 0.1 ml (5 Units) injections to 31 and up to 39 sites. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. A 1-inch needle may be needed in the neck region for patients with extremely thick neck muscles. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck. If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis, and trapezius), up to the maximum dose per muscle as indicated in the table below.

The following diagrams indicate the injection sites:

![Diagrams of injection sites](https://example.com/diagrams)

**BOTOX Dosing By Muscle**

<table>
<thead>
<tr>
<th>Head/Neck Area</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontalis</td>
<td>20 Units (4 sites)</td>
</tr>
<tr>
<td>Corrugator</td>
<td>10 Units (2 sites)</td>
</tr>
<tr>
<td>Procerus</td>
<td>5 Units (1 site)</td>
</tr>
<tr>
<td>Occipitalis</td>
<td>30 Units (6 sites) up to 40 Units (up to 8 sites)</td>
</tr>
<tr>
<td>Temporalis</td>
<td>40 Units (8 sites) up to 50 Units (up to 10 sites)</td>
</tr>
<tr>
<td>Trapezius</td>
<td>30 Units (6 sites) up to 50 Units (up to 10 sites)</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group</td>
<td>20 Units (4 sites)</td>
</tr>
<tr>
<td><strong>Total Dose Range:</strong></td>
<td>155 Units to 195 Units</td>
</tr>
<tr>
<td></td>
<td>31 to 39 sites</td>
</tr>
</tbody>
</table>

\*1 IM injection site = 0.1 mL = 5 Units BOTOX  
\*Dose distributed bilaterally

The recommended re-treatment schedule is every 12 weeks.

**Overactive bladder**
The recommended dose is 100 Units of BOTOX, as 0.5 ml (5 Units) injections across 20 sites in the detrusor muscle.

The reconstituted solution of BOTOX (100 Units/10 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 ml of the reconstituted BOTOX prior to the start of the injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 ml each (total volume 10 ml) should be spaced approximately 1 cm apart (see figure below). For the
final injection, approximately 1 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should not be drained so that the patients can demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

For the patient preparation and monitoring, see section 4.4.

Re-treatment
Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median duration in phase 3 clinical studies was ~24 weeks), but no sooner than 3 months from the prior bladder injection.

Urinary incontinence due to neurogenic detrusor overactivity
The recommended dose is 200 Units of BOTOX, as 1 ml (~6.7 Units) injections across 30 sites in the detrusor muscle.

The reconstituted solution of BOTOX (200 Units/30 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 ml prior to the start of the injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 ml each (total volume 30 ml) should be spaced approximately 1 cm apart (see figure above). For the final injection, approximately 1 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection should be injected so the full dose is delivered. After the injections are given, the saline used for bladder wall visualisation should be drained.

For the patient preparation and monitoring, see section 4.4.

Re-treatment
Patients should be considered for reinjection when the clinical effect of the previous injection has diminished, but no sooner than 3 months from the prior bladder injection. In phase 3 clinical studies, the median interval between the first and second administrations was 42 weeks in patients with spinal cord injury and 45 weeks in patients with multiple sclerosis.
Limited data are available beyond 2 treatments. No urodynamic data beyond 2 treatments and no histopathological data after repeated treatment are currently available.

Patients should not receive multiple treatments in the event of limited symptomatic improvement.

**Glabellar lines seen at maximum frown**
Reconstituted BOTOX (50 Units/1.25 mL) is injected using a sterile 30 gauge needle. A volume of 0.1 mL (4 Units) is administered in each of the 5 injection sites (see Figure 1): 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units.

Before injection, the thumb or index finger is to be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection. In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercili). Injections in the corrugator muscle must be done in the central part of that muscle, a distance of at least 1 cm above the arch of the eyebrows.

Figure 1:

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the vertical lines between the eyebrows seen at maximum frown (also known as glabellar lines), see section 4.4.

Improvement of severity of vertical lines between the eyebrows seen at maximum frown (glabellar lines) generally occurs within one week after treatment. The effect was demonstrated for up to 4 months after injection.

Treatment intervals should not be more frequent than every three months. In the event of treatment failure or diminished effect following repeat injections, alternative treatment methods should be employed.

In case of insufficient dose initiate a second treatment session by, adjusting the total dose up to 40 or 50 units, taking into account the analysis of the previous treatment failure (see information in All indications).

The efficacy and safety of repeat injections of BOTOX for the treatment of glabellar lines beyond 12 months has not been evaluated.
Crow’s feet lines seen at maximum smile
Reconstituted BOTOX (50 Units/1.25 ml) is injected using a sterile 30 gauge needle 0.1 ml (4 Units) is administered in each of the 3 injection sites per side (total of 6 injection sites) in the lateral orbicularis oculi muscle, for a total dose of 24 Units in a total volume of 0.6 ml (12 Units per side).

In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded. In addition, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

Injections should be given with the needle tip bevel up and oriented away from the eye. The first injection (A) should be made approximately 1.5 to 2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow’s feet region are above and below the lateral canthus, inject as shown in Figure 2. Alternatively, if the lines in the crow’s feet region are primarily below the lateral canthus, inject as shown in Figure 3.

Figure 2:     Figure 3:

For simultaneous treatment with glabellar lines seen at maximum frown, the dose is 24 Units for crow’s feet lines seen at maximum smile and 20 Units for glabellar lines (see Administration Instructions for glabellar lines, and Figure 1), for a total dose of 44 Units in a total volume of 1.1 ml.

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the lateral canthal lines seen at maximum smile (also known as crow’s feet lines), see section 4.4.

Improvement of severity of crow’s feet lines seen at maximum smile, when assessed by the investigator, occurred within one week of treatment. The effect was demonstrated for a median of 4 months after injection.

Treatment intervals should not be more frequent than every 3 months.

The efficacy and safety of repeat injections of BOTOX for the treatment of crow’s feet lines beyond 12 months has not been evaluated.

All indications
In case of treatment failure after the first treatment session, i.e. absence, at one month after injection, of significant clinical improvement from baseline, the following actions should be taken:

- Clinical verification, which may include electromyographic examination in a specialist setting, of the action of the toxin on the injected muscle(s);
Analysis of the causes of failure, e.g. bad selection of muscles to be injected, insufficient dose, poor injection technique, appearance of fixed contracture, antagonist muscles too weak, formation of toxin-neutralising antibodies;

Re-evaluation of the appropriateness of treatment with botulinum toxin type A;

In the absence of any undesirable effects secondary to the first treatment session, instigate a second treatment session as following: i) adjust the dose, taking into account the analysis of the earlier treatment failure; ii) use EMG; and iii) maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections alternative treatment methods should be employed.

4.4 Special warnings and precautions for use

The recommended dosages and frequencies of administration of BOTOX should not be exceeded due to the potential for overdose, exaggerated muscle weakness, distant spread of toxin and the formation of neutralising antibodies. Initial dosing in treatment naïve patients should begin with the lowest recommended dose for the specific indication.

Prescribers and patients should be aware that side effects can occur despite previous injections being well tolerated. Caution should therefore be exercised on the occasion of each administration.

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exaggerated muscle weakness.

Elderly and debilitated patients should be treated with caution.

Consideration should be given to the risk-benefit implications for the individual patient before embarking on treatment with BOTOX.

Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 ‘Cervical Dystonia’).

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Lambert-Eaton Syndrome in patients with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) and in patients with underlying neurological disorders. Such patients may have an increased sensitivity to agents such as BOTOX, even at therapeutic doses, which may result in excessive muscle weakness and an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

As with any treatment with the potential to allow previously-sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually.
The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX and injection into vulnerable anatomic structures must be avoided.

Pneumothorax associated with injection procedure has been reported following the administration of BOTOX near the thorax. Caution is warranted when injecting in proximity to the lung (particularly the apices) or other vulnerable anatomic structures.

Serious adverse events including fatal outcomes have been reported in patients who had received off-label injections of BOTOX directly into salivary glands, the oro-lingual-pharyngeal region, oesophagus and stomach. Some patients had pre-existing dysphagia or significant debility.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted. One case of anaphylaxis has been reported in which the patient died after being injected with BOTOX inappropriately diluted with 5 ml of 1% lidocaine.

As with any injection, procedure-related injury could occur. An injection could result in localised infection, pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.

Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

There have been rare reports of adverse events following administration of BOTOX involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to botulinum toxin injection has not been established. The reports in children were predominantly from cerebral palsy patients treated for spasticity.

Formation of neutralising antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest clinically indicated intervals between injections.

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

**Paediatric use**

The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 has not been established. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

**Blepharospasm**
Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles.

**Cervical dystonia**
Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 Units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the oesophageal musculature. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia may contribute to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX injection.

**Primary hyperhidrosis of the axillae**
Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

**Focal spasticity associated with paediatric cerebral palsy and spasticity of the ankle, hand and wrist in adult post-stroke patients**
BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

BOTOX should only be used for the treatment of focal spasticity in adult post-stroke patients if muscle tone reduction is expected to result in improved function (e.g. improvements in gait), or improved symptoms (e.g. reduction in muscle spasms or pain), and/or to facilitate care.
Caution should be exercised when treating adult patients with post-stroke spasticity who may be at increased risk of fall. In clinical studies where patients were treated for lower limb spasticity (some of whom also received concurrent treatment for upper limb spasticity), the incidence of fall was 7.2% and 4.9% of patients in the BOTOX and placebo groups, respectively.

There have been post-marketing reports of death (sometimes associated with aspiration pneumonia) and of possible distant spread of toxin in children with co-morbidities, predominantly cerebral palsy following treatment with botulinum toxin. See warnings under section 4.4, ‘Paediatric use’.

**Chronic migraine**
No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

**Bladder dysfunctions**

*Patient preparation and monitoring*
Prophylactic antibiotics should be administered to patients with sterile urine or asymptomatic bacteriuria in accordance with local standard practice.

The decision to discontinue anti-platelet therapy should be subject to local guidance and benefit/risk consideration for the individual patient. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate medical caution should be exercised when performing the cystoscopy. The patient should be observed for at least 30 minutes post-injection.

In patients who are not regularly practicing catheterisation, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate. Patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required.

**Overactive bladder**
Prior to injection an intravesical instillation of diluted local anaesthetic, with or without sedation, may be used, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.

**Urinary incontinence due to neurogenic detrusor overactivity**
BOTOX injection can be performed under general or local anaesthesia with or without sedation. If a local anaesthetic intravesical instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.

Autonomic dysreflexia associated with the procedure can occur and greater vigilance is required in patients known to be at risk.

**Glabellar lines seen at maximum frown and/or crow’s feet lines seen at maximum smile**
It is mandatory that BOTOX is used for one single patient treatment only during a single session. The excess of unused product must be disposed of as detailed in section 6.6. Particular precautions should be taken for product preparation and administration as well as for the inactivation and disposal of the remaining unused solution (see section 6.6).

The use of BOTOX is not recommended in individuals under 18 years. There is limited phase 3 clinical data with BOTOX in patients older than 65 years.

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the vertical lines between the eyebrows seen at maximum frown (also known as glabellar lines) or in the lateral canthal lines seen at maximum smile (also known as crow’s feet lines), see section 4.2. There is a risk of eyelid ptosis following treatment, refer to Section 4.2 for administration instructions on how to minimise this risk.
4.8 Undesirable effects

a) General
In controlled clinical trials adverse events considered by the investigators to be related to BOTOX were reported in 35% of the patients with blepharospasm, 28% with cervical dystonia, 17% with paediatric cerebral palsy, 11% with primary hyperhidrosis of the axillae, 16% with focal spasticity of the upper limb associated with stroke, 15% with focal spasticity of the lower limb associated with stroke, 26% with overactive bladder, and 32% with neurogenic detrusor overactivity. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In controlled clinical trials for glabellar lines seen at maximum frown, adverse events considered by the investigators to be related to BOTOX were reported in 23% (placebo 19%) of patients. In treatment cycle 1 of the pivotal controlled clinical trials for crow’s feet lines seen at maximum smile, such events were reported in 8% (24 Units for crow’s feet lines alone) and 6% (44 Units: 24 Units for crow’s feet lines administered simultaneously with 20 Units for glabellar lines) of patients compared to 5% for placebo.

Adverse reactions may be related to treatment, injection technique or both. In general, adverse reactions occur within the first few days following injection and, while generally transient, may have a duration of several months or, in rare cases, longer.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue.

As is expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope. Fever and flu syndrome have also been reported after injections of botulinum toxin.

b) Adverse reactions - frequency by indication
For each indication the frequency of adverse reactions arising from clinical experience is given. The frequency is defined as follows:
Very Common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000).

Blepharospasm/hemifacial spasm

Nervous system disorders
Uncommon: Dizziness, facial paresis and facial palsy

Eye Disorders
Very common: Eyelid ptosis
Common: Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation and lacrimation increase
Uncommon: Keratitis, ectropion, diplopia, entropion, visual disturbance and vision blurred
Rare: Eyelid oedema
Very rare: Corneal ulceration, corneal epithelium defect and corneal perforation

Skin and subcutaneous tissue disorders
Common: Echymosis
Uncommon: Rash/dermatitis

General disorders and administration site conditions
Common: Irritation and face oedema
Uncommon: Fatigue

**Cervical dystonia**

**Infections and infestations**
Common: Rhinitis and upper respiratory infection

**Nervous system disorders**
Common: Dizziness, hypertonia, hypoesthesia, somnolence and headache

**Eye Disorders**
Uncommon: Diplopia and eyelid ptosis

**Respiratory, thoracic and mediastinal disorders**
Uncommon: Dyspnoea and dysphonia

**Gastrointestinal disorders**
Very common: Dysphagia (see section c. “Additional information” below)
Common: Dry mouth and nausea

**Musculoskeletal and connective tissue disorders**
Very common: Muscular weakness
Common: Musculoskeletal stiffness and soreness

**General disorders and administration site conditions**
Very common: Pain
Common: Asthenia, influenza like illness and malaise
Uncommon: Pyrexia

**Paediatric cerebral palsy**

**Infections and infestations**
Very common: Viral infection and ear infection

**Nervous system disorders**
Common: Somnolence, gait disturbance and paraesthesia

**Skin and subcutaneous tissue disorders**
Common: Rash

**Musculoskeletal and connective tissue disorders**
Common: Myalgia, muscular weakness and pain in extremity

**Renal and urinary disorders**
Common: Urinary incontinence

**Injury, poisoning and procedural complications**
Common: Fall

**General disorders and administration site conditions**
Common: Malaise, injection site pain and asthenia

**Focal upper limb spasticity associated with stroke**

**Psychiatric disorders**
Uncommon: Depression and insomnia
Nervous system disorders
Common: Hypertonia
Uncommon: Hypoaesthesia, headache, paraesthesia, incoordination and amnesia

Ear and labyrinth disorders
Uncommon: Vertigo

Vascular disorders
Uncommon: Orthostatic hypotension

Gastrointestinal disorders
Uncommon: Nausea and paraesthesia oral

Skin and subcutaneous tissue disorders
Common: Ecchymosis and purpura
Uncommon: Dermatitis, pruritus and rash

Musculoskeletal and connective tissue disorders
Common: Pain in extremity and muscle weakness
Uncommon: Arthralgia and bursitis

General disorders and administration site conditions
Common: Injection site pain, pyrexia, influenza-like illness, injection site haemorrhage and injection site irritation
Uncommon: Asthenia, pain, injection site hypersensitivity, malaise and peripheral oedema

Some of the uncommon events may be disease related.

Focal lower limb spasticity associated with stroke

Skin and subcutaneous tissue disorders
Common: Rash

Musculoskeletal and connective tissue disorder
Common: Arthralgia, musculoskeletal stiffness

General disorders and administration site conditions
Common: Peripheral oedema

Primary hyperhidrosis of the axillae

Nervous system disorders
Common: Headache and paraesthesia

Vascular disorders
Common: Hot flushes

Gastrointestinal disorders
Uncommon: Nausea

Skin and subcutaneous tissue disorders
Common: Hyperhidrosis (non-axillary sweating) skin odour abnormal, pruritus, subcutaneous nodule and alopecia

Musculoskeletal and connective tissue disorders
Common: Pain in extremity
Uncommon: Muscular weakness, myalgia and arthropathy

**General disorders and administration site conditions**

Common: Injection site pain

Uncommon: Pain, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site irritation, asthenia and injection site reactions

In the management of primary axillary hyperhidrosis, increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment, injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

In an uncontrolled safety study of BOTOX (50 Units per axilla) in paediatric patients 12 to 17 years of age (N= 144), adverse reactions occurring in more than a single patient (2 patients each) comprised injection site pain and hyperhidrosis (non-axillary sweating).

**Chronic Migraine**

**Nervous system disorders**

Common: Headache*, migraine*, facial paresis

**Eye disorders**

Common: Eyelid ptosis

Uncommon: Eyelid oedema

**Skin and subcutaneous tissue disorders**

Common: Pruritus, rash

Uncommon: Pain of skin

**Musculoskeletal and connective tissue disorders**

Common: Neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness

Uncommon: Pain in jaw

**General disorders and administration site conditions**

Common: Injection site pain

**Gastrointestinal disorders**

Uncommon: Dysphagia

* In placebo-controlled trials, headache and migraine, including serious cases of intractable or worsening of headache/migraine, were reported more frequently with BOTOX (9%) than with placebo (6%). They typically occurred within the first month after the injections and their incidence declined with repeated treatments.

**Overactive bladder**

**Infections and infestations**

Very common: Urinary tract infection

Common: Bacteriuria

**Renal and urinary disorders**
Very common: Dysuria†
Common: Urinary retention, residual urine volume*, pollakiuria, leukocyturia

*elevated post-void residual urine volume (PVR) not requiring catheterisation
†procedure-related adverse reactions

In the phase 3 clinical trials, urinary tract infection was reported in 25.5% of patients treated with BOTOX 100 Units and 9.6% of patients treated with placebo. Urinary retention was reported in 5.8% of patients treated with BOTOX 100 Units and in 0.4% of patients treated with placebo. Clean intermittent catheterisation was initiated in 6.5% of patients following treatment with BOTOX 100 Units versus 0.4% in the placebo group.

Overall, 42.5% of patients (n = 470) were ≥ 65 years of age and 15.1% (n = 167) were ≥ 75 years of age. No overall difference in the safety profile following Botox treatment was observed between patients ≥ 65 years compared to patients < 65 years in these studies, with the exception of urinary tract infection where the incidence was higher in elderly patients in both the placebo and BOTOX groups compared to the younger patients.

No change was observed in the overall safety profile with repeat dosing.

Urinary incontinence due to neurogenic detrusor overactivity

Infections and infestations
Very common: Urinary tract infection

Psychiatric disorders
Common: Insomnia†

Gastrointestinal disorders
Common: Constipation†

Musculoskeletal and connective tissue disorders
Common: Muscular weakness†, muscle spasm

Renal and urinary disorders
Very common: Urinary retention
Common: Haematuria*, bladder diverticulum

General disorders and administration site conditions
Common: Fatigue†, gait disturbance†

Injury, poisoning and procedural complications
Common: Autonomic dysreflexia*, fall†

* procedure-related adverse reactions
† only in multiple sclerosis

In the phase 3 clinical trials, urinary tract infection was reported in 49% of patients treated with BOTOX 200 Units and in 36% of patients treated with placebo (in multiple sclerosis patients: 53% vs. 29%, respectively; in spinal cord injury patients: 45% vs. 42%, respectively). Urinary retention was reported in 17% of patients treated with BOTOX 200 Units and in 3% of patients treated with placebo (in multiple sclerosis patients: 29% vs. 4%, respectively; in spinal cord injury patients: 5% vs. 1%, respectively). Among patients who were not catheterising at baseline prior to treatment, catheterisation was initiated in 39% following treatment with BOTOX 200 Units versus 17% on placebo. The risk of urinary retention increased in patients older than 65 years.

No change in the type and frequency of adverse reactions was observed following 2 treatments.
Glabellar lines

Infections and infestations
Uncommon: Infection

Psychiatric disorders
Uncommon: Anxiety

Nervous system disorders
Common: Headache
Uncommon: Paraesthesia, dizziness

Eye disorders
Common: Eyelid ptosis
Uncommon: Blepharitis, eye pain, visual disturbance

Gastrointestinal disorders
Uncommon: Nausea, oral dryness

Skin and subcutaneous tissue disorders
Common: Erythema
Uncommon: Skin tightness, oedema (face, eyelid, periorbital), photosensitivity reaction, pruritus, dry skin

Musculoskeletal and connective tissue disorders
Common: Localised muscle weakness
Uncommon: Muscle twitching

General disorders and administration site conditions
Common: Face pain
Uncommon: Flu syndrome, asthenia, fever

Crow’s feet lines

The following adverse drug reactions were reported in the double-blind, placebo-controlled clinical studies following injection of BOTOX 24 Units for crow’s feet lines alone:

Eye disorders
Common: Eyelid oedema

General disorders and administration site conditions
Common: Injection site haemorrhage*, injection site haematoma*
Uncommon: Injection site pain*, injection site paraesthesia

*procedure-related adverse reactions

Crow’s feet lines and glabellar lines

The following adverse drug reactions were reported in double-blind, placebo-controlled clinical studies following injection of BOTOX 44 Units (simultaneous treatment of crow’s feet lines and glabellar lines):

General disorders and administration site conditions
Common: Injection site haematoma*
Uncommon: Injection site haemorrhage*, injection site pain*

*procedure-related adverse reactions
No change was observed in the overall safety profile following repeat dosing.

c) Additional information
The following list includes adverse drug reactions or other medically relevant adverse events that have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in Section 4.4 (Special warnings and precautions for use), and Section 4.8 (Undesirable effects);

Cardiac disorders
Arrhythmia, myocardial infarction

Ear and labyrinth disorders
Hypoacusis, tinnitus, and vertigo

Eye disorders
Angle-closure glaucoma (for treatment of blepharospasm), strabismus, vision blurred, and visual disturbance

Gastrointestinal disorders
Abdominal pain, diarrhoea, constipation, dry mouth, dysphagia, nausea, and vomiting

General disorders and administration site conditions
Denervation atrophy, malaise, and pyrexia

Immune system disorders
Anaphylaxis, angioedema, serum sickness, and urticaria

Metabolism and nutrition disorders
Anorexia

Musculoskeletal and connective tissue disorders
Muscle atrophy, and myalgia

Nervous system disorders
Brachial plexopathy, dysphonia, dysarthria, facial paresis, hypoaesthesia, muscle weakness, myasthenia gravis, peripheral neuropathy, paraesthesia, radiculopathy, seizures, syncope, and facial palsy

Respiratory, thoracic and mediastinal disorders
Aspiration pneumonia (some with fatal outcome), dyspnoea, respiratory depression, and respiratory failure

Skin and subcutaneous tissue disorders
Alopecia, dermatitis psoriasiform, erythema multiforme, hyperhidrosis, madarosis, pruritus, and rash

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from Clostridium botulinum. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.

Clostridium botulinum toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.
Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse transmission is by newly formed nerve endings and motor end plates. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

There is limited clinical trial experience of the use of BOTOX in primary axillary hyperhidrosis in adolescents between the ages of 12 and 18. A single, year long, uncontrolled, repeat dose, safety study was conducted in US paediatric patients 12 to 17 years of age (N=144) with severe primary hyperhidrosis of the axillae. Participants were primarily female (86.1%) and Caucasian (82.6%). Participants were treated with a dose of 50 Units per axilla for a total dose of 100 Units per patient per treatment. However, no dose finding studies have been conducted in adolescents so no recommendation on posology can be made. Efficacy and safety of BOTOX in this group have not been established.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitisation, as suggested by pre-clinical and clinical pharmacodynamic studies.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition BOTOX inhibits afferent neurotransmitters and sensory pathways.

Clinical Data

Focal lower limb spasticity associated with stroke

A double-blind, placebo-controlled, randomised, multi-centre, phase 3 clinical study was conducted in adult post-stroke patients with lower limb spasticity affecting the ankle. A total of 120 patients were randomised to receive either BOTOX (n=58; total dose of 300 Units) or placebo (n=62).

Significant improvement compared to placebo was observed in the primary endpoint for the overall change from baseline up to week 12 in Modified Ashworth Scale (MAS) ankle score, which was calculated using the area under the curve (AUC) approach. Significant improvements compared to placebo were also observed for the mean change from baseline in MAS ankle score at individual post-treatment visits at weeks 4, 6 and 8. The proportion of responders (patients with at least a 1-grade improvement) was also significantly higher (67%-68%) than in placebo-treated patients (31%-36%) at these visits.

BOTOX treatment was also associated with significant improvement in the investigator’s clinical global impression (CGI) of functional disability compared to placebo although the difference was not significant for the patient’s CGI.

Chronic migraine

Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.
During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.

<table>
<thead>
<tr>
<th>Mean change from baseline at Week 24</th>
<th>BOTOX</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache days</td>
<td>-8.4</td>
<td>-6.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47%</td>
<td>35%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cumulative hours of headache on headache days</td>
<td>120</td>
<td>80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8</td>
<td>-2.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (N=188) than in the whole study population.

**Overactive bladder**

Two double-blind, placebo-controlled, randomised, 24-week phase 3 clinical studies were conducted in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. A total of 1105 patients (mean age of 60 years), whose symptoms had not been adequately managed with at least one anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 Units of BOTOX (n=557), or placebo (n=548), after having discontinued anticholinergics for more than one week.

Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies:
The median duration of response following BOTOX treatment, based on patient request for re-treatment, was 166 days (~24 weeks).

In the pivotal studies, none of the 615 patients with analysed serum specimens developed neutralising antibodies after 1 – 3 treatments.

**Urinary incontinence due to neurogenic detrusor overactivity**

Two double-blind, placebo-controlled, randomised phase 3 clinical studies were conducted in a total of 691 patients with spinal cord injury or multiple sclerosis, who were not adequately managed with at least one anticholinergic agent and were either spontaneously voiding or using catheterisation. These patients were randomised to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

**Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies:**

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units (N=227)</th>
<th>Placebo (N=241)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary Incontinence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.4</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Mean Change&lt;sup&gt;a&lt;/sup&gt; at Week 2</td>
<td>-16.8</td>
<td>-9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change&lt;sup&gt;a&lt;/sup&gt; at Week 6</td>
<td>-20.0</td>
<td>-10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change&lt;sup&gt;b&lt;/sup&gt; at Week 12</td>
<td>-19.8</td>
<td>-9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>250.2</td>
<td>253.5</td>
<td></td>
</tr>
<tr>
<td>Mean Change&lt;sup&gt;b&lt;/sup&gt; at Week 6</td>
<td>+140.4</td>
<td>+6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH2O)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>51.5</td>
<td>47.3</td>
<td></td>
</tr>
<tr>
<td>Mean Change&lt;sup&gt;b&lt;/sup&gt; at Week 6</td>
<td>-27.1</td>
<td>-0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incontinence Quality of Life Total Score(^{c,d})</td>
<td>Mean Baseline</td>
<td>Mean Change(^{a}) at Week 6(^{b})</td>
<td>Mean Change(^{a}) at Week 12</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>---------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td></td>
<td>35.4</td>
<td>+23.6</td>
<td>+26.9</td>
</tr>
<tr>
<td></td>
<td>35.3</td>
<td>+8.9</td>
<td>+7.1</td>
</tr>
</tbody>
</table>

*The percentage of patients achieving at least a 75% reduction from baseline, in incontinence episodes, was 63% for the BOTOX 200 Unit group and 24% for the placebo group. The percentages achieving at least a 50% reduction from baseline were 76% and 39% respectively.

\(^{†}\) LS mean changes are presented

\(^{a}\) Primary endpoint

\(^{b}\) Secondary endpoints

\(^{c}\) I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

\(^{d}\) In the pivotal studies, the pre-specified minimally important difference (MID) for I-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

The median duration of response (time to < 50% reduction in incontinence episodes) was 42 weeks in the 200 Unit dose group.

For all efficacy endpoints in the pivotal phase 3 studies, patients experienced consistent response with re-treatment (N=116).

None of the 475 patients with analysed serum specimens developed neutralising antibodies after 1-2 treatments.

In the multiple sclerosis (MS) patients enrolled in the pivotal studies, the MS exacerbation annualised rate (i.e., number of MS exacerbation events per patient year) was 0.23 in the 200 Unit dose group and 0.20 in the placebo group. With repeated BOTOX treatments, including data from a long term study, the MS exacerbation annualised rate was 0.19 during each of the first two BOTOX treatment cycles.

**Glabellar lines**

537 patients with moderate to severe vertical lines between the eyebrows (glabellar lines) seen at maximum frown have been included in clinical studies.

BOTOX injections significantly reduced the severity of glabellar lines seen at maximum frown for up to 4 months, as measured by the investigator assessment of glabellar line severity at maximum frown and by subject’s global assessment of change in appearance of his/her vertical lines between the eyebrows (glabellar lines) seen at maximum frown. None of the clinical endpoints included an objective evaluation of the psychological impact. Thirty days after injection, 80% (325/405) of BOTOX-treated patients were considered by investigators as treatment responders (none or mild severity at maximum frown), compared to 3% (4/132) of placebo-treated patients. At this same timepoint, 89% (362/405) of BOTOX-treated patients felt they had a moderate or better improvement, compared to 7% (9/132) of placebo-treated patients.

BOTOX injections also significantly reduced the severity of glabellar lines at rest. Of the 537 patients enrolled, 39% (210/537) had moderate to severe glabellar lines at rest (15% had no lines at rest). Of these, 74% (119/161) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 20% (10/49) of placebo-treated patients.

There is limited phase 3 clinical data with BOTOX in patients older than 65 years. Only 6.0% (32/537) of subjects were >65 years old and efficacy results obtained were lower in this population.

**Crow’s feet lines**
1362 patients with moderate to severe crow’s feet lines seen at maximum smile, either alone (N=445, Study 191622-098) or also with moderate to severe glabellar lines seen at maximum frown (N=917, Study 191622-099), were enrolled.

BOTOX injections significantly reduced the severity of crow’s feet lines seen at maximum smile compared to placebo at all timepoints (p <0.001) for up to 5 months. This was measured by the proportion of patients achieving a crow’s feet lines severity rating of none or mild at maximum smile in both pivotal studies; until day 150 (end of study) in Study 191622-098 and day 120 (end of first treatment cycle) in Study 191622-099. For both investigator and subject assessments, the proportion of subjects achieving none or mild crow’s feet lines severity seen at maximum smile was greater in patients with moderate crow’s feet lines seen at maximum smile at baseline, compared to patients with severe crow’s feet lines seen at maximum smile at baseline. Table 1 summarises results at day 30, the timepoint of the primary efficacy endpoint.

In Study 191622-104 (extension to Study 191622-099), 101 patients previously randomised to placebo were enrolled to receive their first treatment at the 44 Units dose. Patients treated with BOTOX had a statistically significant benefit in the primary efficacy endpoint compared to placebo at day 30 following their first active treatment. The response rate was similar to the 44 Units group at day 30 following first treatment in Study 191622-099. A total of 123 patients received 4 cycles of 44 Units BOTOX for combined crow’s feet and glabellar lines treatment.

Table 1. Day 30: Investigator and Patient Assessment of Crow’s Feet Lines Seen at Maximum Smile - Responder Rates (% of Patients Achieving Crow’s Feet Lines Severity Rating of None or Mild)

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Dose</th>
<th>BOTOX Investigator Assessment</th>
<th>Placebo Investigator Assessment</th>
<th>BOTOX Patient Assessment</th>
<th>Placebo Patient Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>191622-098</td>
<td>24 Units (crow’s feet lines)</td>
<td>66.7%* (148/222)</td>
<td>6.7% (15/223)</td>
<td>58.1%* (129/222)</td>
<td>5.4% (12/223)</td>
</tr>
<tr>
<td>191622-099</td>
<td>24 Units (crow’s feet lines)</td>
<td>54.9%* (168/306)</td>
<td>3.3% (10/306)</td>
<td>45.8%* (140/306)</td>
<td>3.3% (10/306)</td>
</tr>
<tr>
<td></td>
<td>44 Units (24 Units crow’s feet lines; 20 Units glabellar lines)</td>
<td>59.0%* (180/305)</td>
<td>3.3% (10/306)</td>
<td>48.5%* (148/305)</td>
<td>3.3% (10/306)</td>
</tr>
</tbody>
</table>

*p < 0.001 (BOTOX vs placebo)

Improvements from baseline in subject-assessment of the appearance of crow’s feet lines seen at maximum smile were seen for BOTOX (24 Units and 44 Units) compared to placebo, at day 30 and at all timepoints following each treatment cycle in both pivotal studies (p<0.001).

Treatment with BOTOX 24 Units also significantly reduced the severity of crow’s feet lines at rest. Of the 528 patients treated, 63% (330/528) had moderate to severe crow’s feet lines at rest at baseline. Of these, 58% (192/330) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 11% (39/352) of placebo-treated patients.

Improvements in subject’s self-assessment of age and attractiveness were also seen for BOTOX (24 Units and 44 Units) compared to placebo using the Facial Line Outcomes (FLO-11) questionnaire, at the primary timepoint of day 30 (p<0.001) and at all subsequent timepoints in both pivotal studies.

In the pivotal studies, 3.9% (53/1362) of patients were older than 65 years of age. Patients in this age group had a treatment response as assessed by the investigator, of 36% (at day 30) for BOTOX (24 Units and 44 Units). When analysed by age groups of ≤50 years and >50 years, both populations demonstrated statistically significant improvements compared to placebo. Treatment response for BOTOX 24 Units, as assessed by the investigator, was lower in the group of subjects >50 years of age than those ≤50 years of age (42.0% and 71.2%, respectively).
Overall BOTOX treatment response for crow’s feet lines seen at maximum smile is lower (60%) than that observed with treatment for glabellar lines seen at maximum frown (80%).

916 patients (517 patients at 24 Units and 399 patients at 44 Units) treated with BOTOX had specimens analysed for antibody formation. No patients developed the presence of neutralising antibodies.

10 DATE OF REVISION OF THE TEXT

25/01/2014
Botox®

ALLERGAN

PACK LEAFLET
INFORMATION FOR THE USER

50 Allergan Units
100 Allergan Units
200 Allergan Units
Powder for solution for injection
BOTOX® (botox) type A

Please read this leaflet carefully before you start using this medicine.

1. What is Botox and what is it used for

Botox is a muscle relaxant that is injected into the muscles to reduce the amount of muscle activity in an area. It is used to treat muscle spasms and other conditions where muscle activity needs to be reduced. Botox is also used to treat some conditions such as muscle spasms of the eye and facial area and the muscles that control the movement of the eyelid.

2. Before You Use Botox

Do not use Botox if:
- You are allergic to Botox or any other component of this product.
- You have any skin infections or skin disorders in the area where the injection will be made.
- You are pregnant or breast feeding.
- You have a bleeding disorder.
- You have any history of anaphylaxis (allergic reaction) to any component of this product.

Take special care with Botox:

Get medical help if:
- You develop a fever or other signs of infection at the injection site.
- You develop any unusual reactions to Botox.
- You have any skin infections or skin disorders in the area where the injection will be made.
- You are pregnant or breast feeding.
- You have a bleeding disorder.
- You have any history of anaphylaxis (allergic reaction) to any component of this product.

3. How To Use Botox

Botox should be used under the supervision of a qualified medical professional.

4. General Information About Botox

The injection should be given by a qualified medical professional.

5. Side Effects

Side effects of Botox may include:

- Weakness or numbness of the affected area
- Difficulty moving the area where the injection was given
- Redness or swelling at the injection site
- Fatigue

6. Further Information

If you have any questions or concerns about using Botox, please contact your doctor or pharmacist.
The dosage of BOTOX® and the duration of its effect will vary depending on the condition for which it is used. Below are dosage recommendations for each condition:

- **The safety and effectiveness of BOTOX® in the treatment of primary musculature disorders of the eyelid, face, neck, and shoulder in children (under 15 years) have not been established and should not be recommended.**
- **The safety and effectiveness of BOTOX® in the treatment of chronic strabismus in children (under 12 years) have not been established and should not be recommended.**
- **The safety and effectiveness of BOTOX® in the treatment of chronic headache disorders in adults (under 55 years) have not been established and should not be recommended.**
- **The safety and effectiveness of BOTOX® in the treatment of upper and lower limb spasticity associated with stroke have not been established in patients of all ages.**
- **The safety and effectiveness of BOTOX® in the treatment of upper and lower limb spasticity associated with stroke have not been established in patients of all ages.**

For persistent contracture of the upper and lower extremities:

- **Dosage:**
  - The total dose for the first treatment session is 1.25 units per site. The maximum recommended dose is 1.5 units per site. The maximal dose for the first month is 1.5 units per site. The minimal recommended dose is 0.5 units per site.

**Duration of treatment:**
- **Dosage:**
  - The total dose for the first treatment session is 1.25 units per site. The maximum recommended dose is 1.5 units per site. The maximal dose for the first month is 1.5 units per site. The minimal recommended dose is 0.5 units per site.

**Dosage:**
- **Dosage:**
  - The total dose for the first treatment session is 1.25 units per site. The maximum recommended dose is 1.5 units per site. The maximal dose for the first month is 1.5 units per site. The minimal recommended dose is 0.5 units per site.

**Dosage:**
- **Dosage:**
  - The total dose for the first treatment session is 1.25 units per site. The maximum recommended dose is 1.5 units per site. The maximal dose for the first month is 1.5 units per site. The minimal recommended dose is 0.5 units per site.

**Dosage:**
- **Dosage:**
  - The total dose for the first treatment session is 1.25 units per site. The maximum recommended dose is 1.5 units per site. The maximal dose for the first month is 1.5 units per site. The minimal recommended dose is 0.5 units per site.

**Dosage:**
- **Dosage:**
  - The total dose for the first treatment session is 1.25 units per site. The maximum recommended dose is 1.5 units per site. The maximal dose for the first month is 1.5 units per site. The minimal recommended dose is 0.5 units per site.
4. POSSIBLE SIDE EFFECTS

If you have any difficulty in breathing, swallowing or speaking after receiving BOTOX®, consult your doctor immediately.

If you experience less serious side effects, which may occur in general, consult your doctor before the next dose is due.

The side effects are usually mild and temporary and may disappear with time.

Injections in the back and shoulder

- Very common side effects:
  - Difficulty in swallowing
  - Headache
  - Redness
  - Localised pain

Injections for excessive sweating of the armpits

- Very common side effects:
  - Palmar sweating

Common side effects:

- Headache
- Constipation
- Feeling of weakness
- Insomnia

Less common side effects:

- Increased sweating of a part other than the armpit
- Abnormal smell
- Blurred vision
- Hoarseness
- Unusual taste

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Injections in the legs of children with cerebral palsy

- Very common side effects:
  - Palmar sweating

Other common side effects:

- Headache
- Constipation
- Feeling of weakness

Uncommon side effects:

- Muscle pain
- Stiffness
- Swelling

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Injections in the head and face for migraine prophylaxis

- Very common side effects:
  - Headache

Other common side effects:

- Headache
- Constipation
- Feeling of weakness

Uncommon side effects:

- Muscle pain
- Stiffness

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Injections in the bladder wall for overactive bladder with leakage of urine

- Very common side effects:
  - Urinary tract infection
  - Painful urination after the injection
### Common side effects:
- Pain or discomfort at the injection site
- Swelling around the eye (may last 1-2 days)
- Dryness or redness around the eye
- Itching, feeling like something is in the eye
- Temporary change in vision
- Blurred vision
- Feeling of something in the eye

### Uncommon side effects:
- Decreased ability to focus
- Increased tearing
- Blurred vision
- Redness of the eye
- Sensitivity to light

### Injections in the fan-shaped lines from the corner of the eye:
- Swelling or bruising at the injection site
- Temporary change in vision
- Blurred vision
- Feeling of something in the eye
- Itching
- Redness

### Common side effects:
- Pain or discomfort at the injection site
- Swelling around the eye (may last 1-2 days)
- Dryness or redness around the eye
- Itching, feeling like something is in the eye
- Temporary change in vision
- Blurred vision
- Feeling of something in the eye

### Uncommon side effects:
- Decreased ability to focus
- Increased tearing
- Blurred vision
- Redness of the eye
- Sensitivity to light

### General information about injection sites:
- The eye is a sensitive area, and complications can occur if a large number of injections are given in a short period.
- The eye is a sensitive area, and complications can occur if a large number of injections are given in a short period.
- The eye is a sensitive area, and complications can occur if a large number of injections are given in a short period.
- The eye is a sensitive area, and complications can occur if a large number of injections are given in a short period.

### How to store BOTOX:
- Keep out of the reach and sight of children.
- Store in the refrigerator at 2°C to 8°C (36°F to 46°F).
- Do not shake the vial before use.

### Further information:
- The active substance in BOTOX is botulinum toxin A from Clostridium botulinum.
- The other ingredients are human albumin and sodium chloride.
- BOTOX is a sterile solution.
The following information is intended for medical or healthcare professionals only.

Please refer to the Summary of Product Characteristics for complete prescribing information for BOTOX.

For all indications:
- Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which is a rare, severe adverse event associated with dysphagia, respiratory difficulty and/or rapid-onset hypotension. The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greater in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for hyperhidrosis, and those treated with systemic corticosteroids.

- Pneumonia associated with injection procedure has been reported after administration of BOTOX near the nose. Caution is warranted when injecting in proximity to the paranasal sinuses, particularly the anterior ethmoidal sinuses. Serious adverse events including fatal outcomes have been reported in patients who had received off-label injections of BOTOX directly into salivary glands, the parotid gland, the submandibular gland, the sublingual gland, the salivary ducts, and/or the salivary orifices. Some patients had pre-existing dysphagia or significant salivary hydrotherapy.

- Reconstitute the medicinal product

It is good practice to perform intraluminal reconstitution and syringe preparation on a separate set of surfaces to avoid contamination.

- Reconstitute the medicinal product only with sterile, bacteriostatic, unsprayed normal saline (0.9% sodium chloride for injection). Draw up an appropriate amount of diluent (see dilution table or instructions below) into a syringe.

Dilution table for BOTOX 20, 100 and 200 Allergen Units, vial size

<table>
<thead>
<tr>
<th>Resulting dose (Units per 0.1 ml)</th>
<th>Amount of diluent (sodium chloride)</th>
<th>Amount of diluent (sodium chloride)</th>
<th>Amount of diluent (sodium chloride)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 unit vial</td>
<td>0.5 ml</td>
<td>0.5 ml</td>
<td>0.5 ml</td>
</tr>
<tr>
<td>100 unit vial</td>
<td>2.5 ml</td>
<td>2.5 ml</td>
<td>2.5 ml</td>
</tr>
<tr>
<td>200 unit vial</td>
<td>7.5 ml</td>
<td>7.5 ml</td>
<td>7.5 ml</td>
</tr>
<tr>
<td>1/2 vial</td>
<td>8 ml</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Since BOTOX is denatured by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Discard the vial if a vacuum is not visible or if the diluent moves in the vial. Reconstituted BOTOX is a clear solution to slightly yellow solution free of particulate matter. The reconstituted BOTOX solution should be used immediatedly if not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and products should not be stored longer than 24 hours at 2°C to 8°C.

Dilution instructions for treatment of primary incineration due to neurapexia, dermophreny, dermophrenic:

It is recommended that a 100 unit or two 50 unit vials are used for treatment of incineration due to neurapexia, dermophreny, dermophrenic.

- Reconstitute 50 or 200 unit vials of BOTOX with 2 ml of 0.9% non-preserved saline solution and gently. Draw 2 ml from the vial into a 10 ml syringe. This will result in a total of 200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 200 Unit vials of BOTOX with 6 ml of 0.9% non-preserved saline solution and gently. Draw 6 ml from the vial into a 10 ml syringe. This will result in a total of 1200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 100 Unit vials of BOTOX with 3 ml of 0.9% non-preserved saline solution and gently. Draw 3 ml from the vial into a 10 ml syringe. This will result in a total of 300 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 200 Unit vials of BOTOX with 6 ml of 0.9% non-preserved saline solution and gently. Draw 6 ml from the vial into a 10 ml syringe. This will result in a total of 1200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

Dilution instructions for treatment of incineration due to toxiapexia, dermophrenic, dermophrenic:

It is recommended that a 100 unit or two 50 unit vials are used for treatment of incineration due to toxiapexia, dermophrenic, dermophrenic.

- Reconstitute 50 or 200 unit vials of BOTOX with 2 ml of 0.9% non-preserved saline solution and gently. Draw 2 ml from the vial into a 10 ml syringe. This will result in a total of 200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 200 Unit vials of BOTOX with 6 ml of 0.9% non-preserved saline solution and gently. Draw 6 ml from the vial into a 10 ml syringe. This will result in a total of 1200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 100 Unit vials of BOTOX with 3 ml of 0.9% non-preserved saline solution and gently. Draw 3 ml from the vial into a 10 ml syringe. This will result in a total of 300 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 200 Unit vials of BOTOX with 6 ml of 0.9% non-preserved saline solution and gently. Draw 6 ml from the vial into a 10 ml syringe. This will result in a total of 1200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 100 Unit vials of BOTOX with 3 ml of 0.9% non-preserved saline solution and gently. Draw 3 ml from the vial into a 10 ml syringe. This will result in a total of 300 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 200 Unit vials of BOTOX with 6 ml of 0.9% non-preserved saline solution and gently. Draw 6 ml from the vial into a 10 ml syringe. This will result in a total of 1200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 100 Unit vials of BOTOX with 3 ml of 0.9% non-preserved saline solution and gently. Draw 3 ml from the vial into a 10 ml syringe. This will result in a total of 300 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.

- Reconstitute 200 Unit vials of BOTOX with 6 ml of 0.9% non-preserved saline solution and gently. Draw 6 ml from the vial into a 10 ml syringe. This will result in a total of 1200 Units of reconstituted BOTOX in the syringe. Dispose of any unused saline.
Annex 4

Our Reference: PL 00426/0074–0162
Product: PL 00426/0074 Botox
Marketing Authorisation Holder: ALLERGAN LIMITED

Reason:
To update sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 6.6 (Special precautions for disposal) of the SPC and consequentially the leaflet in line with company core data sheet, (CCDS), QRD template and also some minor reformatting changes.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 154118 and covers the following submissions PL 00426/0074 - 0162, PL 00426/0118 & PL 00426/0119 - 0070.

Supporting Evidence
This variation is a complete revision of the PI:
- in order to improve its readability
- and also to update the information regarding elderly patients based on a cumulative analysis of clinical and post-marketing safety data. Further to the assessment of the BOTOX PSUR covering the period 01-Jan-2012 to 31-Dec-2012 and the detailed cumulative analysis of clinical and post marketing safety data in the elderly population, which were presented in Appendix 11.5 as part of the worksharing procedure IE/H/PSUR/OOI51007, the geriatric section of the CCDS 16.1 was updated to include relevant information regarding elderly patient exposure and clinical experience. Consequently the MAH has proposed changes to section 4.2 and 4.4 as follows:

Section 4.2

Current
Elderly patients
Overall, with the exception of overactive bladder, adequate studies on geriatric dosing have not been performed. The lowest effective dose with the longest clinically indicated interval between injections is recommended. Elderly patients with significant medical history and concomitant medications should be treated with caution (for Overactive bladder see sections 4.8 and 5.1).

Proposed
Elderly patients
Dosages for elderly patients are the same as for younger adults. Initial dosing should begin at the lowest recommended dose for the specific indication. Elderly patients with significant medical history and concomitant medications should be treated with caution.

Section 4.4

Current
Elderly and debilitated patients should be treated with caution.

Proposed
Elderly and debilitated patients should be treated with caution. Generally clinical studies of BOTOX did not identify differences in responses between the elderly and younger patients. Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

The list of changes is summarised in the Overview.
Evaluation

Overall, the reformatting of the PI is fully supported as the presentation of the numerous various indications is very heterogeneous.

The change regarding the elderly patients is supported by the safety analysis provided. However, the statement in section 4.4 is not fully agreed as there were indeed lower responses for facial lines in older patients as indicated in section 5.1.

Other changes are in general supported. However, there is a number of additional relocation and deletion of text, which are deemed necessary. In particular, clinical trial results should not be mentioned in section 4.2.

Finally, the presentation of the side effects in the PL is not reader-friendly at all and needs to be reconsidered.

Conclusion

More changes to the PI are requested.

Following adequate responses from the MAH this variation can be granted.

Decision - Approve

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BOTOX is indicated for:

Neurologic disorders:

- treatment of focal spasticity, including:
  - dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older
  - wrist and hand disability due to upper limb spasticity associated with stroke in adults
  - ankle disability due to lower limb spasticity associated with stroke in adults
- symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis)
- prophylaxis of headaches in adults with chronic migraine (headaches on at least 15 days per month of which at least 8 days are with migraine)

Bladder disorders:

- management of bladder dysfunctions in adult patients who are not adequately managed with anticholinergics
  - overactive bladder with symptoms of urinary incontinence, urgency and frequency
  - neuropgenic detrusor overactivity with urinary incontinence due to subcervical spinal cord injury (traumatic or non-traumatic), or multiple sclerosis

Skin and skin appendage disorder:

- management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics
• temporary improvement in the appearance of the following facial lines, when the severity of these lines has an important psychological impact in adult patients:
  ➢ moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines)
  ➢ moderate to severe lateral canthal lines (crow’s feet lines) seen at maximum smile
  ➢ moderate to severe crow’s feet lines seen at maximum smile and glabellar lines seen at maximum frown when treated simultaneously.

4.2 Posology and method of administration

Posology

Botulinum toxin units are not interchangeable from one product to another. Doses recommended in Allergan Units are different from other botulinum toxin preparations.

Elderly patients

Dosages for elderly patients are the same as for younger adults. Initial dosing should begin at the lowest recommended dose for the specific indication. Elderly patients with significant medical history and concomitant medications should be treated with caution.

There is limited data in patients older than 65 years managed with BOTOX for urinary incontinence with neurogenic detrusor overactivity and for facial lines (see section 5.1).

Paediatric population

The safety and efficacy of BOTOX in the treatment of individual indications have not been established in children and adolescents under the ages listed in the table below. No data are available.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Age Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal spasticity associated with paediatric cerebral palsy</td>
<td>2 years</td>
</tr>
<tr>
<td>Upper and lower limb spasticity associated with stroke</td>
<td>18 years</td>
</tr>
<tr>
<td>Blepharospasm/Hemifacial spasm/ Idiopathic Cervical dystonia</td>
<td>12 years</td>
</tr>
<tr>
<td>Chronic migraine (CM)</td>
<td>18 years</td>
</tr>
<tr>
<td>Overactive Bladder (OAB) and Neurogenic Detrusor Overactivity (NDO)</td>
<td>18 years</td>
</tr>
<tr>
<td>Primary hyperhidrosis of the axillae</td>
<td>12 years</td>
</tr>
<tr>
<td>(limited experience in adolescents between 12 and 17 years, see sections 4.8 and 5.1)</td>
<td></td>
</tr>
<tr>
<td>Glabellar lines seen at maximum frown and/or crow’s feet lines seen at maximum smile</td>
<td>18 years</td>
</tr>
</tbody>
</table>

Method of Administration

BOTOX should only be administered by physicians with appropriate qualifications and expertise in the treatment and the use of the required equipment.

This product is for single use only and any unused solution should be discarded. The most appropriate vial size should be selected for the indication.
An injection volume of approximately 0.1 ml is recommended. A decrease or increase in the BOTOX dose is possible by administering a smaller or larger injection volume. The smaller the injection volume the less discomfort and less spread of toxin in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

For instructions on reconstitution of the powder for solution for injection, handling and disposal of vials please refer to section 6.6.

Refer to specific guidance for each indication described below.

Generally valid optimum dose levels and number of injection sites per muscle have not been established for all indications. In these cases, individual treatment regimens should therefore be drawn up by the physician. Optimum dose levels should be determined by titration but the recommended maximum dose should not be exceeded.

**NEUROLOGIC DISORDERS**

Focal spasticity associated with paediatric cerebral palsy

**Recommended needle:** Sterile 23-26 gauge/0.60-0.45 mm needle.

**Administration guidance:** To be administered as a divided dose through single injections into the medial and lateral heads of the affected gastrocnemius muscle.

**Recommended dose:** Hemiplegia: the initial recommended total dose is 4 Units/kg body weight in the affected limb. Diplegia: the initial recommended total dose is 6 Units/kg body weight divided between the affected limbs.

**Maximum dose:** 200 Units in total

**Additional information:** Clinical improvement generally occurs within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months. It may be possible to adapt the dosage regimen to obtain an interval of at least six months between treatment sessions.

Focal upper limb spasticity associated with stroke

**Recommended needle:** Sterile 25, 27 or 30 gauge needle. Needle length should be determined based on muscle location and depth.

**Administration guidance:** Localisation of the involved muscles with techniques such as electromyographic guidance, nerve stimulation, or ultrasound is recommended. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

**Recommended dose:** The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, the presence of local muscle weakness, and the patient response to previous treatment.

The following doses are recommended:
Maximum dose: Between 200 and 240 Units divided among selected muscles.

Additional information: If it is deemed appropriate by the treating physician, the patient should be considered for re-injection when the clinical effect of the previous injection has diminished. Re-injections should occur no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected. The lowest effective dose should be used.

Focal lower limb spasticity associated with stroke

Recommended needle: Sterile 25, 27 or 30 gauge needle. Needle length should be determined based on muscle location and depth.

Administration guidance: Localisation of the involved muscles with techniques such as electromyographic guidance, nerve stimulation, or ultrasound is recommended. Multiple injection sites may allow BOTOX to have more uniform contact with the innervation areas of the muscle and are especially useful in larger muscles.

The following diagrams indicate the injection sites for adult lower limb spasticity:

Recommended dose: The recommended dose for treating adult lower limb spasticity involving the ankle is 300 Units divided among 3 muscles.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Total Dosage; Number of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexor digitorum profundus</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor digitorum sublimis</td>
<td>15 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>15 - 60 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>10 - 50 Units; 1-2 sites</td>
</tr>
<tr>
<td>Adductor Pollicis</td>
<td>20 Units; 1-2 sites</td>
</tr>
<tr>
<td>Flexor Pollicis Longus</td>
<td>20 Units; 1-2 sites</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius</td>
<td>Total Dosage; Number of Sites</td>
</tr>
</tbody>
</table>

Medial head of gastrocnemius  
Lateral head of gastrocnemius  
Soleus  
Tibialis posterior
Additional information: If it is deemed appropriate by the treating physician, the patient should be considered for re-injection when the clinical effect of the previous injection has diminished, but generally no sooner than 12 weeks after the previous injection.

Blepharospasm/hemifacial spasm

Recommended needle: Sterile, 27-30 gauge/0.40-0.30 mm needle.

Administrative guidance: Electromyographic guidance is not necessary.

Recommended dose: The initial recommended dose is 1.25-2.5 Units (0.05-0.1 ml volume at each site) injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision.

The following diagrams indicate the possible injection sites:

Maximum dose: The initial dose should not exceed 25 Units per eye. In the management of blepharospasm total dosing should not exceed 100 Units in total every 12 weeks.

Additional information: Avoiding injection near levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia.

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated indefinitely. Normally no additional benefit is conferred by treating more frequently than every three months.

At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient - usually defined as an effect that does not last longer
than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site.

Patients with hemifacial spasm or VII\textsuperscript{th} nerve disorders should be treated as for unilateral blepharospasm, with other affected facial muscles being injected as needed. Electromyographic control may be necessary to identify affected small circumoral muscles.

Cervical dystonia

Recommended needle: A 25, 27 or 30 gauge/0.50-0.30 mm needle may be used for superficial muscles, and a 22 gauge needle may be used for deeper musculature.

Administrative guidance: The treatment of cervical dystonia typically may include injection of BOTOX into the sternocleidomastoid, levator scapulae, scalene, splenius capitis, semispinalis, longissimus and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment. The muscle mass and the degree of hypertrophy are factors to be taken into consideration when selecting the appropriate dose. Muscle activation patterns can change spontaneously in cervical dystonia without a change in the clinical presentation of dystonia.

In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance.

Multiple injection sites allow BOTOX to have more uniform contact with the innervation areas of the dystonic muscle and are especially useful in larger muscles. The optimal number of injection sites is dependent upon the size of the muscle to be chemically denervated.

Recommended dose: Dosing must be tailored to the individual patient based on the patient's head and neck position, location of pain, muscle hypertrophy, patient's body weight, and patient response. Initial dosing in a naïve patient should begin at the lowest effective dose.

To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally.

The following doses are recommended:

<table>
<thead>
<tr>
<th>Type I</th>
<th>Head rotated toward side of shoulder elevation</th>
<th>Sternomastoid</th>
<th>Levetor scapulae</th>
<th>Scalenae</th>
<th>Splenius capitis</th>
<th>Trapezius</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>50 - 100 Units; at least 2 sites</td>
<td>50 Units; 1 - 2 sites</td>
<td>25 - 50 Units; 1 - 2 sites</td>
<td>25 - 75 Units; 1 - 3 sites</td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
<tr>
<td>Type II</td>
<td>Head rotation only</td>
<td>Sternomastoid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 - 100 Units; at least 2 sites if &gt;25 Units given</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Type III
**Head tilted toward side of shoulder elevation**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternomastoid</td>
<td>25 - 100 Units at posterior border; at least 2 sites if &gt;25 Units given</td>
</tr>
<tr>
<td>Levator scapulae</td>
<td>25 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td>Scalene</td>
<td>25 - 75 Units; at least 2 sites</td>
</tr>
<tr>
<td>Trapezius</td>
<td>25 - 100 Units; 1 - 8 sites</td>
</tr>
</tbody>
</table>

Maximum dose: No more than 50 Units should be given at any one injection site. No more than 100 Units should be given to the sternomastoid. No more than 200 Units in total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response, up to a maximum total dose of 300 Units.

Additional information: Treatment intervals of less than 10 weeks are not recommended.

### Type IV
**Bilateral posterior cervical muscle spasm with elevation of the face**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenius capitis and cervicis</td>
<td>50 - 200 Units; 2 - 8 sites, treat bilaterally (This is the total dose and not the dose for each side of the neck)</td>
</tr>
</tbody>
</table>

**Chronic migraine**

**Recommended needle:** Sterile 30 gauge, 0.5 inch needle.

A 1 inch needle may be needed in the neck region for patients with extremely thick neck muscles.

**Administration guidance:** Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams below. With the exception of the procerus muscle, which should be injected at 1 site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck.

The following diagrams indicate the injection sites:

![Diagram 1](image1)

- A. Corrugator: 5 U each side
- B. Procerus: 1 U (one site)
- C. Frontalis: 10 U each side

![Diagram 2](image2)

- D. Temporalis: 10 U each side

![Diagram 3](image3)

- E. Occipitalis: 15 U each side

![Diagram 4](image4)

- F. Cervical Paraspinal: 10 U each side
- G. Trapezius: 15 U each side

If there is a predominant pain location(s), additional injections to one or both sides may be administered in up to 3 specific muscle groups (occipitalis, temporalis and trapezius), up to the maximum dose per muscle as indicated in the table below.
The following diagrams indicate recommended muscle groups for optional additional injections:

![Diagrams showing recommended muscle groups](image)

**Recommended dose:** 155 Units to 195 Units administered intramuscularly as 0.1 ml (5 Units) injections to 31 and up to 39 sites.

<table>
<thead>
<tr>
<th>Head/Neck Area</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrugator(^b)</td>
<td>10 Units (2 sites)</td>
</tr>
<tr>
<td>Procerus(^b)</td>
<td>5 Units (1 site)</td>
</tr>
<tr>
<td>Frontalis(^b)</td>
<td>20 Units (4 sites)</td>
</tr>
<tr>
<td>Temporalis(^b)</td>
<td>40 Units (8 sites) up to 50 Units (up to 10 sites)</td>
</tr>
<tr>
<td>Occipitalis(^b)</td>
<td>30 Units (6 sites) up to 40 Units (up to 8 sites)</td>
</tr>
<tr>
<td>Cervical Paraspinal Muscle Group(^b)</td>
<td>20 Units (4 sites)</td>
</tr>
<tr>
<td>Trapezius(^b)</td>
<td>30 Units (6 sites) up to 50 Units (up to 10 sites)</td>
</tr>
<tr>
<td>Total Dose Range:</td>
<td>155 Units to 195 Units</td>
</tr>
<tr>
<td></td>
<td>31 to 39 sites</td>
</tr>
</tbody>
</table>

\(^a\)1 IM injection site = 0.1 ml = 5 Units BOTOX  
\(^b\)Dose distributed bilaterally

**Additional information:** The recommended re-treatment schedule is every 12 weeks.

**BLADDER DISORDERS**

**Overactive bladder**

**Recommended needle:** The injection needle should be filled (primed) with approximately 1 ml of the reconstituted BOTOX solution prior to the start of the injections (depending on the needle length) to remove any air.

**Administration guidance:** The reconstituted solution of BOTOX (100 Units/10 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 ml each (total volume 10 ml)
should be spaced approximately 1 cm apart (see figure below). For the final injection, approximately 1 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection should be injected so the full dose is delivered.

Recommended dose: The recommended dose is 100 Units of BOTOX, as 0.5 ml (5 Units) injections across 20 sites in the detrusor muscle.

Additional information: For the patient preparation and monitoring, see section 4.4.

After the injections are given, the saline used for bladder wall visualisation should not be drained so that the patients can demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished but no sooner than 3 months from the prior bladder injection.

Urinary incontinence due to neurogenic detrusor overactivity

Recommended needle: The injection needle should be filled (primed) with approximately 1 ml of the reconstituted BOTOX solution prior to the start of the injections (depending on the needle length) to remove any air.

Administration guidance: The reconstituted solution of BOTOX (200 Units/30 ml) is injected via a flexible or rigid cystoscope, avoiding the trigone and base. The bladder should be instilled with enough saline to achieve adequate visualisation for the injections and avoid backflow of the product, but over-distension should be avoided.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 ml each (total volume 30 ml) should be spaced approximately 1 cm apart (see figure above). For the final injection, approximately 1 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection should be injected so the full
dose is delivered. After the injections are given, the saline used for bladder wall visualisation should be drained.

**Recommended dose:**

The recommended dose is 200 Units of BOTOX, as 1 ml (~6.7 Units) injections across 30 sites in the detrusor muscle.

**Additional information:**

Recommended dose: The recommended dose is 200 Units of BOTOX, as 1 ml (~6.7 Units) injections across 30 sites in the detrusor muscle.

For the patient preparation and monitoring, see section 4.4.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished, but no sooner than 3 months from the prior bladder injection.

Limited data are available beyond 2 treatments. No urodynamic data beyond 2 treatments and no histopathological data after repeated treatment are currently available.

Patients should not receive multiple treatments in the event of limited symptomatic improvement.

**SKIN AND SKIN APPENDAGE DISORDERS:**

**Primary hyperhidrosis of the axillae**

**Recommended needle:** Sterile 30 gauge needle.

**Administration guidance:** The hyperhidrotic area to be injected may be defined by using standard staining techniques, e.g. Minor’s iodine-starch test.

**Recommended dose:** 50 Units of BOTOX is injected intradermally to each axilla, evenly distributed in multiple sites approximately 1-2 cm apart.

The recommended injection volume for intradermal injection is 0.1-0.2 ml.

**Maximum dose:** Doses other than 50 Units per axilla cannot be recommended.

**Additional information:** Clinical improvement generally occurs within the first week after injection and persists for 4-7 months.

Repeat injection of BOTOX can be administered when the clinical effect of a previous injection diminishes and the treating physician deems it necessary. Injections should not be repeated more frequently than every 16 weeks.

**Glabellar lines seen at maximum frown**

**Recommended needle:** Sterile 30 gauge needle.

**Administration guidance:** Before injection, the thumb or index finger is to be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection. In addition, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercili). Injections in the corrugator muscle must be done in the...
central part of that muscle, a distance of at least 1 cm above the arch of the eyebrows (see figure).

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the glabellar lines seen at maximum frown, see section 4.4.

Recommended dose: A volume of 0.1 ml (4 Units) is administered in each of the 5 injection sites (see Figure): 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units.

Maximum dose: In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded.

Additional Information Treatment intervals should not be more frequent than every three months. In the event of treatment failure or diminished effect following repeat injections, alternative treatment methods should be employed.

In case of insufficient dose a second treatment session should be initiated by adjusting the total dose up to 40 or 50 Units, taking into account the analysis of the previous treatment failure (see information in All indications).

The efficacy and safety of repeat injections of BOTOX for the treatment of glabellar lines beyond 12 months has not been evaluated.

Crow’s feet lines seen at maximum smile

Recommended needle: Sterile 30 gauge needle.

Administration guidance: Injections should be given with the needle tip bevel up and oriented away from the eye. The first injection (A) should be made approximately 1.5 to 2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the crow’s feet region are above and below the lateral canthus, inject as shown in Figure 1.
Alternatively, if the lines in the crow’s feet region are primarily below the lateral canthus, inject as shown in Figure 2.

In order to reduce the risk of eyelid ptosis, injections should be made temporal to the orbital rim, thereby maintaining a safe distance from the muscle controlling eyelid elevation.

Figure 1: Figure 2:

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the crow’s feet lines seen at maximum smile (see section 4.4).

Recommended dose: A volume of 0.1 ml (4 Units) is administered in each of the 3 injection sites per side (total of 6 injection sites) in the lateral orbicularis oculi muscle, for a total dose of 24 Units in a total volume of 0.6 ml (12 Units per side).

For simultaneous treatment with glabellar lines seen at maximum frown, the dose is 24 Units for crow’s feet lines seen at maximum smile and 20 Units for glabellar lines (see Administration guidance for glabellar lines) for a total dose of 44 Units in a total volume of 1.1 ml.

Maximum dose: In order to reduce the risk of eyelid ptosis, the maximum dose of 4 Units for each injection site as well as the number of injection sites should not be exceeded.

Additional information: Treatment intervals should not be more frequent than every 3 months.

The efficacy and safety of repeat injections of BOTOX for the treatment of crow’s feet lines beyond 12 months has not been evaluated.

**ALL INDICATIONS:**

In case of treatment failure after the first treatment session, i.e. absence, at one month after injection, of significant clinical improvement from baseline, the following actions should be taken:
Clinical verification, which may include electromyographic examination in a specialist setting, of the action of the toxin on the injected muscle(s);

Analysis of the causes of failure, e.g. bad selection of muscles to be injected, insufficient dose, poor injection technique, appearance of fixed contracture, antagonist muscles too weak, formation of toxin-neutralising antibodies;

Re-evaluation of the appropriateness of treatment with botulinum toxin type A;

In the absence of any undesirable effects secondary to the first treatment session, instigate a second treatment session as following: i) adjust the dose, taking into account the analysis of the earlier treatment failure; ii) use EMG; and iii) maintain a three-month interval between the two treatment sessions.

In the event of treatment failure or diminished effect following repeat injections alternative treatment methods should be employed.

### 4.3 Contraindications

- known hypersensitivity to botulinum toxin type A or to any of the excipients listed in section 6.1;
- presence of infection at the proposed injection site(s).

For the management of bladder disorders:
- urinary tract infection at the time of treatment;
- acute urinary retention at the time of treatment, in patients who are not routinely catheterising;
- patients who are not willing and/or able to initiate catheterisation post-treatment if required;
- presence of bladder calculi.

### 4.4 Special warnings and precautions for use

The recommended dosages and frequencies of administration of BOTOX should not be exceeded due to the potential for overdose, exaggerated muscle weakness, distant spread of toxin and the formation of neutralising antibodies. Initial dosing in treatment naïve patients should begin with the lowest recommended dose for the specific indication.

Prescribers and patients should be aware that side effects can occur despite previous injections being well tolerated. Caution should therefore be exercised on the occasion of each administration.

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8), sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exaggerated muscle weakness.

Elderly and debilitated patients should be treated with caution. Generally, clinical studies of BOTOX did not identify differences in responses between the elderly and younger patients except for facial lines (see section 5.1). Dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range.

Consideration should be given to the risk-benefit implications for the individual patient before embarking on treatment with BOTOX.
Dysphagia has also been reported following injection to sites other than the cervical musculature (see section 4.4 ‘Cervical Dystonia’).

BOTOX should only be used with extreme caution and under close supervision in patients with subclinical or clinical evidence of defective neuromuscular transmission e.g. myasthenia gravis or Lambert-Eaton Syndrome in patients with peripheral motor neuropathic diseases (e.g. amyotrophic lateral sclerosis or motor neuropathy) and in patients with underlying neurological disorders. Such patients may have an increased sensitivity to agents such as BOTOX, even at therapeutic doses, which may result in excessive muscle weakness and an increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk. Patients with a history of dysphagia and aspiration should be treated with extreme caution.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

As with any treatment with the potential to allow previously-sedentary patients to resume activities, the sedentary patient should be cautioned to resume activity gradually.

The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering BOTOX and injection into vulnerable anatomic structures must be avoided.

Pneumothorax associated with injection procedure has been reported following the administration of BOTOX near the thorax. Caution is warranted when injecting in proximity to the lung (particularly the apices) or other vulnerable anatomic structures.

Serious adverse events including fatal outcomes have been reported in patients who had received off-label injections of BOTOX directly into salivary glands, the oro-lingual-pharyngeal region, oesophagus and stomach. Some patients had pre-existing dysphagia or significant debility.

Serious and/or immediate hypersensitivity reactions have been rarely reported including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of BOTOX either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs further injection of BOTOX should be discontinued and appropriate medical therapy, such as epinephrine, immediately instituted. One case of anaphylaxis has been reported in which the patient died after being injected with BOTOX inappropriately diluted with 5 ml of 1% lidocaine.

As with any injection, procedure-related injury could occur. An injection could result in localised infection, pain, inflammation, paraesthesia, hypoesthesia, tenderness, swelling, erythema, and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension, etc.

Caution should be used when BOTOX is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle. Caution should also be exercised when BOTOX is used for treatment of patients with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy).

There have been reports of adverse events following administration of BOTOX involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease.

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to botulinum toxin injection has not
been established. The reports in children were predominantly from cerebral palsy patients treated for spasticity.

Formation of neutralising antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. Results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest clinically indicated intervals between injections.

Clinical fluctuations during the repeated use of BOTOX (as with all botulinum toxins) may be a result of different vial reconstitution procedures, injection intervals, muscles injected and slightly differing potency values given by the biological test method used.

**Paediatric use**

The safety and efficacy of BOTOX in indications other than those described for the paediatric population in section 4.1 has not been established. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended (see section 4.8).

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease.

Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

**NEUROLOGIC DISORDERS**

_Focal spasticity associated with paediatric cerebral palsy and spasticity of the ankle, hand and wrist in adult post-stroke patients_

BOTOX is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not intended as a replacement for these treatment modalities. BOTOX is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

BOTOX should only be used for the treatment of focal spasticity in adult post-stroke patients if muscle tone reduction is expected to result in improved function (e.g. improvements in gait), or improved symptoms (e.g. reduction in muscle spasms or pain), and/or to facilitate care.

Caution should be exercised when treating adult patients with post-stroke spasticity who may be at increased risk of fall. In clinical studies where patients were treated for lower limb spasticity (some of whom also received concurrent treatment for upper limb spasticity), the incidence of fall was 7.2% and 4.9% of patients in the BOTOX and placebo groups, respectively.

There have been post-marketing reports of death (sometimes associated with aspiration pneumonia) and of possible distant spread of toxin in children with co-morbidities, predominantly cerebral palsy following treatment with botulinum toxin. See warnings under section 4.4, ‘Paediatric use’.

__Blepharospasm__

Reduced blinking following botulinum toxin injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect
should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

Ecchymosis occurs easily in the soft eyelid tissues. This can be minimised by applying gentle pressure at the injection site immediately after injection.

Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles.

**Cervical dystonia**

Patients with cervical dystonia should be informed of the possibility of experiencing dysphagia which may be very mild, but could be severe. Dysphagia may persist for two to three weeks after injection, but has been reported to last up to five months post-injection. Consequent to the dysphagia there is the potential for aspiration, dyspnoea and occasionally the need for tube feeding. In rare cases dysphagia followed by aspiration pneumonia and death has been reported.

Limiting the dose injected into the sternocleidomastoid muscle to less than 100 Units may decrease the occurrence of dysphagia. Patients with smaller neck muscle mass, or patients who receive bilateral injections into the sternocleidomastoid muscle, have been reported to be at greater risk of dysphagia. Dysphagia is attributable to the spread of the toxin to the oesophageal musculature. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Dysphagia may contribute to decreased food and water intake resulting in weight loss and dehydration. Patients with subclinical dysphagia may be at increased risk of experiencing more severe dysphagia following a BOTOX injection.

**Chronic migraine**

No efficacy has been shown for BOTOX in the prophylaxis of headaches in patients with episodic migraine (headaches on < 15 days per month).

**BLADDER DISORDERS**

**Patient preparation and monitoring**

Prophylactic antibiotics should be administered to patients with sterile urine or asymptomatic bacteriuria in accordance with local standard practice.

The decision to discontinue anti-platelet therapy should be subject to local guidance and benefit/risk consideration for the individual patient. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate medical caution should be exercised when performing the cystoscopy. The patient should be observed for at least 30 minutes post-injection.

In patients who are not regularly practicing catheterisation, post-void residual urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate. Patients should be instructed to contact their physician if they experience difficulties in voiding as catheterisation may be required.

**Overactive bladder**

Prior to injection an intravesical instillation of diluted local anaesthetic, with or without sedation, may be used, per local site practice. If a local anaesthetic instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.
Urinary incontinence due to neurogenic detrusor overactivity

BOTOX injection can be performed under general or local anaesthesia with or without sedation. If a local anaesthetic intravesical instillation is performed, the bladder should be drained and rinsed with sterile saline before the next steps of the injection procedure.

Autonomic dysreflexia associated with the procedure can occur and greater vigilance is required in patients known to be at risk.

SKIN AND SKIN APPENDAGE DISORDER

Primary hyperhidrosis of the axillae

Medical history and physical examination, along with specific additional investigations as required, should be performed to exclude potential causes of secondary hyperhidrosis (e.g. hyperthyroidism, phaeochromocytoma). This will avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of underlying disease.

Glabellar lines seen at maximum frown and/or crow’s feet lines seen at maximum smile

It is mandatory that BOTOX is used for one single patient treatment only during a single session. The excess of unused product must be disposed of as detailed in section 6.6. Particular precautions should be taken for product preparation and administration as well as for the inactivation and disposal of the remaining unused solution (see section 6.6).

The use of BOTOX is not recommended in individuals under 18 years. There is limited phase 3 clinical data with BOTOX in patients older than 65 years.

Care should be taken to ensure that BOTOX is not injected into a blood vessel when it is injected in the glabellar seen at maximum frown or in the crow’s feet lines seen at maximum smile, see section 4.2. There is a risk of eyelid ptosis following treatment, refer to Section 4.2 for administration instructions on how to minimise this risk.

4.8 Undesirable effects

a) General

In controlled clinical trials adverse events considered by the investigators to be related to BOTOX were reported in 35% of the patients with blepharospasm, 28% with cervical dystonia, 17% with paediatric cerebral palsy, 11% with primary hyperhidrosis of the axillae, 16% with focal spasticity of the upper limb associated with stroke, 15% with focal spasticity of the lower limb associated with stroke, 26% with overactive bladder, and 32% with neurogenic detrusor overactivity. In clinical trials for chronic migraine, the incidence was 26% with the first treatment and declined to 11% with a second treatment.

In controlled clinical trials for glabellar lines seen at maximum frown, adverse events considered by the investigators to be related to BOTOX were reported in 23% (placebo 19%) of patients. In treatment cycle 1 of the pivotal controlled clinical trials for crow’s feet lines seen at maximum smile, such events were reported in 8% (24 Units for crow’s feet lines alone) and 6% (44 Units: 24 Units for crow’s feet lines administered simultaneously with 20 Units for glabellar lines) of patients compared to 5% for placebo.

Adverse reactions may be related to treatment, injection technique or both. In general, adverse reactions occur within the first few days following injection and, while generally transient, may have a duration of several months or, in rare cases, longer.
Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. However, weakness of adjacent muscles and/or muscles remote from the site of injection has been reported.

As is expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope. Fever and flu syndrome have also been reported after injections of botulinum toxin.

b) Adverse reactions - frequency by indication

The frequency of adverse reactions reported in the clinical trials is defined as follows:
Very Common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (<1/10,000).

**NEUROLOGIC DISORDERS:**

*Focal spasticity associated with paediatric cerebral palsy*

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Viral infection, ear infection</td>
<td>Very Common</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Somnolence, gait disturbance, paraesthesia</td>
<td>Common</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia, muscular weakness, pain in extremity</td>
<td>Common</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary incontinence</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Malaise, injection site pain, asthenia</td>
<td>Common</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Fall</td>
<td>Common</td>
</tr>
</tbody>
</table>

*Focal upper limb spasticity associated with stroke*

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Depression, insomnia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Hypertonia</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Hypoaesthesia, headache, paraesthesia, incoordination, amnesia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Vertigo</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Orthostatic hypotension</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, oral paraesthesia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Ecchymosis, purpura</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Dermatitis, pruritus, rash</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity, muscle weakness</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Arthralgia, bursitis</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
General disorders and administration site conditions | Injection site pain, pyrexia, influenza-like illness, injection site haemorrhage, injection site irritation | Common

- Asthenia, pain, injection site hypersensitivity, malaise, peripheral oedema | Uncommon

Some of the uncommon events may be disease related.

**Focal lower limb spasticity associated with stroke**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia, musculoskeletal stiffness</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Peripheral oedema</td>
<td>Common</td>
</tr>
</tbody>
</table>

**Blepharospasm/hemifacial spasm**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, facial paresis, facial palsy</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eyelid ptosis</td>
<td>Very Common</td>
</tr>
<tr>
<td></td>
<td>Punctate keratitis, lagophthalmos, dry eye, photophobia, eye irritation, lacrimation increase</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Keratitis, ectropion, diplopia, entropion, visual disturbance, blurred vision</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Eyelid oedema</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>Corneal ulceration, corneal epithelium defect, corneal perforation</td>
<td>Very Rare</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Ecchymosis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Rash/dermatitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Irritation, face oedema</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

**Cervical dystonia**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Rhinitis, upper respiratory infection</td>
<td>Common</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness, hypertonia, hypoaesthesia, somnolence, headache</td>
<td>Common</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Diplopia, eyelid ptosis</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnoea, dysphonia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dysphagia</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Dry mouth, nausea</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscular weakness</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal stiffness and musculoskeletal soreness</td>
<td>Common</td>
</tr>
</tbody>
</table>
### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Very common</td>
</tr>
<tr>
<td>Asthenia, influenza-like illness, malaise</td>
<td>Common</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

### Chronic migraine

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache*, migraine*, facial paresis</td>
<td>Common</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eyelid ptosis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Eyelid oedema</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dysphagia</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritis, rash</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pain of skin</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Neck pain, myalgia, musculoskeletal pain, musculoskeletal stiffness, muscle spasms, muscle tightness, muscular weakness</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Pain in jaw</td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site pain</td>
<td>Common</td>
</tr>
</tbody>
</table>

* In placebo-controlled trials, headache and migraine, including serious cases of intractable or worsening of headache/migraine, were reported more frequently with BOTOX (9%) than with placebo (6%). They typically occurred within the first month after the injections and their incidence declined with repeated treatments.

### BLADDER DISORDERS:

#### Overactive bladder

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Bacteriuria</td>
<td>Common</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Dysuria†</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Urinary retention, residual urine volume*, pollakiuria, leukocyturia</td>
<td>Common</td>
</tr>
</tbody>
</table>

*<i>elevated post-void residual urine volume (PVR) not requiring catheterisation</i>
†<i>procedure-related adverse reactions</i>

In the phase 3 clinical trials urinary tract infection was reported in 25.5% of patients treated with BOTOX 100 Units and 9.6% of patients treated with placebo. Urinary retention was reported in 5.8% of patients treated with BOTOX 100 Units and in 0.4% of patients treated with placebo. Clean intermittent catheterisation was initiated in 6.5% of patients following treatment with BOTOX 100 Units versus 0.4% in the placebo group.

Overall, 42.5% of patients (n = 470) were ≥ 65 years of age and 15.1% (n = 167) were ≥ 75 years of age. No overall difference in the safety profile following BOTOX treatment was observed between patients ≥ 65 years compared to patients < 65 years in these studies, with the exception of urinary tract infection where the incidence was higher in elderly patients in both the placebo and BOTOX groups compared to the younger patients.

No change was observed in the overall safety profile with repeat dosing.
Urinary incontinence due to neurogenic detrusor overactivity

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Urinary tract infection</td>
<td>Very Common</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia†</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Constipation†</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscular weakness†, muscle spasm</td>
<td>Common</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Urinary retention</td>
<td>Very Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue†, gait disturbance†</td>
<td>Common</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Autonomic dysreflexia*, fall†</td>
<td>Common</td>
</tr>
</tbody>
</table>

*procedure-related adverse reactions
† only in multiple sclerosis

In the phase 3 clinical trials, urinary tract infection was reported in 49% of patients treated with BOTOX 200 Units and in 36% of patients treated with placebo (in multiple sclerosis patients: 53% vs. 29%, respectively; in spinal cord injury patients: 45% vs. 42%, respectively). Urinary retention was reported in 17% of patients treated with BOTOX 200 Units and in 3% of patients treated with placebo (in multiple sclerosis patients: 29% vs. 4%, respectively; in spinal cord injury patients: 5% vs. 1%, respectively). Among patients who were not catheterising at baseline prior to treatment, catheterisation was initiated in 39% following treatment with BOTOX 200 Units versus 17% on placebo. The risk of urinary retention increased in patients older than 65 years.

No change in the type and frequency of adverse reactions was observed following 2 treatments.

SKIN AND SKIN APPENDAGE DISORDER:

Primary hyperhidrosis of the axillae

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache, paraesthesia</td>
<td>Common</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flushes</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hyperhidrosis (non axillary sweating), abnormal skin odour, pruritus, subcutaneous nodule, alopecia</td>
<td>Common</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in extremity</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site pain</td>
<td>Very common</td>
</tr>
<tr>
<td></td>
<td>Pain, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site irritation, asthenia, injection site reactions</td>
<td>Common</td>
</tr>
</tbody>
</table>

Increase in non axillary sweating was reported in 4.5% of patients within 1 month after injection and showed no pattern with respect to anatomical sites affected. Resolution was seen in approximately 30% of the patients within four months.

Weakness of the arm has been also reported uncommonly (0.7%) and was mild, transient, did not require treatment and recovered without sequelae. This adverse event may be related to treatment,
injection technique, or both. In the uncommon event of muscle weakness being reported a neurological examination may be considered. In addition, a re-evaluation of injection technique prior to subsequent injection is advisable to ensure intradermal placement of injections.

In an uncontrolled safety study of BOTOX (50 Units per axilla) in paediatric patients 12 to 17 years of age (n= 144), adverse reactions occurring in more than a single patient (2 patients each) comprised injection site pain and hyperhidrosis (non-axillary sweating).

**Glabellar lines**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Infection</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, dizziness</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eyelid ptosis</td>
<td>Common</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, oral dryness</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Erythema</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Skin tightness, oedema (face, eyelid, periorbital), photosensitivity reaction, pruritus, dry skin</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Localised muscle weakness</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site haemorrhage*, injection site haematoma*</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Injection site pain*, injection site paraesthesia</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

*Crow’s feet lines*

The following adverse drug reactions were reported in the double-blind, placebo-controlled clinical studies following injection of BOTOX 24 Units for crow’s feet lines alone:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td>Eyelid oedema</td>
<td>Common</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site haemorrhage*, injection site haematoma*</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Injection site pain*, injection site paraesthesia</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

*procedure-related adverse reactions

**Crow’s feet lines and glabellar lines**

The following adverse drug reactions were reported in double-blind, placebo-controlled clinical studies following injection of BOTOX 44 Units (simultaneous treatment of crow’s feet lines and glabellar lines):

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site haematoma*</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Injection site haemorrhage*, injection site pain*</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

*procedure-related adverse reactions

No change was observed in the overall safety profile following repeat dosing.
c) Additional information
The following list includes adverse drug reactions or other medically relevant adverse events that have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in section 4.4 (Special warnings and precautions for use), and section 4.8 (Undesirable effects).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Anaphylaxis, angioedema, serum sickness, urticaria</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Brachial plexopathy, dysphonia, dysarthria, facial paresis, hypoesthesia, muscle weakness, myasthenia gravis, peripheral neuropathy, paraesthesia, radiculopathy, seizures, syncope, facial palsy</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Angle-closure glaucoma (for treatment of blepharospasm), lagophthalmos, strabismus, blurred vision, visual disturbance</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Hypoacusis, tinnitus, vertigo</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Arrhythmia, myocardial infarction</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Aspiration pneumonia (some with fatal outcome), dyspnoea, respiratory depression, respiratory failure</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, diarrhoea, constipation, dry mouth, dysphagia, nausea, vomiting</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia, dermatitis psoriasiform, erythema multiforme, hyperhidrosis, madarosis, pruritus, rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Muscle atrophy, myalgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Denervation atrophy, malaise, pyrexia</td>
</tr>
</tbody>
</table>

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC class M03A X01 and ATC class D11AX.

The active constituent in BOTOX is a protein complex derived from Clostridium botulinum. The protein consists of type A neurotoxin and several other proteins. Under physiological conditions it is presumed that the complex dissociates and releases the pure neurotoxin.

Clostridium botulinum toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals.

Intramuscular injection of the neurotoxin complex blocks cholinergic transport at the neuromuscular junction by preventing the release of acetylcholine. The nerve endings of the neuromuscular junction no longer respond to nerve impulses and secretion of the chemotransmitter is prevented (chemical denervation). Re-establishment of impulse transmission is by newly formed nerve
endings and motor end plates. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

After intradermal injection, where the target is the eccrine sweat glands, the effect lasted for about 4-7 months in patients treated with 50 Units per axilla.

There is limited clinical trial experience of the use of BOTOX in primary axillary hyperhidrosis in adolescents between the ages of 12 and 18. A single, year long, uncontrolled, repeat dose, safety study was conducted in US paediatric patients 12 to 17 years of age (N=144) with severe primary hyperhidrosis of the axillae. Participants were primarily female (86.1%) and Caucasian (82.6%). Participants were treated with a dose of 50 Units per axilla for a total dose of 100 Units per patient per treatment. However, no dose finding studies have been conducted in adolescents so no recommendation on posology can be made. Efficacy and safety of BOTOX in this group have not been established.

BOTOX blocks the release of neurotransmitters associated with the genesis of pain. The presumed mechanism for headache prophylaxis is by blocking peripheral signals to the central nervous system, which inhibits central sensitisation, as suggested by pre-clinical and clinical pharmacodynamic studies.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition BOTOX inhibits afferent neurotransmitters and sensory pathways.

**Clinical efficacy and safety**

**NEUROLOGIC DISORDERS**

**Focal upper limb spasticity associated with stroke**

In controlled and open, non-controlled studies, doses between 200 and 240 Units in wrist and flexor muscles were divided among the selected muscles at a given treatment session. In controlled studies, improvement in muscle tone occurred within two weeks with the peak effect generally seen within four to six weeks. In an open, non-controlled continuation study, most patients were re-injected after an interval of 12 to 16 weeks, when the effect on muscle tone had diminished. These patients received up to four injections with a maximal cumulative dose of 960 Units over 54 weeks.

**Focal lower limb spasticity associated with stroke**

A double-blind, placebo-controlled, randomised, multi-centre, phase 3 clinical study was conducted in adult post-stroke patients with lower limb spasticity affecting the ankle. A total of 120 patients were randomised to receive either BOTOX (n=58; total dose of 300 Units) or placebo (n=62).

Significant improvement compared to placebo was observed in the primary endpoint for the overall change from baseline up to week 12 in Modified Ashworth Scale (MAS) ankle score, which was calculated using the area under the curve (AUC) approach. Significant improvements compared to placebo were also observed for the mean change from baseline in MAS ankle score at individual post-treatment visits at weeks 4, 6 and 8. The proportion of responders (patients with at least a 1-grade improvement) was also significantly higher (67%-68%) than in placebo-treated patients (31%-36%) at these visits.

BOTOX treatment was also associated with significant improvement in the investigator’s clinical global impression (CGI) of functional disability compared to placebo although the difference was not significant for the patient’s CGI.
Cervical dystonia

In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted BOTOX ranged from 140 to 280 Units. In more recent studies, doses ranged from 95 to 360 Units (with an approximate mean of 240 Units). Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs by six weeks post-injection. The duration of beneficial effect reported in clinical studies showed substantial variation (from 2 to 33 weeks) with a typical duration of approximately 12 weeks.

Chronic migraine

Chronic migraine patients without any concurrent headache prophylaxis who, during a 28-day baseline, had at least 4 episodes and ≥ 15 headache days (with at least 4 hours of continuous headache) with at least 50% being migraine/probable migraine, were studied in two Phase 3 clinical trials. Patients were allowed to use acute headache treatments and 66% overused acute treatments during the baseline period.

During the double-blind phase of the trials, the main results achieved after two BOTOX treatments administered at a 12-week interval are shown in the table below.

<table>
<thead>
<tr>
<th>Mean change from baseline at Week 24</th>
<th>BOTOX (N=688)</th>
<th>Placebo (N=696)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of headache days</td>
<td>-8.4</td>
<td>-6.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7</td>
<td>-5.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2</td>
<td>-6.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47%</td>
<td>35%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total cumulative hours of headache on headache days</td>
<td>120</td>
<td>80</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2</td>
<td>-4.9</td>
<td>0.009</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8</td>
<td>-2.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* Headache Impact Test

The treatment effect appeared smaller in the subgroup of male patients (n=188) than in the whole study population.

BLADDER DISORDERS

Overactive bladder

Two double-blind, placebo-controlled, randomised, 24-week phase 3 clinical studies were conducted in patients with overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. A total of 1105 patients (mean age of 60 years), whose symptoms had not been adequately managed with at least one anticholinergic therapy (inadequate response or intolerable side effects), were randomised to receive either 100 Units of BOTOX (n=557), or placebo (n=548), after having discontinued anticholinergics for more than one week.

Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies:

<table>
<thead>
<tr>
<th></th>
<th>Botox 100 Units (N=557)</th>
<th>Placebo (N=548)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Frequency of Urinary Incontinence Episodes Mean Baseline</td>
<td>5.49</td>
<td>5.39</td>
<td></td>
</tr>
<tr>
<td>Mean Change¹ at Week 2</td>
<td>-2.66</td>
<td>-1.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean Change⁸ at Week 6</td>
<td>-2.97</td>
<td>-1.13</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Mean Change at Week 12

<table>
<thead>
<tr>
<th>endpoints</th>
<th>Mean Baseline</th>
<th>Mean Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion with Positive Treatment Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>using Treatment Benefit Scale (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>64.4</td>
<td>34.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 6</td>
<td>68.1</td>
<td>32.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 12</td>
<td>61.8</td>
<td>28.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Daily Frequency of Micturition Episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>11.99</td>
<td>11.48</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-2.19</td>
<td>-0.82</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Daily Frequency of Urgency Episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>8.82</td>
<td>8.31</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-3.08</td>
<td>-1.12</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Incontinence Quality of Life Total Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>34.1</td>
<td>34.7</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>+21.3</td>
<td>+5.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>King’s Health Questionnaire: Role Limitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>65.4</td>
<td>61.2</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-24.3</td>
<td>-3.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>King’s Health Questionnaire: Social Limitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>44.8</td>
<td>42.4</td>
<td></td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-16.1</td>
<td>-2.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Percentage of patients achieving full continence at Week 12 (dry patients over a 3-day diary)</td>
<td>27.1%</td>
<td>8.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Percentage of patients achieving reduction from baseline in urinary incontinence episodes at Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at least 75%</td>
<td>46.0%</td>
<td>17.7%</td>
<td></td>
</tr>
<tr>
<td>at least 50%</td>
<td>60.5%</td>
<td>31.0%</td>
<td></td>
</tr>
</tbody>
</table>

† Least Squares (LS) mean changes are presented

a Co-primary endpoints

b Secondary endpoints

c Pre-defined minimally important change from baseline was +10 points for I-QOL and -5 points for KHQ

The median duration of response following BOTOX treatment, based on patient request for re-treatment, was 166 days (~24 weeks).

A total of 839 patients were evaluated in a long-term open-label extension study. For all efficacy endpoints, patients experienced consistent response with re-treatments. The mean reductions from baseline in daily frequency of urinary incontinence were -3.07 (n=341), -3.49 (n=292), and -3.49 (n=204) episodes at week 12 after the first, second, and third BOTOX 100 Unit treatments, respectively. The corresponding proportions of patients with a positive treatment response on the Treatment Benefit Scale were 63.6% (n=346), 76.9% (n=295), and 77.3% (n=207), respectively.

In the pivotal studies, none of the 615 patients with analysed serum specimens developed neutralising antibodies after 1 – 3 treatments.

**Urinary incontinence due to neurogenic detrusor overactivity**

Two double-blind, placebo-controlled, randomised phase 3 clinical studies were conducted in a total of 691 patients with spinal cord injury or multiple sclerosis, who were not adequately managed with at least one anticholinergic agent and were either spontaneously voiding or using catheterisation. These patients were randomised to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).
Primary and Secondary Endpoints at Baseline and Change from Baseline in Pooled Pivotal Studies:

<table>
<thead>
<tr>
<th></th>
<th>BOTOX 200 Units (N=227)</th>
<th>Placebo (N=241)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weekly Frequency of Urinary Incontinence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>32.4</td>
<td>31.5</td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 2</td>
<td>-16.8</td>
<td>-9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change‡ at Week 6</td>
<td>-20.0</td>
<td>-10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change‡ at Week 12</td>
<td>-19.8</td>
<td>-9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Cystometric Capacity (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>250.2</td>
<td>253.5</td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 6</td>
<td>+140.4</td>
<td>+6.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH20)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>51.5</td>
<td>47.3</td>
<td></td>
</tr>
<tr>
<td>Mean Change‡ at Week 6</td>
<td>-27.1</td>
<td>-0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Incontinence Quality of Life Total Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>35.4</td>
<td>35.3</td>
<td></td>
</tr>
<tr>
<td>Mean Change‡ at Week 6</td>
<td>+23.6</td>
<td>+8.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change‡ at Week 12</td>
<td>+26.9</td>
<td>+7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Percentage of patients achieving full continence at Week 6 (dry patients over a 7 day diary)</strong></td>
<td>37%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td><strong>Percentage of patients achieving reduction from baseline in urinary incontinence episodes at Week 6</strong></td>
<td>at least 75%</td>
<td>63%</td>
<td>24%</td>
</tr>
<tr>
<td>at least 50%</td>
<td>76%</td>
<td>39%</td>
<td></td>
</tr>
</tbody>
</table>

† LS mean changes are presented
‡ Secondary endpoints
§ 1-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).
* In the pivotal studies, the pre-specified minimally important difference (MID) for 1-QOL total score was 8 points based on MID estimates of 4-11 points reported in neurogenic detrusor overactivity patients.

The median duration of response (time to < 50% reduction in incontinence episodes) was 42 weeks in the 200 Unit dose group. The median interval between the first and second administrations was 42 weeks in patients with spinal cord injury and 45 weeks in patients with multiple sclerosis.

For all efficacy endpoints in the pivotal phase 3 studies, patients experienced consistent response with re-treatment (n=116).

None of the 475 patients with analysed serum specimens developed neutralising antibodies after 1-2 treatments.

In the multiple sclerosis (MS) patients enrolled in the pivotal studies, the MS exacerbation annualised rate (i.e., number of MS exacerbation events per patient year) was 0.23 in the 200 Unit dose group and 0.20 in the placebo group. With repeated BOTOX treatments, including data from a long term study, the MS exacerbation annualised rate was 0.19 during each of the first two BOTOX treatment cycles.
SKIN AND SKIN APPENDAGE DISORDER

Glabellar lines

537 patients with moderate to severe glabellar lines between the eyebrows seen at maximum frown have been included in clinical studies.

BOTOX injections significantly reduced the severity of glabellar lines seen at maximum frown for up to 4 months, as measured by the investigator assessment of glabellar line severity at maximum frown and by subject’s global assessment of change in appearance of his/her glabellar lines seen at maximum frown. Improvement generally occurred within one week of treatment. None of the clinical endpoints included an objective evaluation of the psychological impact. Thirty days after injection, 80% (325/405) of BOTOX-treated patients were considered by investigators as treatment responders (none or mild severity at maximum frown), compared to 3% (4/132) of placebo-treated patients. At this same timepoint, 89% (362/405) of BOTOX-treated patients felt they had a moderate or better improvement, compared to 7% (9/132) of placebo-treated patients.

BOTOX injections also significantly reduced the severity of glabellar lines at rest. Of the 537 patients enrolled, 39% (210/537) had moderate to severe glabellar lines at rest (15% had no lines at rest). Of these, 74% (119/161) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 20% (10/49) of placebo-treated patients.

There is limited phase 3 clinical data with BOTOX in patients older than 65 years. Only 6.0% (32/537) of subjects were >65 years old and efficacy results obtained were lower in this population.

Crow’s feet lines

1362 patients with moderate to severe crow’s feet lines seen at maximum smile, either alone (n=445, Study 191622-098) or also with moderate to severe glabellar lines seen at maximum frown (n=917, Study 191622-099), were enrolled.

BOTOX injections significantly reduced the severity of crow’s feet lines seen at maximum smile compared to placebo at all timepoints (p <0.001) for up to 5 months (median 4 months). Improvement assessed by the investigator occurred within one week of treatment. This was measured by the proportion of patients achieving a crow’s feet lines severity rating of none or mild at maximum smile in both pivotal studies; until day 150 (end of study) in Study 191622-098 and day 120 (end of first treatment cycle) in Study 191622-099. For both investigator and subject assessments, the proportion of subjects achieving none or mild crow’s feet lines severity seen at maximum smile was greater in patients with moderate crow’s feet lines seen at maximum smile at baseline, compared to patients with severe crow’s feet lines seen at maximum smile at baseline. Table 1 summarises results at day 30, the timepoint of the primary efficacy endpoint.

In Study 191622-104 (extension to Study 191622-099), 101 patients previously randomised to placebo were enrolled to receive their first treatment at the 44 Units dose. Patients treated with BOTOX had a statistically significant benefit in the primary efficacy endpoint compared to placebo at day 30 following their first active treatment. The response rate was similar to the 44 Units group at day 30 following first treatment in Study 191622-099. A total of 123 patients received 4 cycles of 44 Units BOTOX for combined crow’s feet and glabellar lines treatment.

Day 30: Investigator and Patient Assessment of Crow’s Feet Lines Seen at Maximum Smile - Responder Rates (% of Patients Achieving Crow’s Feet Lines Severity Rating of None or Mild)

| Clinical Study | Dose                  | BOTOX  | Placebo | BOTOX  | Placebo |
|               | (crow’s feet lines)   | Investigator Assessment | Patient Assessment | Investigator Assessment | Patient Assessment |
| 191622-098    | 24 Units              | 66.7%* (148/222)        | 6.7% (15/223)      | 58.1%* (129/222)        | 5.4% (12/223) |

Improvements from baseline in subject-assessment of the appearance of crow’s feet lines seen at maximum smile were seen for BOTOX (24 Units and 44 Units) compared to placebo, at day 30 and at all timepoints following each treatment cycle in both pivotal studies (p<0.001).

Treatment with BOTOX 24 Units also significantly reduced the severity of crow’s feet lines at rest. Of the 528 patients treated, 63% (330/528) had moderate to severe crow’s feet lines at rest at baseline. Of these, 58% (192/330) of BOTOX-treated patients were considered treatment responders (none or mild severity) thirty days after injection, compared with 11% (39/352) of placebo-treated patients.

Improvements in subject’s self-assessment of age and attractiveness were also seen for BOTOX (24 Units and 44 Units) compared to placebo using the Facial Line Outcomes (FLO-11) questionnaire, at the primary timepoint of day 30 (p<0.001) and at all subsequent timepoints in both pivotal studies.

In the pivotal studies, 3.9% (53/1362) of patients were older than 65 years of age. Patients in this age group had a treatment response as assessed by the investigator, of 36% (at day 30) for BOTOX (24 Units and 44 Units). When analysed by age groups of ≤50 years and >50 years, both populations demonstrated statistically significant improvements compared to placebo. Treatment response for BOTOX 24 Units, as assessed by the investigator, was lower in the group of subjects >50 years of age than those ≤50 years of age (42.0% and 71.2%, respectively).

Overall BOTOX treatment response for crow’s feet lines seen at maximum smile is lower (60%) than that observed with treatment for glabellar lines seen at maximum frown (80%).

916 patients (517 patients at 24 Units and 399 patients at 44 Units) treated with BOTOX had specimens analysed for antibody formation. No patients developed the presence of neutralising antibodies.

### 6.6 Special precautions for disposal

**Reconstitution**

BOTOX is reconstituted prior to use with sterile 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection. It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of diluent (see dilution table below) is drawn up into a syringe. The exposed portion of the rubber septum of the vial is cleaned with alcohol (70%) prior to insertion of the needle. Since BOTOX is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. When reconstituted, BOTOX may be stored in a refrigerator (2–8°C) for up to 24 hours prior to use. After this period used or unused vials should be discarded.

Each vial is for single use only.
Care should be taken to use the correct diluent volume for the presentation chosen to prevent accidental overdose. If different vial sizes of BOTOX are being used as part of one injection procedure, care should be taken to use the correct amount of diluent when reconstituting a particular number of units per 0.1 ml. The amount of diluent varies between BOTOX 50 Allergan Units, BOTOX 100 Allergan Units and BOTOX 200 Allergan Units. Each syringe should be labelled accordingly.

Dilution table for BOTOX 50, 100 and 200 Allergan Units vial size for all indications except bladder disorders:

<table>
<thead>
<tr>
<th>Resulting dose (Units per 0.1 ml)</th>
<th>50 Unit vial</th>
<th>100 Unit vial</th>
<th>200 Unit vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 Units</td>
<td>0.25 ml</td>
<td>0.5 ml</td>
<td>1 ml</td>
</tr>
<tr>
<td>10 Units</td>
<td>0.5 ml</td>
<td>1 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>5 Units</td>
<td>1 ml</td>
<td>2 ml</td>
<td>4 ml</td>
</tr>
<tr>
<td>4 Units</td>
<td>1.25 ml</td>
<td>2.5 ml</td>
<td>5 ml</td>
</tr>
<tr>
<td>2.5 Units</td>
<td>2 ml</td>
<td>4 ml</td>
<td>8 ml</td>
</tr>
<tr>
<td>1.25 Units</td>
<td>4 ml</td>
<td>8 ml</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Overactive bladder:**
It is recommended that a 100 Unit or two 50 Unit vials are used for convenience of reconstitution.

**Dilution instructions using two 50 Unit vials:**
- Reconstitute two 50 Unit vials of BOTOX each with 5 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution and mix the vials gently.
- Draw the 5 ml from each of the vials into a single 10 ml syringe. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

**Dilution instructions using a 100 Unit vial:**
- Reconstitute a 100 Unit vial of BOTOX with 10 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution and mix gently.
- Draw the 10 ml from the vial into a 10 ml syringe. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

**Dilution instructions using a 200 Unit vial:**
- Reconstitute a 200 Unit vial of BOTOX with 8 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution and mix gently.
- Draw 4 ml from the vial into a 10 ml syringe.
- Complete the reconstitution by adding 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution into the 10 ml syringe and mix gently. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

This product is for single use only and any unused reconstituted product should be disposed of.

**Urinary incontinence due to neurogenic detrusor overactivity:**
It is recommended that a 200 Unit vial or two 100 Unit vials are used for convenience of reconstitution.
**Dilution instructions using four 50 Unit vials:**
- Reconstitute four 50 Unit vials of BOTOX, each with 3 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection and mix the vials gently.
- Draw 3 ml from the first vial and 1 ml from the second vial into one 10 ml syringe.
- Draw 3 ml from the third vial and 1 ml from the fourth vial into a second 10 ml syringe.
- Draw the remaining 2 ml from the second and fourth vials into a third 10 ml syringe.
- Complete the reconstitution by adding 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection into each of the three 10 ml syringes, and mix gently.

This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

**Dilution instructions using two 100 Unit vials:**
- Reconstitute two 100 Unit vials of BOTOX, each with 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection and mix the vials gently.
- Draw 4 ml from each vial into each of two 10 ml syringes.
- Draw the remaining 2 ml from each vial into a third 10 ml syringe.
- Complete the reconstitution by adding 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection into each of the 10 ml syringes, and mix gently.

This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

**Dilution instructions using a 200 Unit vial:**
- Reconstitute a 200 Unit vial of BOTOX with 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection and mix the vials gently.
- Draw 2 ml from the vial into each of three 10 ml syringes.
- Complete the reconstitution by adding 8 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection into each of the 10 ml syringes, and mix gently.

This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

The 'unit' by which the potency of preparations of BOTOX is measured should be used to calculate dosages of BOTOX only and is not transferable to other preparations of botulinum toxin.

**Disposal**
For safe disposal, unused vials should be reconstituted with a small amount of water then autoclaved. Any used vials, syringes, and spillages etc. should be autoclaved, or the residual BOTOX inactivated using dilute hypochlorite solution (0.5%).

Any unused product or waste material should be disposed of in accordance with local requirements.
ALLERGAN®

Package leaflet: Information for the user

BOTOX®
50 Allergan Units,
100 Allergan Units,
200 Allergan Units,
Powder for Solution for Injection
Botulinum toxin type A

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:
1. What BOTOX is and what it is used for
2. What you need to know before you use BOTOX
3. How to use BOTOX
4. Possible side effects
5. How to store BOTOX
6. Contents of the pack and other information

1. What BOTOX is and what it is used for

BOTOX is a muscle relaxant used to treat a number of conditions within the body. It contains the active substance Botulinum toxin type A and is injected into either the muscles, the bladder wall or deep into the skin. It works by partially blocking the nerve impulses to any muscles that have been injected and reduces excessive contractions of these muscles. In the case of chronic migraine, it is thought that BOTOX blocks pain signals, which indirectly block the development of a migraine.

When injected into the skin, BOTOX works on sweat glands to reduce the amount of sweat produced.

When injected into the bladder wall, BOTOX works on the bladder muscle to prevent leakage of urine urinary incontinence due to uncontrolled contractions of the bladder muscle.

1) BOTOX can be injected directly into the muscles, and can be used to control the following conditions:
• In children aged two years or older with cerebral palsy, who can walk, BOTOX is used to control foot deformity caused by the persistent muscle spasms in the legs.
• BOTOX relieves the persistent muscle spasms in the leg.
• In adults:
  • Persistent muscle spasms in the wrist hand or ankle of patients who have suffered a stroke;
  • Persistent muscle spasms in the eyelid and face;
  • Persistent muscle spasms in the neck and shoulders.

2) BOTOX is used to prevent headaches in adult patients with chronic migraine.

Chronic migraine is a disease affecting the nervous system. To be diagnosed with chronic migraine, you must have headaches 15 days or more a month. In addition, on 8 or more days a month, your headaches must have at least two of the following characteristics:
• affect only one side of the head
• cause a pulsating pain

• cause moderate to severe pain
• are aggravated by routine physical activity and they must cause at least one of the following:
• nausea, vomiting, or both
• sensitivity to light and sound.

BOTOX has been shown to significantly reduce the frequency of days with headache and to improve the quality of life of patients suffering from chronic migraine. After two treatment sessions, approximately 47% of patients had a 50% or greater reduction from baseline in the number of days with headache they experienced.

3) When injected into the bladder wall, BOTOX works on the bladder muscle to reduce leakage of urine urinary incontinence and control the following conditions:
• overactive bladder with leakage of urine, the sudden urge to empty your bladder and needing to go to the toilet more than usual;
• leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis.

In patients who have not managed to control overactive bladder with leakage of urine with medicines called anticholinergics, BOTOX has been shown to reduce leakage of urine from an average of about 3 episodes per day down to 2 after 12 weeks. 27% of patients had no leakage of urine at all.

In patients with bladder problems associated with spinal cord injury or multiple sclerosis who have not managed to control leakage of urine with medicines called anticholinergics, BOTOX has been shown to reduce leakage of urine, from an average of about 3 episodes per week down to 1 after 8 weeks. 33% of patients had no leakage of urine at all.

4) In adults, BOTOX can be injected deep into the skin and can work on sweat glands to reduce excessive sweating of the armpits, which affects the activities of daily living where other local treatments do not help.

5) When the severity of the following facial lines has an important psychological impact in adult patients, BOTOX is used for the temporary improvement in the appearance of:
• Vertical lines between the eyebrows seen at maximum frown;
• Fan-shaped lines from the corners of the eyes seen at maximum smile;
• Fan-shaped lines from the corner of the eyes seen at maximum smile when treated at the same time at the lateral lines between the eyebrows seen at maximum frown.

2. What you need to know before you use BOTOX

Do not use BOTOX
• If you are allergic (hypersensitive) to botulinum toxin type A or any of the other ingredients of this medicine (listed in section 6);
• If you have an infection at the proposed site of injection;
• If you are being treated for leakage of urine and you have either a urinary tract infection on a sudden inability to empty your bladder (and are not regularly using a catheter), or if you have bladder stones;
• If you are being treated for leakage of urine and are not willing to begin using a catheter if required.

Warnings and precautions
Talk to your doctor or pharmacist before using BOTOX:
• If you have ever had problems with swallowing or food or liquid accidentally going into your lungs, especially if you will be treated for persistent muscle spasms in the neck and shoulders;
• If you are over 65 years of age and have other serious illnesses;
• If you suffer from any other muscle problems or chronic diseases affecting your muscles (such as myasthenia gravis or Eaton Lambert Syndrome);
• Suffer from certain diseases affecting your nervous system (such as amyotrophic lateral sclerosis or motor neurone disease);
• If you have significant weakness or wasting of the muscles which your doctor plans to inject;
• If you have had any surgery that may have in some way changed the muscle to be injected;
• If you have had any problems with injections (such as fainting) in the past;
• If you have inflammation in the muscles or skin area where your doctor plans to inject;

PL 00426/0074, PLs 00426/0118-0119
After you have been given Botox

You or your caregiver should contact your doctor and seek medical attention immediately if you experience any of the following:

- difficulty in breathing, swallowing, or speaking;
- hives, swelling, including swelling of the face or throat, wheezing, feeling faint and shortness of breath (possible symptoms of severe allergic reaction).

If you have been treated for vertical and/or fan-shaped lines, please inform your doctor if you see no significant improvement of your lines one month after your first course of treatment.

General precautions

As with any injection, it is possible for the procedure to result in infection, pain, swelling, burning and stinging, increased sensitivity, tenderness, redness, and/or bleeding/redness at the site of injection.

Side effects possibly related to the spread of toxin distant from the site of administration have been reported with botulinum toxin (e.g., muscle weakness, difficulty swallowing or unwanted food or liquid in the airways). This is a particular risk for patients with an underlying illness that makes them susceptible to these symptoms.

If you are given Botox too often or the dose is too high, you may experience muscle weakness and side effects related to the spread of toxin, or your body may start producing some antibodies, which can reduce the effect of Botox. To limit this risk, the interval between two treatments must not be less than two or three months depending on the indication.

When Botox is used in the treatment of a condition that is not listed in this leaflet, it could result in serious reactions, particularly in patients who already experience difficulty in swallowing or have significant disability.

If you have not done much exercise for a long time before receiving Botox treatment, then after your injections you should start any activity gradually.

It is unlikely that this medicine will improve the range of motion of joints where the surrounding muscle has lost its ability to stretch.

When treating adults with post-stroke or stroke-like muscle spasms, Botox should only be used if it is expected to result in improvement in function (e.g., walking) or symptoms (e.g., spasms or pain) or to help with patient care. Furthermore, for patients who may be more likely to fail, your doctor will judge if this treatment is suitable.

When Botox is used in the treatment of persistent muscle spasms in the eyelid, it could make your eyes blink less often, which may harm the surface of your eyes. In order to prevent this, you may need treatment with eye drops, contact lenses, soft contact lenses or even protective covering which closes the eye. Your doctor will tell you if this is required.

Botox does not prevent headaches in patients with episodic migraine, which occur less than 15 days a month.

When Botox is used in the treatment of vertical lines and fan-shaped lines drooping of eyelid may occur after treatment.

Other medicines with Botox

Tell your doctor or pharmacist if:

- you are using any antibiotics (used to treat infections), or any medicines that affect the nerves that control muscles
- you have had problems in the past with previous botulinum toxin injections;
- you suffer from cardiovascular disease (disease of the heart or blood vessels);
- you suffer of have suffered from seizures;
- you have an eye disease called closed-angle glaucoma (high pressure in the eye) or were told you are at risk for developing this type of glaucoma;
- you will have an operation soon;
- you are taking any blood thinning medicine.

(for example anticholinesterase medicines or muscle relaxants). Some of these medicines may increase the effect of Botox.

- you have recently been injected with a medicine containing a botulinum toxin (the active substance of Botox), as this may increase the effect of Botox too much.
- you are using any anti-platelet (aspirin-like) products and/or anticoagulants (blood thinners).

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicine.

Pregnancy and breastfeeding

The use of Botox is not recommended during pregnancy and in women of childbearing potential not using contraception. Botox is not recommended in breast-feeding women.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Driving and using machines

Botox may cause dizziness, sleepiness, tiredness or problems with your vision. If you experience any of these effects, do not drive or use any machines. If you are not sure, ask your doctor for advice.

3. How to use Botox

Botox must only be injected by doctors with specific skills and experience on how to use the medicine.

Method and route of administration

Botox is injected into your muscles (intramuscularly), into the bladder wall via a specific instrument (cystoscope) to inject into the bladder or into the skin (intradermally). It is injected directly into the affected area of your body; your doctor will usually inject Botox into several sites within each affected area.

General information about dosage

- The number of injections per muscle and the dose vary depending on the indication. Therefore, your doctor will decide how much, how often, and in which muscle(s) Botox will be given to you. It is recommended that your doctor uses the lowest effective dose;
- Dosages for older people are the same as for other adults.

The dosage of Botox and the duration of its effect will vary depending on the condition for which you are treated. Below are details corresponding to each condition.

The safety and effectiveness of Botox has not been established in children/adolescents under the following ages:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>2 years</td>
</tr>
<tr>
<td>Persistent muscle spasms in the</td>
<td>18 years</td>
</tr>
<tr>
<td>wrist, hand or ankle of patients who have suffered a stroke</td>
<td></td>
</tr>
<tr>
<td>Persistent muscle spasms in the</td>
<td>12 years</td>
</tr>
<tr>
<td>eyelid, face</td>
<td></td>
</tr>
<tr>
<td>Neck and shoulder</td>
<td>12 years</td>
</tr>
<tr>
<td>Chronic migraine</td>
<td>18 years</td>
</tr>
<tr>
<td>Leakage of urine</td>
<td>18 years</td>
</tr>
<tr>
<td>Excessive sweating of the arms</td>
<td>12 years (limited experience in adolescents between 12 and 17 years, speak to your doctor for further information)</td>
</tr>
<tr>
<td>Vertical lines between the</td>
<td>16 years</td>
</tr>
<tr>
<td>eyebrows and/or fan-shaped</td>
<td></td>
</tr>
<tr>
<td>lines from the inner corners of the eyes</td>
<td></td>
</tr>
</tbody>
</table>

In addition, there is limited experience of using Botox in the treatment of vertical and/or fan-shaped lines in patients older than 65 years.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Maximum dose (Units per affected area)</th>
<th>Minimal time between treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent muscle spasms in the legs of children who have cerebral palsy</td>
<td>4 Units/kg, 6 Units/kg (hemiplegia)</td>
<td>3 months*</td>
</tr>
<tr>
<td>Persistent muscle spasms in the wrist and hand of patients who have had a stroke</td>
<td>The exact dosage and number of injection sites is tailored to individual needs up to a maximum of 240 Units</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Persistent muscle spasms in the ankle of patients who have had a stroke</td>
<td>Multiple injections in the affected muscles. The total dose is 300 Units divided among 3 muscles</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Persistent muscle spasms of the eyelid and face</td>
<td>Up to 25 Units</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Persistent muscle spasms of the neck and shoulders</td>
<td>Up to 200 Units</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Headache in adults who have chronic migraine</td>
<td>155 to 195 Units</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Overactive bladder with leakage of urine</td>
<td>100 Units</td>
<td>3 months</td>
</tr>
<tr>
<td>Leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis</td>
<td>200 Units</td>
<td>3 months</td>
</tr>
<tr>
<td>Excessive sweating of the armpits</td>
<td>50 Units per armpit</td>
<td>16 weeks</td>
</tr>
<tr>
<td>Vertical lines between the eyebrows seen at maximum from</td>
<td>Up to 50 Units</td>
<td>3 months</td>
</tr>
<tr>
<td>Fan-shaped lines from the corner of the eyes seen at maximum smile</td>
<td>24 Units</td>
<td>3 months</td>
</tr>
</tbody>
</table>

* The doctor may select a dose that would mean the treatment may be up to 6 months apart.
** If you are treated for fan-shaped lines from the corner of the eyes seen at maximum from the same time as vertical lines between the eyebrows seen at maximum from, you will receive a total dose of 44 Units.

Information for patients treated for leakage of urine

Your doctor will give you antibiotics around the time of the injection to help prevent urinary tract infection. The injection will be administered by a procedure called cystoscopy. An instrument with a light source at the end will be introduced into your bladder through the opening by which you let out the urine (called urethra). This enables the doctor to see the inside of the bladder and place the injections into the bladder wall. Please ask your doctor to explain further details of the procedure to you.

If you were not using a catheter (a soft, hollow tube that is inserted into your urethra to help empty urine from the bladder) before treatment with BOTOX, you should be seen by your doctor approximately 2 weeks after the injection. You will be asked to pass urine and will then have the volume of urine let in your bladder measured. If your doctor assesses you have too much urine left in your bladder you will be instructed to use a catheter to empty your bladder. Your doctor will decide if and when you need to return for the same test.

For overactive bladder with leakage of urine.

You may be given a local anaesthetic before the injections (your bladder would be filled with anaesthetic solution for 1-2 hours) and then drained. You may also be given a sedative.

You will be observed for at least 30 minutes after the injection before you can leave to see if you can pass urine spontaneously.

You must contact your doctor if at any time you are unable to pass urine because it is possible that you may need to start using a catheter. In clinical trials, approximately 15% of patients reported an inability to completely empty their bladder after BOTOX treatment. At least one third of patients not using a catheter before treatment may need to use a catheter after treatment.

Time to Improvement and Duration of Effect

For persistent muscle spasms in the legs of children who have cerebral palsy, the improvement usually appears within the first 2 weeks after the injection.

For persistent muscle spasms in the wrist and hand of patients who have had a stroke, you will usually see an improvement within the first 2 weeks after the injection. The maximum effect is usually seen about 4 to 6 weeks after treatment.

For persistent muscle spasms of the eyelid and face, you will usually see an improvement within 3 days after the injection and the maximum effect is usually seen after 1 to 2 weeks.

For persistent muscle spasms of the neck and shoulders, you will usually see an improvement within 2 weeks after the injection. The maximum effect is usually seen about 8 weeks after treatment.

For leakage of urine due to overactive bladder, you will usually see an improvement within 2 weeks after the injection. Typically, the effect lasts approximately 6 months after the injection.

For leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis, you will usually see an improvement within 2 weeks after the injection. Typically, the effect lasts approximately 10 months after the injection.

For excessive sweating of the armpits, you will usually see an improvement within the first week after injection. On average, the effect usually lasts 4-7 months after the first injection.
# Possible side effects

If you experience any difficulty in breathing, swallowing, or speaking after receiving BOTOX, contact your doctor immediately.

Below are lists of side effects which vary depending on the part of the body where BOTOX is injected. If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

### Injections in the eyelid and face for muscle spasms

**Very Common**
- Dropping of the eyelid

**Common**
- Swelling of the face

**Uncommon**
- Dizziness, weakness of the face and eye muscles, drooping of the muscles on one side of the face

**Rare**
- Swelling of the eyelid

**Very rare**
- Damage to the cornea (transparent surface covering the front of the eye) including ulcer and perforation

### Injections in the neck and shoulder

**Very Common**
- Difficulty in swallowing

**Common**
- Dizziness, sleepiness, headache

**Uncommon**
- Shortness of breath, changes in voice

### Injections in the legs of patients who have had a stroke

**Common**
- Rash

**Uncommon**
- Joint pain or inflammation, stiff or sore muscles

### Injections in the wrist and hand of patients who have had a stroke

**Common**
- Muscle weakness, increased muscle tension

**Uncommon**
- Depression, difficulty in sleeping (insomnia)

### Injections in the legs of children with cerebral palsy

**Very Common**
- Viral infection, ear infection

**Common**
- Sleepiness, problems with waking, numbness

**Uncommon**
- Shortness of breath, changes in voice

### Injections in the thighs of patients who have had a stroke

**Common**
- Joint pain or inflammation, stiff or sore muscles

**Uncommon**
- Inflammation of the skin (dermatitis), rash, itching, increased sensitivity where the injection was given

### Injections in the head and neck

**Common**
- Muscle weakness, increased muscle tension

**Uncommon**
- Depression, difficulty in sleeping (insomnia)

## Possible side effects

For vertical lines between the eyebrows seen at a maximum frown, you will usually not see an improvement within 1 week after treatment. The maximum effect being observed 5 to 6 weeks after injection. The treatment effect has been demonstrated for up to 4 months after injection.

For fanning lines from the corner of the eyes seen at maximum smile, you will usually see an improvement within 1 week after treatment. The treatment effect has been demonstrated for an average of 4 months after injection.

If you have received more BOTOX than you should be, you should see your doctor. He/she will decide if you have to go to hospital:

- Muscle weakness which could be local or distant from the site of injection.
- Difficulty in breathing, swallowing or speaking due to muscle paralysis.
- Food or fluid accidentally going into your lungs which might cause pneumonia (infection of the lungs) due to muscle paralysis.
- Drooping of the eyelids, double vision.
- Generalised weakness.

If you have any further questions on the use of this product, ask your doctor or pharmacist.
Injections in the head and neck to prevent headache in patients who suffer from chronic migraine

Common
- Increase in headache or migraine
- Weakness of the face muscles
- Drooping of the eyelid
- Muscle twitching
- Pain where the injection was given
- Muscle weakness, neck pain, muscle pain or cramp, muscle stiffness or tightness

Uncommon
- Difficulty in swallowing
- Swollen eyelid
- Skin pain
- Jaw pain

Injections in the bladder wall for overactive bladder with leakage of urine

Very common
- Urinary infection, painful urination after the injection
  - Urinary infection (in about half the patients)
  - Inability to empty the bladder (urinary retention; see section 3)

Common
- Muscle spasm
- Bulge in the bladder wall (bladder diverticulum)
  - The following side effects have only been reported in multiple sclerosis:
    - Difficulty in sleeping (insomnia)
    - Tiredness, problems with walking (gait disturbance)
    - Constipation
    - Muscle weakness, fall
  - The following side effects are related to the injection procedure:
    - Pain in the bladder after the injection
    - Uncontrolled reflex reaction in the body
    - Uncontrolled increase in pulse rate around the time of the injection (autonomic dysreflexia; see section 3)

Injections in the bladder wall for leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis

Common
- Urinary infection (in about half the patients)

Very common
- Urinary infection, painful urination after the injection

Injections for excessive sweating of the axillae

Common
- Headache, numbness, hot flushes

Very common
- Pain where the injection was given

Common
- Increased sweating at sites other than the axilla, abnormal skin odour, itching, lump under the skin
- Hair loss
- Pain in the extremities, such as the hands and fingers
- Pain, reaction where the injection was given such as swelling, bleeding, burning or increased sensitivity

Uncommon
- Muscle weakness, muscle pain, problem with the joints
- Feeling weak

Injections in the forehead for vertical lines

Common
- Headache, drooping of the eyelid, localized muscle weakness, face pain, skin redness

Uncommon
- Infection
- Anxiety
- Malaise, dizziness
- Inflammation of the eyelid, eye pain, visual disturbance
- Swelling (face, eyelid, around the eyes), skin tightness, skin sensitivity to light, dry skin, itching
- Feeling sick, dry mouth
- Muscle twitching
- Fever, flu manifestations, feeling weak

Injections in the fan-shaped lines from the corner of the eyes

Common
- Swelling of the eyelid
- Injection site bleeding*, injection site bruising

Uncommon
- Injection site pain*, injection site tingling or numbness

*Side effects related to the injection procedure.

Injections in the fan-shaped lines from the corner of the eyes, when treated at the same time as injections in the forehead for vertical lines

Common
- Injection site bruising*

Uncommon
- Injection site bleeding*, injection site pain*

*Side effects related to the injection procedure.

General information about other side effects

The following list describes additional side effects reported for BOTOX, in any disease, since it has been marketed:

- Affecting the immune system:
  - Sudden allergic reactions, which can be serious (swelling of the face or throat, difficulty in breathing, feeling faint)
  - Delayed reaction which may include fever, skin reaction, joint pain (serum sickness)
  - Arthritis

- Affecting metabolism:
  - Loss of appetite

- Affecting the nervous system:
  - Nerve damage (brachial plexopathy)
  - Slurred speech, speech problems
  - Weakness or drooping of the muscles on one side of the face
  - Increased muscle weakness
  - Chronic disease affecting the muscles (myasthenia gravis)
  - Difficulty moving the arm and shoulder
  - Numbness, tingling, pain in hands and feet
  - Pain in the back
  - Seizures, fainting

- Affecting the eyes:
  - Increased eye pressure
  - Difficulty completely closing the eye
  - Strabismus (squint)
  - Blurred vision
  - Visual disturbance

- Affecting the heart:
  - Decreased hearing
  - Numbness in the ear
  - Feeling dizziness or "spinning" (vertigo)

- Affecting the cardiovascular system:
  - Heart problems including heart attack

- Affecting the respiratory system:
  - Asthma pneumonia (lung inflammation caused by accidentally breathing in food, drink, saliva or vomit)
  - Breathing problems, respiratory depression and/or respiratory failure

- Affecting the gastrointestinal system:
  - Abdominal pain
  - Diarrhoea, constipation
  - Dry mouth
  - Difficulty swallowing
  - Feeling sick, vomiting

- Affecting the skin:
  - Hair loss, loss of eyebrows
  - Acne, breakouts
  - Different types of red or bluish skin rashes
  - Excessive sweating
  - Itching
  - Rash

- Affecting muscles:
  - Muscles pain, loss of nerve supply to/shrinkage of injected muscle

PL 00426/0118 Botox Injection 50 allergan units
Affecting the body
  • feeling generally unwell
  • fever

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store BOTOX
Keep out of the sight and reach of children.
Store in a refrigerator (2°C - 8°C), or store in a freezer (at or below -20°C). After the solution is made up, immediate use of the solution is recommended; however it can be stored for up to 24 hours in a refrigerator (2°C - 8°C).
Your doctor should not use BOTOX after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

6. Contents of the pack and other information
What BOTOX contains
  • The active substance is: Botulinum toxin type A from Clostridium botulinum.
  • The other ingredients are human albumin and sodium chloride.
What BOTOX looks like and content of the pack
BOTOX is presented as a white powder in a transparent glass vial. Prior to injection, the product must be dissolved in sterile saline solution. Each vial contains either 50, 100 or 200 Allergan Units of botulinum toxin type A. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder:
Allergan Ltd.
Marlow International.
The Parkway, Marlow,
Bucks, SL7 1YL
UK

Manufacturer:
Allergan Pharmaceuticals Ireland
Castledare Road
Westport
County Mayo
Ireland

This leaflet was last revised in March 2015.
The following information is intended for medical or healthcare professionals only.

Please refer to the Summary of Product Characteristics for complete prescribing information for BOTOX.

For all indications:

Side effects related to spread of toxin distant from the site of administration have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. The symptoms are consistent with the mechanism of action of botulinum toxin and have been reported hours to weeks after injection. The risk of symptoms is probably greatest in patients who have underlying conditions and comorbidities that would predispose them to these symptoms, including children and adults treated for spasticity, and are treated with high doses.

Patients treated with therapeutic doses may also experience exaggerated muscle weakness.

Pneumonia associated with injection procedure has been reported following administration of BOTOX near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices or other unusual anatomic structures.

Serious adverse events including fatal outcomes have been reported in patients who had received off-label injections of BOTOX directly into salivary glands, the oro-lingual-pharyngeal region, oesophagus and stomach. Some patients had pre-existing dysphagia or significant debility. There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with scoliosis.

Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

Refer to the Summary of Product Characteristics for complete information for BOTOX.

Reconstruction of the medical product:

It is good practice to perform via reconstitute the solution preparation on plastic paper towels to catch any spillage.

Reconstitute BOTOX only with sterile preservative-free saline (0.9% sodium chloride solution for injection). Draw up an appropriate amount of diluent (see dilution table or instructions below) into the syringe.

Dilution table for BOTOX 50, 100 and 200 Allergan Units:

<table>
<thead>
<tr>
<th>Units per 0.1 ml</th>
<th>50 unit vial</th>
<th>100 unit vial</th>
<th>200 unit vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 ml</td>
<td>0.5 ml</td>
<td>1 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>0.5 ml</td>
<td>1 ml</td>
<td>2 ml</td>
<td></td>
</tr>
<tr>
<td>1 ml</td>
<td>2 ml</td>
<td>4 ml</td>
<td></td>
</tr>
<tr>
<td>2 ml</td>
<td>4 ml</td>
<td>8 ml</td>
<td></td>
</tr>
<tr>
<td>4 ml</td>
<td>8 ml</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Since BOTOX is denatured by bubbling or similar vigorous agitation, inject the diluent gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Reconstituted BOTOX is a clear colourless to slightly yellow solution free of particulate matter. The reconstituted solutions should be visually inspected for particulate matter and clarity absence of particles prior to use. When reconstituted, the vial should be stored in a refrigerator (2°C - 8°C) for up to 24 hours prior to use.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not normally be longer than 24 hours at 2°C - 8°C.

Dilution instructions for treatment of urinary incontinence due to overactive bladder:

It is recommended that a 100 Unit or two 50 Unit vials are used for reconstitution. Should you need to use a 200 Unit vial, reconstitute a 200 Unit of BOTOX with 8 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution and mix gently. Draw 4 ml from the vial into a 10 ml syringe. Complete the reconstitution by adding 8 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution into the 10 ml syringe and mix gently. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Or, reconstitute a 100 Unit vial of BOTOX with 10 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution and mix gently. Draw the 10 ml from the vial into a 10 ml syringe. This will result in a 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Or, reconstitute two 50 Unit vials of BOTOX, each with 5 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution and mix gently. Draw the 5 ml from each vial into a single 10 ml syringe. This will result in a single 10 ml syringe containing a total of 100 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

This product is for single use only and any unused reconstituted product should be disposed of.

Dilution instructions for treatment of urinary incontinence due to neurogenic detrusor overactivity:

It is recommended that a 200 Unit or two 100 Unit vials are used for reconstitution. Reconstitute a 200 Unit of BOTOX with 8 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution and mix gently. Draw 2 ml from the vial into each of three 10 ml syringes. Complete the reconstitution by adding 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection into each of the 10 ml syringes, and mix gently. This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Or, reconstitute two 100 Unit vials of BOTOX, each with 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection and mix the vials gently. Draw 4 ml from each vial into each of two 10 ml syringes. Draw the remaining 2 ml from each vial into a third 10 ml syringe. Complete the reconstitution by adding 6 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection into each of the 10 ml syringes, and mix gently. This will result in three 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Should you need to use a 50 Unit vial, reconstitute four 50 Unit vials of BOTOX, each with 3 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection and mix the vials gently. Draw 3 ml from the first vial and 1 ml from the second vial into one 10 ml syringe. Draw 3 ml from the third and fourth vials into a second 10 ml syringe. This will result in 10 ml syringes containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

This product is for single use only and any unused solution should be discarded.

Procedure to follow for safe disposal of vials, syringes and materials used:

For safe disposal, unused vials should be reconstituted with a small amount of water and then autoclaved. Any used vials, syringes, and spillage etc. should be autoclaved, or the residual BOTOX inactivated using dilute hydrochloric solution (0.5%) for 5 minutes.

Identification of the product:

In order to verify receipt of actual BOTOX product from Allergan, look for a tamper-evident seal that contains a translucent silver Allergan logo in the top and bottom flaps. The BOTOX box and a holographic film on the vial label. In order to see this film,