BOTOX® 200 ALLERGAN UNITS POWDER FOR SOLUTION FOR INJECTION

(BOTULINUM TOXIN TYPE A)

PL 00426/0119

UKPAR

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LAY SUMMARY

The MHRA granted Allergan Ltd a Marketing Authorisation (licence) for the medicinal product BOTOX® 200 Allergan Units, Powder for solution for injection (PL 00426/0019) (BOTOX®) on 30 March 2009. This medicine acts principally by relaxing the muscles or nerves to produce the desired effect. It is used in various conditions where muscle(s) or nerve(s) is considered to be overactive. It is to be used on prescription only. The medical conditions for which it is licensed include blepharospasm (overactive eye-lids), hemifacial spasm (spasm of one half of the face) and idiopathic cervical dystonia (overactive neck muscle). It is also indicated for the management of excessive sweating of the axillae, and club foot due to spasticity in children with cerebral palsy and wrist and hand disability due to upper limb spasticity associated with stroke in adults.

The indications are the same as those for the already approved BOTOX® 50 Allergan Units (PL 00426/00118) and 100 Allergan Units (PL 00426/0074), Powder for solution for injection (BOTOX®).

The original data presented to the MHRA demonstrated that BOTOX® 200 Allergan Units, Powder for solution for injection effectively relaxes target muscles and blocks nerve fibres in adults and children suffering from the listed indications and that there were no unexpected safety concerns. It was therefore judged that the benefits of using this product outweigh the risks; hence a licence was granted.
# BOTOX® 200 ALLERGAN UNITS POWDER FOR SOLUTION FOR INJECTION

(\textit{Botulinum toxin type A})

\textbf{PL 00426/0119}

## SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on quality, safety and efficacy the MHRA (UK) granted Allergan Ltd a licence for the medicinal product BOTOX® 200 Allergan Units, Powder for solution for injection (BOTOX®), which contains Botulinum toxin* type A, 200 Allergan units/vial on 30 March 2009.

BOTOX® is indicated for the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis). It is indicated for the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics.

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

- 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

Spasticity can be described as a resistance in the muscle to stretch after an injury to the central nervous system and can cause the affected muscle(s) to clench or the joint they control to flex. Focal spasticity affects a small part of the body, such as the hand or foot. Spasticity is associated with some common neurological disorders such as cerebral palsy. Cerebral palsy is an abnormality of motor function acquired at an early age, usually less then one year of age, and is due to a non-progressive brain lesion. It usually results from abnormalities that occur in the uterus before the baby was born. Equinus foot deformity is a common problem for patients with cerebral palsy who are able to walk.

In spasmodic torticollis the neck muscles that control the position of the head are affected and cause the head to twist and turn to one side. The head may be also pulled forward or backward.

Blepharospasm is the involuntary forcible closure of the eyelids. It may start with uncontrollable blinking and only one eye may be affected initially, but eventually both eyes are usually involved. The spasms may leave the eyelids completely closed causing functional blindness.

Hemifacial spasm is a movement disorder that causes the muscles on one side of the face to contract.

Severe hyperhidrosis of the axillae is a condition characterised by excessive sweating of the armpits. BOTOX® works by blocking nerve fibres that innervate sweat glands.

The original data presented to the MHRA demonstrated that BOTOX® 200 Allergan Units, Powder for solution for injection effectively relaxes target muscles and blocks nerve fibres in adults and children suffering from the listed indications and that there were no unexpected safety concerns. It was therefore judged that the benefits of using this product outweigh the risks; hence a licence was granted.
The injections should be administered by appropriately trained personnel in hospital or specialist centres.

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

BOTOX® 200 Allergan Units, Powder for solution for injection (PL 00426/0019) is a line extension submitted under Article 8.3 (i) of Directive 2001/83/EC to the existing license for BOTOX® 100 Allergan Units, Powder for solution for injection (PL 00426/0074) and cross refers to the pre-clinical and clinical documentation for this product. BOTOX® is a prescription only medicine.
QUALITY ASSESSMENT

BACKGROUND
Botulinum toxin type A is supplied by Allergan as BOTOX® and has been marketed for therapeutic use in the USA since 1990 and then approximately 3 years later in Europe. BOTOX® is variously indicated in different countries for a number of indications, characterised by excessive cholinergic activity. Briefly, these are: blepharospasm, hemifacial spasm, associated focal dystonias, cervical dystonia, focal spasticity (e.g. dynamic equinus foot deformity due to spasticity in ambulatory paediatric cerebral palsy, post stroke focal limb spasticity), oculomotor disorders (including strabismus) and axillary hyperhidrosis. Overall, the doses given for each indication are consistent across countries, the approved starting doses ranging from very low doses (e.g. 1.25-2.5 Allergan U in blepharospasm) to high doses (e.g. 200 Allergan U for the initial treatment of cervical dystonia). To accommodate the wide dose range across indications, Allergan submitted a line extension licence application to register a new product size of 200 Allergan Units. The application was supported only by administrative and pharmaceutical documentation (modules 1-3). The MAH has proposed that the new product size be indicated in the same range of indications as already approved for the 50U and 100U products. No new indications were sought and no new data regarding existing indications are submitted in the dossier.

The active substance is Botulinum Toxin Type A (Ph Eur), 200 Allergan Units per vial. The excipients are Human Albumin and sodium chloride.

SCIENTIFIC EVALUATION
The composition of the 200U presentation consists of twice the amount of the ingredients in the currently licensed 100U presentation. The desired dose (200 U) is achieved by a simple increase in fill volume into the product vial prior to vacuum-drying. The only difference in the manufacture of the 200U presentation is the filling step. The manufacturing formulation and compounding process are exactly the same for the 200 U presentation as for BOTOX® 50U and 100U. Container-closures are constructed from exactly the same materials and size, with a 10ml nominal capacity as for the current 100U presentation. Therefore, the clinical safety, efficacy, and stability of BOTOX® 200 U is the same as BOTOX® 50U and 100U.

BOTOX® is a parenteral product intended for intramuscular and intradermal injection, and the 200U drug product is produced as a preservative-free sterile product. The 50U, 100U and the 200U drug products are reconstituted with saline solution prior to use. The strength of the product is measured in Allergan units per vial.

Manufacture of BOTOX® drug product vials takes place in Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, County Mayo, Ireland. No changes have been made for the drug substance, Botulinum Toxin Type A.

The excipients used in the manufacture of 200U drug product and their routine tests and specifications for raw material release are the same as those employed for the currently
approved BOTOX® 50U and 100U products. Both excipients are compendial and comply with the relevant monographs. Allergan has committed to using only Human Albumin Solution Ph. Eur. that has been batch-released in the European Union by a government-approved laboratory. The human albumin has been granted a certificate under the EMEA Plasma Master File certification scheme.

**Process validation**
Allergan has validated the manufacturing process of the 200U drug product. All lots met the drug product specification at release, demonstrating the consistency and reproducibility of the manufacturing process.

**Validation Batches**
The 200U Validation batches were tested and shown to comply with the specifications. Release tests performed on the drug product include a test for vacuum and a test for sterility according to Ph Eur. The potency and identity specifications/methods conform to the Ph Eur monograph for Botulinum Toxin Type A for Injection.

The batch formula used for the 200U vials is the same as the 100 U vials.

**Filling validation**
Validation of filling was determined and met the acceptance criteria. Environmental monitoring was also carried out during the validation and the results were acceptable.

**Vacuum drying process**
The vacuum drying process was validated for the 200U vials and the acceptance criteria were met for the lyophilisation cycle. Tests for moisture, potency, vacuum, pH, visual clarity, endotoxin and sterility were all satisfactory.

**Container Closure System**
Container-closures are constructed from exactly the same materials and size, with a 10ml nominal capacity as for the current 100U presentation. There is also a 50 U presentation licensed (PL 00426/0118). In order to provide clear differentiation between the three product sizes, the aluminium crimp/plastic flip-off seal assembly affixed to each vial is colour-coded according to product size: 50U: red; 100U: purple; 200U: orange. The product size also appears on the crimp/seal assembly. In addition, the product size is written in corresponding colour-coded text on each carton.

**Stability**
Satisfactory stability data which met current requirements were provided in support of a shelf-life of 18 months with the following storage conditions Store in a refrigerator (2°C-8°C), or store in a freezer (at or below -5°C).

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.
**Specifications**

The product specifications (with the exception of potency and endotoxin) and tests at release and throughout shelf life are the same as the specifications and tests currently approved for the 50U and 100U drug product.

**SPC**

The BOTOX® SPC provides a dilution table for guidance on how to prepare certain dilutions (0.1 ml represents a typical treatment injection volume). This product is for single use only and any unused solution has to be discarded as detailed in the SPC.

**CONCLUSION**

This application can be approved from a Quality perspective.
PRECLINICAL ASSESSMENT

No pre-clinical data have been supplied with this application and none are required for an application of this type.
CLINICAL ASSESSMENT

INTRODUCTION

TYPE OF APPLICATION AND REGULATORY BACKGROUND
Botulinum toxin type A is supplied by Allergan as BOTOX® and has been marketed for therapeutic use in the USA since 1990 and then approximately 3 years later in Europe. BOTOX® is variously indicated in different countries for a number of indications, characterized by excessive cholinergic activity. Briefly, these are: blepharospasm, hemifacial spasm, associated focal dystonias, cervical dystonia, focal spasticity (e.g. dynamic equinus foot deformity due to spasticity in ambulatory paediatric cerebral palsy, post stroke focal limb spasticity), oculomotor disorders (including strabismus) and axillary hyperhidrosis. Overall, the doses given for each indication are consistent across countries, the approved starting doses ranging from very low doses (e.g. 1.25-2.5 Allergan U in blepharospasm) to high doses (e.g. 200 Allergan U for the initial treatment of cervical dystonia). To accommodate the wide dose range across indications, Allergan submitted a line extension licence application to register a new product size of 200 Units. This application was supported only by administrative and pharmaceutical documentation (modules 1-3). The MAH has proposed that the new product size be indicated in the same range of indications as already approved for the 50U and 100U product. No new indications were sought and no new data regarding existing indications are submitted in the dossier.

CLINICAL BACKGROUND
The SPC for BOTOX® has multiple indications, mainly for neurological and ophthalmic use, with a dose range of 25-200 units (in focal spasticity associated with stroke, 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 all clinical trials, the doses did not exceed 360 Units divided among selected muscles at any treatment session).

LEGAL STATUS – POM

CLINICAL PHARMACOLOGY
N/A

CLINICAL EFFICACY
No new clinical studies have been carried out. As the new dose forms cover an existing dose range and no new changes to the clinical section of SPC are sought, this is acceptable.

CLINICAL SAFETY
No new safety issues are expected in relation to the mechanism of action.
ASSESSOR’S OVERALL CONCLUSIONS ON CLINICAL SAFETY
Sufficient warnings appear in SPC, PIL and labels to make prescribers, pharmacists and others involved in the administration of the product (e.g., nurses and technicians) aware of the potential danger of overdosing, which could have serious, potentially fatal, consequences. In fact, deaths have been reported rarely in association with the use of BOTOX®.

EXPERT REPORTS
There is short expert report in the form of a clinical overview. The expert is of the opinion that there is no safety issue, as the safety margin is large and that the vials are colour coded to differentiate between them.

PRODUCT LITERATURE

SPC
PATIENT INFORMATION LEAFLET
LABEL
These are satisfactory and contain adequate warnings and instructions to prevent accidental overdosage.

OVERALL CONCLUSION

RISK BENEFIT
Providing safeguards are in place, it is not considered that the line extension formulation will change the risk: benefit for this product.

RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION
The application for PL 00426/0119 is approvable.

Decision
Approved following submission of an updated SPC, labelling changes to better distinguish the 3 strengths, and several amendments to the Risk Management Plan.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of BOTOX® 200 Allergan Units per vial powder for solution for injection are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new pre-clinical data were submitted and none are required for an application of this type.

CLINICAL

The application was to add a new strength of BOTOX® 200 Allergan Units Powder for Solution for Injection. The current licensed products are BOTOX® 100 Allergan Units (PL 00426/0074) and BOTOX® 50 Allergan Units (PL 00426/00118). No new or unexpected safety concerns arose from this application.

The SPC, PIL and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable and no new pre-clinical or clinical safety concerns have been identified. The risk-benefit assessment is therefore considered to be favourable.
BOTOX® 200 Allergan Units, Powder for solution for injection

PL 00426/0119

**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the marketing authorisation application on 03/06/2005
2. Submission was validated on 15/09/2005
3. RFI on the clinical assessment was sent on 04/11/2005
4. RFI on the quality assessment was sent on 19/10/2005
5. Response received on the quality assessment 14/01/2007
6. Response received on the clinical assessment 01/02/2007
7. RFI on the quality and clinical assessment was sent on 02/02/2007
8. Response received on the quality and clinical assessment 26/06/2007
10. Reminder on 23/04/2008
11. Response received on the clinical assessment 01/07/2008
12. RFI on the clinical assessment 12/08/2008
13. Response received on the clinical assessment 29/12/2008
14. RFI on the clinical assessment 21/01/2009
15. Response received on the clinical assessment 18/03/2009
16. Application approved on 30/03/2009
## 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>
SUMMARY OF PRODUCT CHARACTERISTICS

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 THE CLINICAL INDICATIONS

BOTOX is indicated for the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmodic torticollis). It is indicated for the management of severe hyperhidrosis of the axillae, which does not respond to topical treatment with antiperspirants or antihidrotics.

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, or idiopathic cervical dystonia, or focal hyperhidrosis in children have not been demonstrated.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Doses recommended for BOTOX are not interchangeable with other preparations of botulinum toxin.

Care should be taken to use the correct diluent volume for the dosage chosen to prevent accidental overdose (See section 6.6).

Adequate studies on geriatric dosing have not been performed. Dose selection should be the same; however, the lowest effective dose is recommended.

One vial (200 Units) contains the maximum recommended dose for most cases.

**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>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>

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>Levator scapulae</th>
<th>Scalene</th>
<th>Splenius capitis</th>
<th>Trapezius</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type II</td>
<td>Head rotation only</td>
<td>Sternomastoid</td>
<td>25 - 100 Units; at least 2 sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Type III</td>
<td>Head tilted toward side of shoulder elevation</td>
<td>Sternomastoid</td>
<td>25 - 100 Units at posterior border; at least 2 sites if &gt;25 Units given</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<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>
<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, 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 Total</th>
<th>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.

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. Please see section 4.8c) 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’ for further information).

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 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.

### 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

The effects of BOTOX on the ability to drive or to use machines can only be assessed after treatment.

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 (16%) of participants in clinical trials treated with BOTOX for focal spasticity of the upper limb associated with stroke experienced an adverse reaction.

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, <1/10); Uncommon (>1/1,000, <1/100); Rare (>1/10,000, <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: Hypoesthesia, 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.

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.

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 chemotrigger 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.

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**
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.

Dilution table: Diluent added | Resulting dose in units per 0.1 ml
---|---
0.5 ml | 40 Units
1 ml | 20 Units
2 ml | 10 Units
4 ml | 5 Units
8 ml | 2.5 Units

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

30/03/2009
ALLERGAN®

PACKAGE LEAFLET: INFORMATION FOR THE USER

BOTOX®
200 Allergan units, Powder for solution for injection
Botulinum toxin type A

Head all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- 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.

In this leaflet:
1. WHAT BOTOX IS AND WHAT IT IS USED FOR
2. BEFORE YOU USE BOTOX
3. HOW TO USE BOTOX
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE BOTOX
6. FURTHER 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 impulses to any muscles that have been injected and reducing excessive contractions of those muscles.

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 control:
- 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 armpits that affects the activities of daily living, when other local treatments do not help.

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 leg. BOTOX relieves the persistent muscle spasms 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 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 fainting) in the past;
- have inflammation in the muscles or skin area where your doctor plans to inject;
- have significant weakness or wasting 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 neuronopathy);
- 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;
- have had any surgery that may have in some way changed the muscle to be injected.

After you have been given BOTOX
Consult 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).

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 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 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 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 eyes. In order to prevent this, you may need treatment with eye drops, ointments, soft contact lenses or even protective covering which closes the eye. Your doctor will tell you if this is required.

Taking other medicines
Tell your doctor or pharmacist if:
- you are using any antibodies (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.
Pregnancy and breastfeeding

- The use of BOTOX during pregnancy is not recommended unless clearly necessary.
- 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 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 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

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 (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

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.
4. POSSIBLE SIDE EFFECTS

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

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

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.

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

- **Very common** side effects: occur in more than 1 out of 10 people who use the medicine.
- **Common** side effects: occur in less than 1 out of 10 people but more than 1 out of 100 people who use the medicine.
- **Uncommon** side effects: occur in less than 1 out of 100 people but more than 1 out of 1,000 people who use the medicine.
- **Rare** side effects: occur in less than 1 out of 1,000 people but more than 1 out of 10,000 people who use the medicine.
- **Very rare** side effects: 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 the eyelid.

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

**Uncommon side effects:**
- dizziness;
- difficulties in seeing clearly;
- blurred vision;
- double vision;
- tiredness;
- inflammation of the cornea (transparent outer covering of the eye);
- weakness of the face muscles;
- droop of the muscles on one side of the face;
- rash;
- abnormal turning of the eyelids outwards or inwards.

**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:**
- 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 irritation inside the nose (rhinitis);
- blocked or runny nose, cough, sore throat, itchy or irritation in the throat;
- dry mouth.

**Uncommon side effects:**
- dryness of breath;
- double vision;
- 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 (erythema 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;
- numbness;
- swelling of the extremities such as the hands and feet.

**Rare side effect:**
- inflammation of the skin (dermatitis);
- headache;
- feeling generally unwell;
- feeling sick;
- increased sensitivity where the injection was given;
- rash;
- numbness around the mouth;
- difficulty in sleeping (insomnia);
- itching.

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 armpits**

**Common side effects:**
- hot flushes;
- 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.
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 -5°C).

After the medicine has 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 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 packs sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:
Marketing Authorisation Holder: Allergan Ltd., Marlow, SL7 1VL, UK

Manufacturer:
Allergan Pharmaceuticals Ireland
Castledore Road, Westport, County Mayo, 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 March 2009.

ALLERGAN®

MHRA PAR BOTOX® 200 Allergan units, Powder for injection PL 00426/0119 37

- 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.

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 lungs 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 attacks.

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:
- 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. 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 feeling 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 reaction;
- chronic disease affecting the muscles (myasthenia gravis);
- blurred vision;
- fainting;
- pain/numbness/numbness starting from the spine;
- paralysis of the face;
- difficulty moving the arm and shoulder;
- decreased skin sensation;
- muscles pain;
- abdominal pain;
- diarrhoea, vomiting, loss of appetite;
- fever;
- different types of red blotchy skin rashes;
- feeling generally unwell;
- speech problems;
- itching;
- excessive sweating;
- depressed hearing;
- noises in the ear.
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 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 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 with sterile unpreserved 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 for injection)</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>90 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 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 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. 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 - 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 used vials, syringes, and spillages etc. 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 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 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 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.
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

BOTOX is indicated for:
- the symptomatic relief of blepharospasm, hemifacial spasm and idiopathic cervical dystonia (spasmotic 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
- 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.

Dilution table for BOTOX 50, 100 and 200 Allergan Units vial size:

<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>Amount of diluent (sodium chloride 9 mg/ml (0.9%) solution for injection) added in a 50 unit vial</td>
<td>0.25 ml</td>
<td>0.5 ml</td>
<td>1 ml</td>
</tr>
<tr>
<td>Amount of diluent (sodium chloride 9 mg/ml (0.9%) solution for injection) added in a 100 unit vial</td>
<td>0.5 ml</td>
<td>1 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>Amount of diluent (sodium chloride 9 mg/ml (0.9%) solution for injection) added in a 200 unit vial</td>
<td>1 ml</td>
<td>2 ml</td>
<td>4 ml</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 VII\(^{th}\) 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**
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 elevation</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>
</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**:

The **BOTOX Dosing By Muscle**:

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

<sup>a</sup>1 IM injection site = 0.1 mL = 5 U BOTOX  
<sup>b</sup>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 supercillii). 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, 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 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, 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 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 spams, 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; hypoesthesia; malaise; myalgia; pruritus; hyperhidrosis; alopecia (including madarosis); diarrhoea; anorexia; hypoacusis; tinnitus; vertigo; radiculopathy; syncope; myasthenia gravis; paraesthesia; erythema multiforme; dermatitis psoriasiform; vomiting and brachial plexopathy; anaphylactic reaction (angiodema, 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 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 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 ≥ 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 Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=688 N=696</td>
</tr>
<tr>
<td>Frequency of headache days</td>
<td>-8.4 -6.6</td>
</tr>
<tr>
<td>Frequency of moderate/severe headache days</td>
<td>-7.7 -5.8</td>
</tr>
<tr>
<td>Frequency of migraine/probable migraine days</td>
<td>-8.2 -6.2</td>
</tr>
<tr>
<td>% patients with 50% reduction in headache days</td>
<td>47% 35%</td>
</tr>
<tr>
<td>Total cumulative hours of headache days</td>
<td>120 80</td>
</tr>
<tr>
<td>Frequency of headache episodes</td>
<td>-5.2 -4.9</td>
</tr>
<tr>
<td>Total HIT-6* scores</td>
<td>-4.8 -2.4</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
UKPAR Botox ……………………………………………………………………PL 00426/0074, PLs 00426/0118–0119

Botox 50, 100 and 200 Allergan units – powder for solution for injection
**Duration of treatment effect**

- You will usually see an improvement within 3 days after the injection.
- The maximum effect is usually seen within 1 to 2 weeks after treatment.
- When the effect starts to wear off, further treatment is possible but not more often than every 12 weeks.
- For persistent muscle spasms or structures:
  - The usual dose is 40-100 Units.
  - You will be injected in the affected muscles up to 50 Units of BOTOX in each of 2 injection sites.

**Dose**

- Options: 50, 100, and 200 Allergan units – powder for solution for injection.

**For persistent muscle spasms or structures**

- The usual dose is 40-100 Units. You will be injected in the affected muscles up to 50 Units of BOTOX in each of 2 injection sites.
- 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.

**Adverse effects**

- The side effects are classified into the following categories, depending on how they occur.
### Botox 50, 100 and 200 Allergan units – powder for solution for injection

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injections in the eyelid and face for muscle spasms</strong></td>
<td></td>
</tr>
<tr>
<td>Very common side effects:</td>
<td></td>
</tr>
<tr>
<td>• Drooping of the eyelid.</td>
<td></td>
</tr>
<tr>
<td>• Swelling of the face.</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td>Uncommon side effects:</td>
<td></td>
</tr>
<tr>
<td>• Blurred vision.</td>
<td></td>
</tr>
<tr>
<td>• Folded eyelids.</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>Injections in the neck and shoulder</strong></td>
<td></td>
</tr>
<tr>
<td>Very common side effects:</td>
<td></td>
</tr>
<tr>
<td>• Difficulty in swallowing.</td>
<td></td>
</tr>
<tr>
<td>• Pain.</td>
<td></td>
</tr>
<tr>
<td>• Muscle weakness.</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Common side effects:</td>
<td></td>
</tr>
<tr>
<td>• Dizziness.</td>
<td></td>
</tr>
<tr>
<td>• Bruised or swollen.</td>
<td></td>
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<tr>
<td>• Swelling and irritation inside the nose (rhinitis).</td>
<td></td>
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<tr>
<td>• Itching or burning where the injection was given.</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon side effects:</strong></td>
<td></td>
</tr>
<tr>
<td>• Nausea.</td>
<td></td>
</tr>
<tr>
<td>• Fever.</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Injections in the wrist and hand of patients who have developed a sensitivity to Botox</strong></td>
<td></td>
</tr>
<tr>
<td>Common side effects:</td>
<td></td>
</tr>
<tr>
<td>• Muscle weakness.</td>
<td></td>
</tr>
<tr>
<td>• Increased muscle tension.</td>
<td></td>
</tr>
<tr>
<td>• Bruising and bleeding under the skin covering red patches.</td>
<td></td>
</tr>
<tr>
<td>• Pain in the hand and fingers.</td>
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<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Injections in the head and neck to prevent headaches</strong></td>
<td></td>
</tr>
<tr>
<td>Common side effects:</td>
<td></td>
</tr>
<tr>
<td>• Headache.</td>
<td></td>
</tr>
<tr>
<td>• Increased sensitivity where the injection was given.</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon side effects:</strong></td>
<td></td>
</tr>
<tr>
<td>• Nausea.</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td><strong>Information about other side effects</strong></td>
<td></td>
</tr>
<tr>
<td>Side effects related to the spread of Botox far away from the site of injection have been reported very rarely. Includes:</td>
<td></td>
</tr>
<tr>
<td>• Muscle weakness.</td>
<td></td>
</tr>
<tr>
<td>• Difficulty in swallowing.</td>
<td></td>
</tr>
<tr>
<td>• Fat or lump accidentally going into the large arteries.</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General information about other side effects</strong></td>
<td></td>
</tr>
<tr>
<td>The difficulty and in some cases may lead to permanent:</td>
<td></td>
</tr>
<tr>
<td>• Swallowing problems.</td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Important information about other side effects</strong></td>
<td></td>
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<tr>
<td>If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.</td>
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</tr>
</tbody>
</table>
Botox 50, 100 and 200 Allergan units – powder for solution for injection

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, the product must be dissolved in a sterile saline solution. Each vial contains 50 Allergan botulinum toxin type A units. Each pack contains 1, 2, 3 or 6 vials. Not all pack sizes may be marketed.

Marketing Authorization Holder and Manufacturer:

- Marketing Authorisation Holder: Allergan Ltd.
- 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 names: BOTOX in Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Spain, Sweden, and Slovak Republic.

This leaflet was last approved in September 2011

UKPAR Botox ……………………………………………………………………PL 00426/0074, PLs 00426/0118–0119

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:

- itchy rash;
- 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. These effects occurred mainly when:

- redness;
- 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 arms; difficulty in breathing);
- chronic disease affecting the muscles (myasthenia gravis);
- blurred vision;
- difficulties in seeing clearly;
- tainting;
- pain/numbness or weakness starting from the spine;
- drooping 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;
- lumps;
- different types of red blotchy skin rashes;
- feeling generally unwell;
- speech problems;
- feeling
- 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 the 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 4 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.

Allergan
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UKPAR Botox ……………………………………………………………………PL 00426/0074, PLs 00426/0118–0119

ALLERGAN®

PACKAGE LEAFLET: INFORMATION FOR THE USER

BOTOX®

100 Allergan units, Powder for solution for injection

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have any further questions, ask your doctor or pharmacist.

If you get any side effects after using this medicine, tell your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others.

If you get any side effects while taking this medicine, and you think that they are serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What BOTOX is and what it is used for
2. Before you use BOTOX
3. How to use BOTOX
4. Possible side effects
5. How to store BOTOX
6. Further information

1. WHAT BOTOX IS AND WHAT IT IS USED FOR

BOTOX is a muscle relaxant that works by blocking nerve impulses to muscles that have been injected with BOTOX. It causes muscle relaxation by blocking the release of neurotransmitters, such as acetylcholine, which is essential for muscle movement.

In adults who have headaches, BOTOX is used for the prevention of chronic migraine.

2. BEFORE YOU USE BOTOX

Do not use BOTOX:

- if you have had an allergic reaction to any of the ingredients of BOTOX;
- if you have had an adverse reaction to BOTOX;
- if you have had an adverse reaction to any other medicines you have taken in the past.

Talk to your doctor before using BOTOX:

- if you have a history of aseptic meningitis;
- if you have had a history of cardiac disorder;
- if you have had a history of aseptic meningitis.

Before using BOTOX:

Tell your doctor if you:

- have had any problems with injections (such as pain, swelling, bruising);
- have had any problems with the injection site;
- have had any problems with the injection site.

Take special care with BOTOX:

- if you have had any problems with injections;
- if you have had any problems with the injection site;
- if you have had any problems with the injection site.

3. HOW TO USE BOTOX

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

Method of administration

BOTOX is injected into your muscles (intramuscularly) or into the affected areas of your body.

General information about dosage

- The number of injections per muscle may vary depending on the indication.
- The dosage of BOTOX and the duration of its effect will vary depending on the condition for which you are treated.
- The dosage of BOTOX and the duration of its effect will vary depending on the condition for which you are treated.

Dosage for chronic migraine

In adults who have chronic migraine, BOTOX is used for the prevention of chronic migraine.

In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water. In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.

4. POSSIBLE SIDE EFFECTS

The possible side effects of BOTOX are:

- Injection site reactions:
  - pain, inflammation, redness, swelling;
  - bruising;
  - swelling of the face.

- Other side effects:
  - weakness, fatigue, muscle weakness;
  - dryness of the mouth;
  - constipation;
  - incontinence.

If you get any side effects, talk to your doctor or pharmacist.

In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.

When BOTOX is used in the treatment of persistent muscle spasm, it is usually used in the treatment of persistent muscle spasm.

5. HOW TO STORE BOTOX

BOTOX must be stored in a refrigerator at a temperature between +2°C and +8°C. BOTOX must be stored in a refrigerator at a temperature between +2°C and +8°C.

6. FURTHER INFORMATION

- What is BOTOX used for?
- In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.

In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.

- What is the correct dose of BOTOX?
- In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.

In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.

- What is the maximum dose of BOTOX?
- In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.

In adults who have headaches for more than 15 days a month, your doctor will give you BOTOX in the form of a tablet, which you should swallow with a glass of water.
**For persistent muscle spasms of the neck and shoulders**

**Doseage**
Your doctor may give multiple injections in the affected muscle at intervals of up to 30 Units of BOTOX as the total dose range is between 155 Units and 195 Units per treatment session. The usual dose is 100 Units divided across multiple injection sites.

**Duration of treatment effect**
- When the injection site is effectively treated, you can have the treatment every 3 to 12 months.
- You may need more than one treatment with injection intervals of approximately 3 to 12 weeks.

**Usage**
- The injection site is effectively treated, and the muscle mass is decreased, but not removed.
- Injection of BOTOX® results in no further injections within 3 months.

**Side effects**
- Not applicable.
- No need for special precautions.
- No special precautions are required.
- No special precautions are required.

**Contraindications**
- The use of BOTOX® is contraindicated in patients who have received other botulinum toxin products in the preceding 4 months.
- The use of BOTOX® is contraindicated in patients who have had a stroke.
- The use of BOTOX® is contraindicated in patients who have had a head injury.

**Precautions**
- Patients with a history of dizziness or syncope should be monitored closely.
- Patients with a history of dizziness or syncope should be monitored closely.
- Patients with a history of dizziness or syncope should be monitored closely.

**Botox 50, 100 and 200 Allergan units – powder for solution for injection**

**50 unit vial**
- 50 units of BOTOX®
- 100 units of BOTOX®
- 200 units of BOTOX®

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### Additional Information

The total dose range is between 155 Units and 195 Units per treatment session. The usual dose is 100 Units divided across multiple injection sites.

**Duration of treatment effect**
- When the injection site is effectively treated, you can have the treatment every 3 to 12 months.
- You may need more than one treatment with injection intervals of approximately 3 to 12 weeks.

**Usage**
- The injection site is effectively treated, and the muscle mass is decreased, but not removed.
- Injection of BOTOX® results in no further injections within 3 months.

**Side effects**
- Not applicable.
- No need for special precautions.
- No special precautions are required.
- No special precautions are required.

**Contraindications**
- The use of BOTOX® is contraindicated in patients who have received other botulinum toxin products in the preceding 4 months.
- The use of BOTOX® is contraindicated in patients who have had a stroke.
- The use of BOTOX® is contraindicated in patients who have had a head injury.

**Precautions**
- Patients with a history of dizziness or syncope should be monitored closely.
- Patients with a history of dizziness or syncope should be monitored closely.
- Patients with a history of dizziness or syncope should be monitored closely.

**Botox 50, 100 and 200 Allergan units – powder for solution for injection**

**50 unit vial**
- 50 units of BOTOX®
- 100 units of BOTOX®
- 200 units of BOTOX®

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

**Injections in the orbit and face for muscle spasm**

**Very common side effect:**
- dryness of the eye.

**Common side effects:**
- redness;
- sensitivity;
- pain;
- muscle weakness;
- muscle tightening;
- discomfort during injection;
- injection pain;
- injection site:
  - swelling;
  - bruising;
  - tingling;
  - bruising and swelling;
  - injection mark;
  - edema;
  - feeling of tightness;
  - skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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 limbs**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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 feet**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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 face**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the arms**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the eyes**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the face**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the feet**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the hands**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the legs**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the neck**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the oral mucosa**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the scalp**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the voice**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.

**Insufficiency in the whole body**

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

**Common side effects:**
- dizziness;
- sensitivity;
- pain;
- muscle cramps;
- injection mark;
- bruising and swelling;
- feeling of tightness;
- skin irritation.

**Uncommon side effects:**
- temporary vision changes;
- dryness;
- burning.

**Rare side effect:**
- vision changes.

**Very rare side effect:**
- bruising.

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.
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. These effects occurred mainly when:

**BOTOX was used for the treatment of persistent muscle spasm 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.

**Softness:**
- 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 arms, difficulty in breathing);
- chronic disease affecting the muscles (myasthenia gravis);
- blurred vision;
- difficulties in seeing clearly;
- tingling;
- pain/numbness/weakness starting from the spine;
- drooping 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;
- abdomen pain;
- diarrhea, vomiting, loss of appetite;
- fever;
- different types of red and blotchy skin rash; sweat;
- 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.

**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 -18 °C.

After the solution is reconstituted, immediate use of the solution is recommended but 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 printed on the label after "EXP." The expiry date refers to the last day of that month.
### ALLERGAN

#### PACKAGE LEAFLET: INFORMATION FOR THE USER

**BOTOX®**

**200 Allergan units. Powder for solution for dermal injection**

**Read all of this leaflet carefully before you start using this medicine.**
- 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. Do not pass it on to others. It may harm them if they are not the same age or sex.
- If you have any side effects which get worse, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist.

**Is this leaflet for you?**

1. **What BOTOX is and what it is for**

   BOTOX is a muscle relaxant that works by blocking the nerve impulse to a muscle, thereby reducining muscle activity. It is used for:
   - **Treating excessive sweating in the underarms**
   - **Treating glabellar (between the brows) or frown lines**
   - **Treating eyelid drooping (ptosis)**

2. **Before you use BOTOX**

   **Do not use BOTOX**
   - If you have had an allergic reaction to any of the ingredients of BOTOX.
   - If you have an infection at the site of injection.

3. **How to use BOTOX**

   BOTOX is used in a series of injections into the muscles. In adults, it is used to:
   - **Relax muscles**
   - **Reduce expression lines**
   - **Rejuvenate the appearance**
   - **Reduce the severity**

4. **Possible side effects**

   - **Common**
     - **Dryness in the eyes**
     - **Sore throat**
   - **Rare**
     - **Changes in vision**
     - **Soreness in the head**

5. **Further information**

   - **What BOTOX is and what it is for**
   - **Before you use BOTOX**
   - **How to use BOTOX**

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**Taking other medicines**

- **Tell your doctor or pharmacist if:**
  - you are using any antibiotics (used to treat infections), antiarrhythmics or medicines to control your heart rhythm, 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.
  - you have recently had surgery, or are about to have surgery, or are having serious medical tests. Some of these medicines may increase the effect of BOTOX.

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**Pregnancy and breast-feeding**

BOTOX is not recommended for use 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.

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**Driving and using machines**

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

---

**How to use BOTOX**

BOTOX must only be injected by doctors with specific skills on how to use this medicine.

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**General information about dosage**

- The number of injections per muscle and the dose may depend on the indications. Therefore, your doctor will decide how many, how often, and with which muscles BOTOX will begin to you. It is recommended that your doctor uses the least effective dose.
- Changes for the safer are the same as for other adults.

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**For persistent muscle spasms of the eyelid and face**

In the first treatment session, your doctor may give multiple injections in the affected muscles with 1.25 to 2.5 units (BOTOX) into each injection site.

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**The maximum dose for the first treatment session is 25 units (for example per eye). For the following treatment sessions, the total maximum dose can be increased up to 100 units (if needed).**
UKPAR Botox ……………………………………………………………………PL 00426/0074, PLs 00426/0118–0119

Perforation

**Duration of treatment effect**

- **With the injections:**
  - You will usually see an improvement within 3 days after the injection.

- **With the effect:**
  - The total courses range is between 165 Units and 166 Units per treatment occasion.

- **Duration of treatment effect:**
  - When the effect is to wear off, further treatment is possible, but no more often than every 12 weeks.

- **For persistent muscle spasm of the neck and shoulder:**
  - You doctor may give multiple intramuscular injections with up to 200 units of Botox at intervals of at least 3 months. The maximum dose for the first injection is 200 units.

- **Duration of treatment effect:**
  - When the effect is to wear off, but no more often than every 12 weeks.

- **For persistent muscle spasm of the wrist and hand:**
  - You doctor may give multiple intramuscular injections with up to 100 units of Botox at intervals of at least 3 months.

- **Duration of treatment effect:**
  - When the effect is to wear off, but no more often than every 12 weeks.

- **For severe muscle spasm:**
  - You doctor may give multiple intramuscular injections with up to 50 units of Botox at intervals of at least 3 months.

- **Duration of treatment effect:**
  - When the effect is to wear off, but no more often than every 12 weeks.

The following information is intended for medical or healthcare professional 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 injection have been reported, sometimes resulting in death, which in some cases was associated with dysphagia, aspiration, respiratory failure, or death.

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

- Reconstitution of the medicinal product:

- It is good practice to perform reconstitution and mixing and preparation over plastic-laminate paper trays to minimize any spillage.

- Reconstitute Botox only with sterile unpreserved (0.9% sodium chloride for injection). Draw up an appropriate amount of diluent (see dilution table below) into a syringe.

- Solution table for BOTOX® 100 and 200 Allergan units/mL:

<table>
<thead>
<tr>
<th>Dilution</th>
<th>Amount of diluent</th>
<th>Amount of diluent</th>
<th>Amount of diluent</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 units/mL</td>
<td>1.0 mL</td>
<td>0.3 mL</td>
<td>0.6 mL</td>
</tr>
<tr>
<td>60 units/mL</td>
<td>2.0 mL</td>
<td>0.6 mL</td>
<td>1.2 mL</td>
</tr>
<tr>
<td>100 units/mL</td>
<td>3.0 mL</td>
<td>1.0 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>150 units/mL</td>
<td>4.0 mL</td>
<td>1.3 mL</td>
<td>1.7 mL</td>
</tr>
<tr>
<td>200 units/mL</td>
<td>5.0 mL</td>
<td>1.6 mL</td>
<td>2.0 mL</td>
</tr>
</tbody>
</table>

- If you have received more Botox than you should:

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

4. **Possible side effects**

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

- If you experience difficulty breathing, swallowing, including swallowing of the face or throat, chest pain, feeling faint and shortness of breath, contact your doctor immediately.

- Like all medicines, BOTOX can cause side effects, although not everyone gets them. In general, side effects occur within the first 2 weeks following injection.

- They usually last only a few days, but they may last for several months in rare cases.

- As for any injection procedure, pain/burning, swelling and/or bruising may be associated with the injection.

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

  - **Very common:**
    - Dose in more than 1 out of 10 people who use the medication

  - **Common:**
    - Dose in less than 1 out of 10 people but more than 1 out of 100 people who use the medication

  - **Uncertain:**
    - Dose in less than 1 out of 10 people but more than 1 out of 1,000 people who use the medication

- **Rare:**
  - Dose in less than 1 out of 1,000 people who use the medication

- **Very rare:**
  - Dose in less than 1 out of 10,000 people who use the medication

- Botox 50, 100 and 200 Allergan units – powder for solution for injection
<table>
<thead>
<tr>
<th>Side effect</th>
<th>Description</th>
<th>Important Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Headache generally unwell, increased sensitivity where the injection was given, bullying, hair loss, lump under the skin, pain in the extremities such as the hands and fingers, bleeding or burning and swelling of the eyelids around the eyes.</td>
<td>There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe oral or pharyngeal pain 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.</td>
</tr>
<tr>
<td>Neck pain</td>
<td>Neck pain, muscle weakness, problems with swallowing, numbness, muscle pain, feeling of weakness, being able to control when you want to.</td>
<td>Some of these patients were already suffering from heart complaints.</td>
</tr>
<tr>
<td>Rash</td>
<td>Redness, hives; flushing; increased sweating at the injection site, abnormal sensitivity where the injection was given, skin reaction, skin irritation.</td>
<td>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.</td>
</tr>
<tr>
<td>Itching</td>
<td>Itching, redness, skin reaction, skin irritation.</td>
<td>Injections in the head and neck to prevent headache in patients who suffer from chronic migraine.</td>
</tr>
<tr>
<td>Swelling</td>
<td>Swelling of the eyelids, irritation, and swelling of the extremities such as the hands and feet (vasomotor).</td>
<td>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.</td>
</tr>
<tr>
<td>Injection</td>
<td>Injection in the lags of children with cerebral palsy.</td>
<td></td>
</tr>
<tr>
<td>Distress</td>
<td>Distress; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Stiffness</td>
<td>Stiffness; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Tiredness</td>
<td>Tiredness; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Asthma; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>Sweating; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Pain; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Injection</td>
<td>Injection in the lags of children with cerebral palsy.</td>
<td></td>
</tr>
<tr>
<td>Distress</td>
<td>Distress; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tiredness</td>
<td>Tiredness; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>Asthma; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Pain; anxiety; numbness; dizziness; inflammation of the eye, eye pain, visual disturbance, rashes (feeling sick), dry mouth, skin tightness, swelling of the eyelids around the eyes.</td>
<td></td>
</tr>
<tr>
<td>Injection</td>
<td>Injection in the lags of children with cerebral palsy.</td>
<td></td>
</tr>
</tbody>
</table>
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. 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 allergy.

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 in which 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/swelling starting from the spine;
- drooping 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 red blotchy skin rash;
- feeling generally unwell;
- speech problems;
- itching;
- excessive sweating;
- hair loss;
- loss of eyebrows;
- decreased hearing;
- noises in the ear;
- feeling of dizziness or "spining" (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 the reach and sight of children.

Store in a refrigerator (2°C to 8°C) or at room temperature.

(at or below 5°C).

After the solution is made up, use the solution in a cool place if possible and store it in the refrigerator (2°C to 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.

Marketing Authorisation Holder:
Allergan Ltd.,
Marlborough, MA 01221

Manufacturer:
Allergan Pharmaceuticals Ireland
Castletroy 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 on September 2011.

6. FURTHER INFORMATION

What BOTOX contains:
- The active substance is: Botulinum toxin type A from Clostridium botulinum.
- The other ingredients are: 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.
Botox 50, 100 and 200 Allergan units – powder for solution for injection
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
  - 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
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 I</th>
<th>Head rotated toward side of shoulder elevation</th>
<th>Sternomastoid</th>
<th>50 - 100 Units; at least 2 sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Levator scapulae</td>
<td>50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalene</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>
<tr>
<td>Type II</td>
<td>Head rotation only</td>
<td>Sternomastoid</td>
<td>25 - 100 Units; at least 2 sites if ≥25 Units given</td>
</tr>
<tr>
<td>Type III</td>
<td>Head tilted toward side of shoulder elevation</td>
<td>Sternomastoid</td>
<td>25 - 100 Units at posterior border; at least 2 sites if ≥25 Units given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levator scapulae</td>
<td>25 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalene</td>
<td>25 - 75 Units; at least 2 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, 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.

| Type IV Bilateral posterior cervical muscle spasm with elevation of the face | Splenius capitis and cervicis | 50 - 200 Units; 2 - 8 sites, treat bilaterally (This is the total dose and not the dose for each side of the neck) |
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:

![Injection Sites Diagrams]

**BOTOX Dosing By Muscle:**

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

**Total Dose Range:** 155 Units to 195 Units (31 to 39 sites)

\(^a\)1 IM injection site = 0.1 mL = 5 Units BOTOX  
\(^b\)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.

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), 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, 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**

Botox 50, 100 and 200 Allergan units – powder for solution for injection
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: Parasthesia, 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>&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>
</tbody>
</table>
Frequency of headache episodes  -5.2  -4.9  p = 0.009
Total HIT-6* scores  -4.8  -2.4  p < 0.001

* 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:
### Botox 50, 100 and 200 Allergan units – powder for solution for injection

<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(^1) at Week 2</td>
<td>-2.66</td>
<td>-1.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean Change(^1) at Week 6</td>
<td>-2.97</td>
<td>-1.13</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean Change(^1) at Week 12(^a)</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\(^a\)                                     | 61.8 | 28.0 | < 0.001 |

| Daily Frequency of Micturition Episodes           | | | |
| Mean Baseline                                    | 11.99 | 11.48 |         |
| Mean Change\(^1\) at Week 12\(^b\)              | -2.19 | -0.82 | < 0.001 |

| Daily Frequency of Urgency Episodes              | | | |
| Mean Baseline                                    | 8.82 | 8.31 |         |
| Mean Change\(^1\) at Week 12\(^b\)              | -3.08 | -1.12 | < 0.001 |

| Incontinence Quality of Life Total Score         | | | |
| Mean Baseline                                    | 34.1 | 34.7 |         |
| Mean Change\(^1\) at Week 12\(^b\)^\(^c\)       | +21.3 | +5.4 | < 0.001 |

| King’s Health Questionnaire: Role Limitation     | | | |
| Mean Baseline                                    | 65.4 | 61.2 |         |
| Mean Change\(^1\) at Week 12\(^b\)^\(^c\)       | -24.3 | -3.9 | < 0.001 |

| King’s Health Questionnaire: Social Limitation   | | | |
| Mean Baseline                                    | 44.8 | 42.4 |         |
| Mean Change\(^1\) at Week 12\(^b\)^\(^c\)       | -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.

\(^1\) 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
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>Endpoint</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 6</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 6</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></td>
</tr>
<tr>
<td>Mean Change at Week 6</td>
<td>-27.1</td>
<td>-0.4</td>
<td>p&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>p&lt;0.001</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>+26.9</td>
<td>+7.1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Percentage of patients achieving full continence at Week 6</strong> (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**
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></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>
<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>
</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

## ALLERGAN®

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**BOTOX®**

50 Allergan Units, 
100 Allergan Units, 
200 Allergan Units, 
Powder for solution for injection

**Powder for solution for injection**

**Toxin Type A**

Read all of this leaflet carefully before you start using this medicine:

- Keep the 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. Do not pass it on to others, as it may harm them, even if their symptoms are the same as yours.
- 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.

This leaflet is used for:

1. WHAT BOTOX IS AND WHAT IT IS USED FOR

**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 impulses to the muscle that has been injected and reduces excessive contractions of the affected muscles.

In the case of chronic migraine, it is injected into the scalp to help reduce the number of headaches.

When injected into the skin, BOTOX works to relax the muscles to reduce the amount of wrinkle produced.

When injected into the paddles, BOTOX works on the bands to reduce the muscular tension to prevent the formation of wrinkles (secondary to muscular activity) due to uncontrolled contractions of the band muscle.

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 history of eczema (i.e. eczema on the scalp).
- If you have had any injection in the past 14 days.
- If you are taking any other medical products and/or antibiotics (blood thinner).

Tell your doctor if you have:

- Any history of blood clots or blood disorders in the past or present.
- Any previous blood clots or blood disorders in the past or present.
- Any previous medical problems and/or medications used.

Tell your doctor if you:

- Have any skin disorders or acne.
- Have any skin disorders or acne.
- Have any skin disorders or acne.

3. HOW TO USE BOTOX

**Botox must only be injected by doctors with specific skills in how to use the medicine.**

**Method of route of administration**

BOTOX is injected into the muscles (intramuscularly), into the band well as into the specific area (e.g. subcutaneous). To inject into the band well as into the specific area, use a needle that is long enough to reach the affected area of the 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 individual. Therefore, your doctor will decide how much, how often, and in which muscle(s) BOTOX will be given to you. It is therefore recommended that your doctor uses the lowest effective dose.
- Do not give the dose on the same day as another adult.

**This dosage of BOTOX and the route of injection vary depending on the condition for which it is treated. Below is a list of the side effects in each condition:**

- **The safety and effectiveness of BOTOX in the treatment of persistent muscular spasms of the eyelid, face, neck and shoulders in children (under 12 years) have not been demonstrated.**
The safety and effectiveness of BOTOX in the treatment of chronic migraine have not been studied in children (under 18 years).

The safety and effectiveness of BOTOX in the treatment of vertigo between the symptoms and the duration of the vertigo attacks have not been demonstrated and thus are not recommended.

The safety and effectiveness of BOTOX in the treatment of chronic lichen and/or 12 years. There is limited experience with BOTOX in the treatment of chronic lichen in children (under 12 years) and in children (under 18 years).

The safety and effectiveness of BOTOX in the treatment of chronic skin disease in children (under 12 years) and in children (under 18 years) have not been established in children and adolescents under 12 years of age.

The safety and effectiveness of BOTOX in the treatment of alopecia areata in children have not been established in children (under 18 years) and in children (under 15 years).

The safety and effectiveness of BOTOX in the treatment of alopecia have not been established in children (under 15 years).

There is limited experience with BOTOX in the treatment of alopecia (under 15 years) and in children (under 18 years).

For persistent muscle spasms of the eyelid and face:

Dosage:
In the first treatment session, your doctor may inject your muscles in the affected areas with 1 to 5 U/ml of BOTOX into each site.

The maximum dose for the first treatment session is 200 U/ml of BOTOX into each site.

The duration of treatment effect: The effect usually lasts for 2 to 6 weeks after the injection.

For persistent muscle spasms of the neck and shoulders:

Dosage:
Your doctor may inject your muscles in the affected areas with 20 to 50 U/ml of BOTOX into each site.

The maximum dose for the first treatment session is 200 U/ml of BOTOX into each site.

The duration of treatment effect: The effect usually lasts for 2 to 6 weeks after the injection.

For extensive sweating of the armpits:

Dosage:
Your doctor may inject your muscles in the affected areas with 20 to 50 U/ml of BOTOX into each site.

The duration of treatment effect: The effect usually lasts for 4 to 6 weeks after the injection.
### POSSIBLE SIDE EFFECTS

**If you have any difficulty in breathing, swelling of the face or throat, or become unconscious, contact your doctor immediately.**

If you experience breathing difficulty as described below, call medical services immediately.

**Lesions**

If you experience any difficulty in breathing, contact your doctor immediately.

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

**Very common side effects:**
- vasoconstriction
- respiratory distress

**Common side effects:**
- muscle weakness
- difficulty in swallowing

**Rare side effects:**
- difficulty in breathing
- respiratory distress

**Uncommon side effects:**
- chest pain
- muscle weakness

**Mild side effects:**
- local pain
- swelling
- bruising

**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 and hand of patients who have had a stroke**

**Common side effects:**
- muscle weakness
- difficulty in swallowing

**Uncommon side effects:**
- chest pain
- muscle weakness

**Mild side effects:**
- local pain
- swelling
- bruising

**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**

**Common side effects:**
- urinary tract infection
- painful urination after the injection

**Uncommon side effects:**
- bacteria in the urine, white blood cells in the urine

**Mild side effects:**
- frequency of urination

**Injections in the bladder for leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis**

**Very common side effects:**
- urinary tract infection
- difficulty in emptying your bladder (see section 3)

**Common side effects:**
- difficulty in swallowing (nausea, vomiting)

**Mild side effects:**
- frequency of urination

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

**Injections in the face and neck**

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

**Common side effects:**
- nausea

**Mild side effects:**
- swallowing difficulty

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

Botox 50, 100 and 200 Allergan units – powder for solution for injection
Injections in the forehead for vertical lines

Common side effects are:
- headache
- dryness
- redness
- injection site bruising

Uncommon side effects are:
- infection
- edema
- pain
- sensitivity
- injection site bleeding
- injection site swelling
- injection site hardness

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:
- injection site bruising
- injection site bleeding

Uncommon side effects are:
- injection site swelling
- injection site hardness

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 bruising
- injection site bleeding

Uncommon side effects are:
- injection site swelling
- injection site hardness

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
- double vision
- trouble swallowing
- difficulty swallowing
- breathing difficulties

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.

Do not freeze concentrated solutions. Concentrated solutions should be used immediately after reconstitution.

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.

If you have any questions, please ask 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

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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, in some cases 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.

Pneumonitis associated with injection procedure has been reported following administration of BOTOX near the horns. Caution is warranted 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 lung, i.e., the oropharyngeal region, oesophagus or stomach. Some patients had pre-existing dysphagia or significant obesity.

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 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 (0.9%) solution for injection) added in a 50 unit vial</th>
<th>Amount of diluent (sodium chloride 9 mg/ml (0.9%) solution for injection) added in a 100 unit vial</th>
<th>Amount of diluent (sodium chloride 9 mg/ml (0.9%) 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>

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 10 ml 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 a 200 Unit vial of BOTOX with 20 ml of 0.9% non-preserved saline solution and mix gently. Draw 20 ml from the vial into a 20 ml syringe. Complete the reconstitution by adding 12 ml of 0.9% non-preserved saline solution into the 20 ml syringe and mix gently. This will result in a 20 ml syringe containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Dilution instructions for treatment of urinary incontinence due to overactive bladder:

It is recommended that a 200 Unit vial of BOTOX with 20 ml of 0.9% non-preserved saline solution and mix gently. Draw 20 ml from the vial into a 20 ml syringe. Complete the reconstitution by adding 12 ml of 0.9% non-preserved saline solution into the 20 ml syringe and mix gently. This will result in a 20 ml syringe containing a total of 200 Units of reconstituted BOTOX. Use immediately after reconstitution in the syringe. Dispose of any unused saline.
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 chemoneurolytics (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>
<tr>
<td>BTOX-138/139-8051 (US)</td>
<td>Multicenter, double-blind, randomized (exploratory study)</td>
<td>BOTOX ~ 4 U/kg ± 1 U/kg (N = 33) BOTOX ~ 2 U/kg ± 1 U/kg (N = 36) placebo (N = 27)</td>
<td>Medial and lateral gastrocnemius ± anterior or posterior tibialis</td>
<td>Up to 2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>191622-501 (Europe)</td>
<td>Multicenter, double-blind, randomized (exploratory study)</td>
<td>BOTOX ~ 4 U/kg ± 1 U/kg (N = 45) BOTOX ~ 2 U/kg ± 1 U/kg (N = 45) placebo (N = 41)</td>
<td>Medial and lateral gastrocnemius ± anterior or posterior tibialis</td>
<td>1</td>
</tr>
<tr>
<td>191622-502 (Europe)</td>
<td>Multicenter, double-blind, extension, randomized&lt;sup&gt;b&lt;/sup&gt; (exploratory study)</td>
<td>BOTOX ~ 4 U/kg ± 1 U/kg (N = 48) BOTOX ~ 2 U/kg ± 1 U/kg (N = 43)</td>
<td>Medial and lateral gastrocnemius ± anterior or posterior tibialis</td>
<td>1</td>
</tr>
<tr>
<td>BTOX-702-8051 (Australia)</td>
<td>Part I: multicenter, double-blind, randomized Part II: multicenter, open-label (supportive study)</td>
<td>Part I: BOTOX 300 U (N = 28) BOTOX 200 U (N = 28) placebo 300/200 (N = 15/14) Part II: BOTOX/BOTOX&lt;sup&gt;c&lt;/sup&gt; (N = 44) placebo/BOTOX&lt;sup&gt;c&lt;/sup&gt; (N = 26)</td>
<td>Posterior tibialis, soleus, and either flexor digitorum longus or medial gastrocnemius</td>
<td>Part I: 1 Part II: 1</td>
</tr>
<tr>
<td>191622-030 (US)</td>
<td>Multicenter, double-blind, randomized (exploratory study)</td>
<td>BOTOX 360 U (N = 37) BOTOX 240 U (N = 36) placebo (N = 36)</td>
<td>Up to 6 muscles of upper and/or lower limb&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Up to 2</td>
</tr>
<tr>
<td>191622-911 (Japan)</td>
<td>Multicenter, open-label, step-wise (exploratory study)</td>
<td>BOTOX 75 U ± 25 U (N = 7) BOTOX 150 U ± 50 U (N = 7) BOTOX 225 U ± 75 U (N = 6)</td>
<td>Gastrocnemius and soleus ± posterior tibialis if talipes varus</td>
<td>1</td>
</tr>
<tr>
<td><strong>Phase 3 Study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTX108512 (Japan)</td>
<td>Part I: multicenter, double-blind, randomized Part II: multicenter, open-label (primary efficacy study)</td>
<td>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)</td>
<td>Medial and lateral gastrocnemius, soleus and posterior tibialis</td>
<td>Part I: 1 Part II: up to 3</td>
</tr>
</tbody>
</table>
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:**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>BTOX-138/139-8051</th>
<th>191622-501</th>
<th>191622-502</th>
<th>191622-901</th>
<th>191622-911</th>
<th>SGD/001-191622</th>
<th>BTOX-702-8051</th>
<th>Supportive Studies</th>
<th>Primary Efficacy Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius (medial head)</td>
<td>-2 U/kg</td>
<td>-2 U/kg</td>
<td>-2 U/kg</td>
<td>-2 U/kg</td>
<td>50-200 U</td>
<td>75 U</td>
<td>50 U</td>
<td>40 U</td>
<td>75 U</td>
</tr>
<tr>
<td>Gastrocnemius (lateral head)</td>
<td>-2 U/kg</td>
<td>-2 U/kg</td>
<td>-2 U/kg</td>
<td>-2 U/kg</td>
<td>50-200 U</td>
<td>75 U</td>
<td>50 U</td>
<td>40 U</td>
<td>75 U</td>
</tr>
<tr>
<td>Tibialis (anterior or posterior)</td>
<td>-1 U/kg (only at 2nd injection)</td>
<td>-1 U/kg (if spasticity of tibialis)</td>
<td>-1 U/kg (if spasticity of tibialis)</td>
<td>50-200 U</td>
<td>50 U</td>
<td>25 U</td>
<td>100 U</td>
<td>70 U</td>
<td>50 U</td>
</tr>
<tr>
<td>Soleus</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>50-100 U</td>
<td>75 U</td>
<td>50 U</td>
<td>25 U</td>
<td>100 U</td>
<td>50 U</td>
</tr>
<tr>
<td>Flexor digitorum longus/brevis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>50-100 U</td>
<td>75 U</td>
<td>50 U</td>
<td>25 U</td>
<td>100 U</td>
<td>50 U</td>
</tr>
<tr>
<td>Flexor hallucis longus/brevis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>25-75 U</td>
<td>50 U</td>
<td>25 U</td>
<td>25 U</td>
<td>30 U</td>
<td>15 U</td>
</tr>
</tbody>
</table>

*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 3.6 U/kg to 4.1 U/kg for the ~4 U/kg dose to the tibialis, and from 0.9 kg to 1.1 U/kg for the ~1 U/kg dose to the tibialis.

*Actual doses ranged from 1.1 U/kg to 3.3 U/kg (low dose group) and 3.6 U/kg to 5.6 U/kg (high dose group).

*Study 191622-500 included patients with lower and/or upper limb spasticity; of the 109 patients enrolled, 46 patients received injections in the lower limb.

*Study SGD/001-191622 included patients with lower and/or upper limb spasticity; of the 274 patients enrolled, 204 patients received injections in the lower limb. Maximum doses per muscle as suggested by the protocol are listed above.

*Muscles injected were either the flexor digitorum longus or medial gastrocnemius.

*The minimum recommended BOTOX dose for the ankle planter 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>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>
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<tr>
<td></td>
<td></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 ≥ 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.

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 $\geq 2$ at pre-treatment.
2. At least 12 weeks (84 days) since the last injection.
3. Body weight of $\geq 50$ 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

### Physician’s Rating Scale

<table>
<thead>
<tr>
<th>Gait parameter</th>
<th>Definition</th>
<th>Affected limb score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial foot contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toe</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Forefoot</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Foot-flat</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Heel</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Foot contact at midstance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toe/toe (equinus)</td>
<td></td>
<td>-1</td>
</tr>
<tr>
<td>Foot-flat/early heel rise</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Foot-flat/no early heel rise</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Occasional heel/foot-flat</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Heel/toe (aonal roll-over)</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Gait assistive devices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walker (forward/posterior) with assistance</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Walker (independent)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Crutches, sticks</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>None, independent for 10m</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Total score (score = -1 to 9 per limb)


- 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

### Numeric Rating Scale (NRS)

(Worst Possible) -5 -4 -3 -2 -1 0 1 2 3 4 5 (Best Possible)

- 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 provides as to what effect size would be clinically meaningful.*

**Statistical analysis**

Botox 50, 100 and 200 Allergan units – powder for solution for injection
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 (95%)</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).
Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>BTX-300U (N=58)</th>
<th>Placebo (N=62)</th>
<th>Total (N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>62.4</td>
<td>62.5</td>
<td>62.5</td>
</tr>
<tr>
<td>SD</td>
<td>8.66</td>
<td>9.32</td>
<td>8.97</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 yr</td>
<td>16 (28%)</td>
<td>19 (31%)</td>
<td>35 (29%)</td>
</tr>
<tr>
<td>≥60 yr</td>
<td>42 (72%)</td>
<td>43 (69%)</td>
<td>85 (71%)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>8 (14%)</td>
<td>16 (26%)</td>
<td>24 (20%)</td>
</tr>
<tr>
<td>Male</td>
<td>50 (86%)</td>
<td>46 (74%)</td>
<td>96 (80%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian - Japanese</td>
<td>58 (100%)</td>
<td>62 (100%)</td>
<td>120 (100%)</td>
</tr>
<tr>
<td>Period of time after onset of stroke (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>80.8</td>
<td>72.0</td>
<td>76.3</td>
</tr>
<tr>
<td>SD</td>
<td>72.80</td>
<td>60.26</td>
<td>66.47</td>
</tr>
<tr>
<td>MAS ankle score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.28</td>
<td>3.24</td>
<td>-</td>
</tr>
<tr>
<td>SD</td>
<td>0.451</td>
<td>0.432</td>
<td>-</td>
</tr>
<tr>
<td>MAS ankle score, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42 (72%)</td>
<td>47 (76%)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>16 (28%)</td>
<td>15 (24%)</td>
<td>-</td>
</tr>
</tbody>
</table>

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.

Table 2  AUC for change from baseline in MAS ankle (DB phase; FAS – observed data)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>BTX-300U (N=58)</th>
<th>Placebo (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-8.513</td>
<td>-5.085</td>
</tr>
<tr>
<td>SD</td>
<td>6.6904</td>
<td>8.6496</td>
</tr>
<tr>
<td>Median</td>
<td>-9.500</td>
<td>-2.000</td>
</tr>
<tr>
<td>Minimum</td>
<td>-22.00</td>
<td>-25.50</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Comparison of AUC between groups  Mean difference  95%CI  p value

|                | Mean difference | 95%CI          | p value
|----------------|-----------------|----------------|
| BTX - Placebo  | -3.428          | -5.841, -1.016 | 0.006

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.

<table>
<thead>
<tr>
<th>AUC of Change From Baseline</th>
<th>Original Analysis</th>
<th>New Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed Data</td>
<td>Imputed Data</td>
</tr>
<tr>
<td></td>
<td>BOTOX (N = 58)</td>
<td>Placebo (N = 62)</td>
</tr>
<tr>
<td>Mean</td>
<td>-8.51</td>
<td>-8.44</td>
</tr>
<tr>
<td>(Median)</td>
<td>(-9.50)</td>
<td>(-9.50)</td>
</tr>
</tbody>
</table>

AUC = area under the curve
<sup>a</sup> P-value was based on 2-sample t-test.
<sup>b</sup> P-value was based on an ANCOVA model with treatment as a factor and baseline modified Ashworth score of ankle as a covariate.

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).

### Table 4  Responder rates (DB phase; FAS) – from CSR

<table>
<thead>
<tr>
<th>Visit</th>
<th>BOTOX 300 U (N = 58)</th>
<th>Placebo (N = 62)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>30/57 (52.6%)</td>
<td>24/62 (38.7%)</td>
<td>0.128</td>
</tr>
<tr>
<td>Week 4</td>
<td>38/56 (67.9%)</td>
<td>19/62 (31%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 6</td>
<td>39/57 (68.4%)</td>
<td>22/61 (36.1%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 8</td>
<td>36/54 (66.7%)</td>
<td>20/61 (32.8%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Week 12</td>
<td>24/54 (44.4%)</td>
<td>21/61 (34.4%)</td>
<td>0.272</td>
</tr>
</tbody>
</table>

### Table 5  Change from baseline in MAS ankle score by treatment BOTOX cycle (FAS)

<table>
<thead>
<tr>
<th>No of Treatment Cycles</th>
<th>BTX-300U</th>
<th>1st treatment</th>
<th>2nd treatment</th>
<th>3rd treatment</th>
<th>4th treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean ±SD</td>
<td>n</td>
<td>Mean ±SD</td>
<td>n</td>
<td>Mean ±SD</td>
</tr>
<tr>
<td>Week 4</td>
<td>112</td>
<td>-1.08±0.695</td>
<td>97</td>
<td>-1.44±0.651</td>
<td>72</td>
</tr>
<tr>
<td>Week 8</td>
<td>110</td>
<td>-1.08±0.672</td>
<td>93</td>
<td>-1.36±0.633</td>
<td>71</td>
</tr>
<tr>
<td>Week 12</td>
<td>111</td>
<td>-0.81±0.704</td>
<td>93</td>
<td>-1.12±0.701</td>
<td>70</td>
</tr>
</tbody>
</table>
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</th>
<th>Change from baseline in CGI score (DB phase; FAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>BTX-300U (N=58)</td>
</tr>
<tr>
<td>Investigator</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>58</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>57</td>
</tr>
<tr>
<td>Week 4</td>
<td>56</td>
</tr>
<tr>
<td>Week 6</td>
<td>56</td>
</tr>
<tr>
<td>Week 8</td>
<td>54</td>
</tr>
<tr>
<td>Week 12</td>
<td>53</td>
</tr>
<tr>
<td>Subject</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>58</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>57</td>
</tr>
<tr>
<td>Week 4</td>
<td>56</td>
</tr>
<tr>
<td>Week 6</td>
<td>56</td>
</tr>
<tr>
<td>Week 8</td>
<td>54</td>
</tr>
<tr>
<td>Week 12</td>
<td>53</td>
</tr>
<tr>
<td>Physiotherapist/occupational therapist</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>58</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
</tr>
<tr>
<td>Week 1</td>
<td>57</td>
</tr>
<tr>
<td>Week 4</td>
<td>56</td>
</tr>
<tr>
<td>Week 6</td>
<td>56</td>
</tr>
<tr>
<td>Week 8</td>
<td>54</td>
</tr>
<tr>
<td>Week 12</td>
<td>53</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>Bottox 200 (ITT=28)</th>
<th>Bottox 300 (ITT=20)</th>
<th>Placebo 200 (ITT=16)</th>
<th>Placebo 300 (ITT=2)</th>
<th>Overall (ITT=52)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vixt 3</td>
<td>16</td>
<td>16</td>
<td>9</td>
<td>7</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>-2.0 - -2.51</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>-1.0 - -0.51</td>
<td>6 (42.9%)</td>
<td>7 (43.8%)</td>
<td>0 ( 0.0%)</td>
<td>0 ( 0.0%)</td>
<td>4 ( 7.7%)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.56</td>
<td>-0.69</td>
<td>0.00</td>
<td>-0.57</td>
<td>-0.50</td>
<td>0.0636</td>
</tr>
<tr>
<td>SD</td>
<td>0.64</td>
<td>0.70</td>
<td>0.00</td>
<td>0.63</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>-0</td>
<td>-1.00</td>
<td>0</td>
<td>-1.00</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vixt 4</td>
<td>16</td>
<td>16</td>
<td>9</td>
<td>7</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>-2.0 - -2.51</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>-1.0 - -0.51</td>
<td>3 (21.4%)</td>
<td>9 (56.3%)</td>
<td>0 ( 0.0%)</td>
<td>2 (30.6%)</td>
<td>15 (30.4%)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-0.56</td>
<td>-0.70</td>
<td>0.00</td>
<td>-0.24</td>
<td>-0.42</td>
<td>0.0111</td>
</tr>
<tr>
<td>SD</td>
<td>0.73</td>
<td>0.65</td>
<td>0.02</td>
<td>0.42</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>-1.00</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

[a] Ashworth Scale: 0=mone, 1=mild, 2=moderate, 3=severe, 4=very severe.
[b] P-values obtained using the Type III SS for the PROC GLM model with factors for drug and dose.

#### 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
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 200 U (N = 28)</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.5 (3.0)</td>
<td>2.6 (3.0)</td>
</tr>
<tr>
<td>Week 4</td>
<td>-0.4 (0.0)</td>
<td>-0.4 (0.0)</td>
</tr>
<tr>
<td>Week 8</td>
<td>-0.5 (0.0)</td>
<td>-0.2 (0.0)</td>
</tr>
<tr>
<td>Week 12</td>
<td>-0.5 (0.0)</td>
<td>-0.2 (0.0)</td>
</tr>
<tr>
<td>Week 16</td>
<td>-0.4 (0.0)</td>
<td>-0.3 (0.0)</td>
</tr>
<tr>
<td>AUC up to week 12</td>
<td>-3.86 (0.0)</td>
<td>-2.10 (0.0)</td>
</tr>
<tr>
<td></td>
<td>(0.0)</td>
<td>(0.0)</td>
</tr>
</tbody>
</table>

a  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).

Botox 50, 100 and 200 Allergan units – powder for solution for injection
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

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>
<tr>
<td></td>
<td>2-way ANOVA with drug type (BOTOX versus placebo) and dose stratum (200 U versus 300 U) as factors</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.

<table>
<thead>
<tr>
<th>Summary of Clinical Efficacy</th>
<th>Clinical Study Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 8</td>
<td></td>
</tr>
<tr>
<td>All Patients</td>
<td></td>
</tr>
<tr>
<td>Patients With Baseline</td>
<td>All Patients</td>
</tr>
<tr>
<td>Ankle Ashworth Scale Score ≥ 3</td>
<td></td>
</tr>
<tr>
<td>BOTOX (300 U)</td>
<td>Placebo (Pooled)</td>
</tr>
<tr>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.9 ± 9.26</td>
</tr>
<tr>
<td>BOTOX (300 U)</td>
<td>Placebo (Pooled)</td>
</tr>
<tr>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.5 ± 8.86</td>
</tr>
<tr>
<td>BOTOX (300 U)</td>
<td>Placebo (Pooled)</td>
</tr>
<tr>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.4 ± 10.2</td>
</tr>
</tbody>
</table>

The MAH has provided clarification about the different method of analysis used in the two documents. Regardless of the method, the results showed a statistically significant difference between placebo and the 300U dose 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 9 Goal Attainment Scores by the Physician (DB phase)

<table>
<thead>
<tr>
<th>Week 10 Post Second Injection or Week 24</th>
<th>Patients with Injections in the Gastrocnemius, Soleus, Posterior Tibialis</th>
</tr>
</thead>
<tbody>
<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></td>
<td>N = 29</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
<td>0.0 (0.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number (%) of patients who achieved functional goal (score ≥ 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 34</td>
</tr>
<tr>
<td>N = 29</td>
</tr>
<tr>
<td>Principal functional goal (active)</td>
</tr>
<tr>
<td>16 (47.1)</td>
</tr>
<tr>
<td>10 (33.3)</td>
</tr>
<tr>
<td>0.265f</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
</tr>
<tr>
<td>20 (69.0)</td>
</tr>
<tr>
<td>11 (34.4)</td>
</tr>
<tr>
<td>0.007f</td>
</tr>
</tbody>
</table>

Table 10 Goal Attainment Scores by the Patient (DB phase)

<table>
<thead>
<tr>
<th>Week 10 Post Second Injection or Week 24</th>
<th>Patients with Injections in the Gastrocnemius, Soleus, Posterior Tibialis</th>
</tr>
</thead>
<tbody>
<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>-0.1 (0.0)</td>
</tr>
<tr>
<td></td>
<td>N = 29</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
<td>-0.1 (0.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number (%) of patients who achieved functional goal (score ≥ 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 34</td>
</tr>
<tr>
<td>N = 29</td>
</tr>
<tr>
<td>Principal functional goal (active)</td>
</tr>
<tr>
<td>18 (52.9)</td>
</tr>
<tr>
<td>11 (36.7)</td>
</tr>
<tr>
<td>0.192f</td>
</tr>
<tr>
<td>Secondary functional goal (active or passive)</td>
</tr>
<tr>
<td>20 (69.0)</td>
</tr>
<tr>
<td>10 (31.3)</td>
</tr>
<tr>
<td>0.003f</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)

<table>
<thead>
<tr>
<th>P-value is based on Wilcoxon rank-sum test</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-value based on Pearson’s chi square test or Fisher’s exact test</td>
</tr>
</tbody>
</table>

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
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>
<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><strong>Age (years)</strong></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><strong>Sex (number [%])</strong></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><strong>Race (number [%])</strong></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><strong>Time since stroke (months)</strong></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><strong>Ankle muscle tone at baseline</strong></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 ≥ 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 BOTOX-702-8051, BOTOX response rates were similar among patients with baseline AS scores ≥ 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 ≥ 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

<table>
<thead>
<tr>
<th>Visit</th>
<th>BTX108512 All Patients Baseline Ashworth ≥ 3</th>
<th>BOTOX-702-8051 All-Patients Population Baseline Ashworth ≥ 3</th>
<th>AGN/HOS/SPA/001-191622 Gastrocnemius, Soleus, Posterior Tibialis Baseline Ashworth ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BOTOX 300 U Placebo (N=58)</td>
<td>BOTOX 300 U Pooled Placebo (N=29)</td>
<td>BOTOX 300 U Placebo (N=40)</td>
</tr>
<tr>
<td></td>
<td>30 (52.6%) 24 (38.7%)</td>
<td>11 (39.3%) 10 (35.7%)</td>
<td>18 (51.4%) 8 (23.5%)</td>
</tr>
<tr>
<td></td>
<td>NE NE</td>
<td>NE NE</td>
<td>NE NE</td>
</tr>
<tr>
<td>Week 1</td>
<td>38 (57.9%) 19 (30.6%)</td>
<td>11 (42.3%) 15 (58.5%)</td>
<td>18 (51.4%) 8 (23.5%)</td>
</tr>
<tr>
<td>Week 2</td>
<td>39 (58.4%) 22 (36.1%)</td>
<td>NE NE</td>
<td>NE NE</td>
</tr>
<tr>
<td>Week 3</td>
<td>36 (56.7%) 20 (32.8%)</td>
<td>NE NE</td>
<td>NE NE</td>
</tr>
<tr>
<td>Week 4</td>
<td>24 (44.4%) 21 (34.4%)</td>
<td>10 (40.0%) 8 (33.3%)</td>
<td>14 (58.3%) 6 (22.2%)</td>
</tr>
<tr>
<td>Week 5</td>
<td>NE NE</td>
<td>9 (36.0%) 6 (23.1%)</td>
<td>NE NE</td>
</tr>
<tr>
<td>Week 6</td>
<td>NE NE</td>
<td>7 (46.7%) 4 (26.7%)</td>
<td>NE NE</td>
</tr>
<tr>
<td>Week 7</td>
<td>NE NE</td>
<td>NE NE</td>
<td>NE NE</td>
</tr>
<tr>
<td>Week 8</td>
<td>NE NE</td>
<td>NE NE</td>
<td>14 (58.3%) 6 (22.2%)</td>
</tr>
<tr>
<td>Week 9</td>
<td>NE NE</td>
<td>NE NE</td>
<td>NE NE</td>
</tr>
<tr>
<td>Week 10</td>
<td>NE NE</td>
<td>NE NE</td>
<td>NE NE</td>
</tr>
</tbody>
</table>

---

Modified Ashworth scale scored by the investigator as 0, 1, 2, 3, 4 in study BTX108512; AS score by investigator as 0, 1, 2, 3, 4 in study BOTOX-702-8051; single REPAS item “foot dorsiflexion” rated using AS score by investigator as 0, 1, 2, 3, 4 in study AGN/HOS/SPA/001-191622.

P-values based on Pearson’s chi-square or Fisher’s exact test.

The dose used in individual patients was determined by the treating physician based on their experience and normal practice in order to maximize functional response to treatment. The protocol suggested a maximum pre-muscle dose.

Statistically significant difference favoring BOTOX over placebo, p < 0.001

Statistically significant difference favoring BOTOX over placebo, p ≥ 0.001 and < 0.010

Statistically significant difference favoring BOTOX over placebo, p ≥ 0.01 and < 0.050

Statistically significant difference favoring BOTOX over placebo, p ≥ 0.001 and < 0.001

Statistically significant difference favoring BOTOX over placebo, p ≥ 0.01 and < 0.050

Statistically significant difference favoring BOTOX over placebo, p ≥ 0.050
**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></th>
<th>BOTOX 300 U (N = 28)</th>
<th>BOTOX 200 U (N = 28)</th>
<th>Pooled Placebo (N = 29)</th>
<th>P-value$^a$ 300 U /200 U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of patients by baseline walking speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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/sec$^b$</td>
<td>5 (17.9)</td>
<td>8 (28.6)</td>
<td>6 (20.7)</td>
<td></td>
</tr>
<tr>
<td>Number (%) of patients overall who improved by ≥ 1 category at weeks 4, 8, 12, or 16</td>
<td>16/21 (76.2)</td>
<td>9/16 (56.3)</td>
<td>9/19 (47.4)</td>
<td>0.060/0.600</td>
</tr>
</tbody>
</table>

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, i.e., > 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.
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

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 $\geq 3$, 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) a</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>

a 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>

Botox 50, 100 and 200 Allergan units – powder for solution for injection 144
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 (i.e., ≥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>Forced 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, i.e., 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 (e.g., 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, confusion, 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.

Dyspnœa 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 dyspnœa 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</th>
<th>Preferred Term</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>Arthralgia</td>
<td></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></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></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></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.

Botox 50, 100 and 200 Allergan units – powder for solution for injection
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.

**Table 8-1**

<table>
<thead>
<tr>
<th>Summary of the Safety Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Important Missing Information</strong></td>
</tr>
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<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

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; Treatment in Pediatric Lower Limb Spasticity: Double-blind Study (91062-111)</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 standardized physical therapy in pediatric patients with lower limb spasticity</td>
<td>Dysphagia in cervical dystonia</td>
<td>US/EU/APAC studies started</td>
<td>No interim analysis is planned Submission: May 2014 Approval: June 2017</td>
</tr>
<tr>
<td>Post-marketing commitment study (FDA): BOTOX&lt;sup&gt;®&lt;/sup&gt; Treatment of Pediatric Lower Limb Spasticity: Open-label Study (91062-112)</td>
<td>To evaluate the long-term safety of repeated doses of BOTOX&lt;sup&gt;®&lt;/sup&gt; for the treatment of pediatric lower limb spasticity</td>
<td>Dysphagia in cervical dystonia Distinct spasm of toxin</td>
<td>US/EU/APAC studies started</td>
<td>Interim Topline available December 2015 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 Groups</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Rotated toward side of shoulder elevation</td>
<td>Sternomastoid</td>
<td>50 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Levator scapulae</td>
<td>50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalenae</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>
<tr>
<td>Type 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>Type III</td>
<td>Tilted toward side of shoulder elevation</td>
<td>Sternomastoid</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>Levator scapulae</td>
<td>25 - 100 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalenae</td>
<td>25 - 75 Units; at least 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trapezius</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 (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:

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) 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, 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 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, 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

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 (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.

**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:
Mean Baseline | Mean Change at Week 12bc | Mean Changea at Week 12bc | Mean Change at Week 12bc | Mean Change at Week 12bc
--- | --- | --- | --- | ---
King’s Health Questionnaire: Social Limitation | 65.4 | 61.2 | <0.001 | <0.001
Mean Baseline | 44.8 | 42.4 | <0.001 | <0.001
Mean Change at Week 12bc | -24.3 | -3.9 | -16.1 | -2.5
Mean Change at Week 12bc | 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.
† 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: |
|---|---|---|---|
| BOTOX 200 Units (N=227) | Placebo (N=241) | P-value |
| Weekly Frequency of Urinary Incontinence | 32.4 | 31.5 | <0.001 |
| Mean Baseline | -16.8 | -9.1 | <0.001 |
| Mean Change at Week 2 | -20.0 | -10.5 | <0.001 |
| Mean Change at Week 6a | -19.8 | -9.3 | <0.001 |
| Mean Change at Week 12 | Maximum Cystometric Capacity (ml) | 250.2 | 253.5 | <0.001 |
| Mean Baseline | +140.4 | +6.9 | <0.001 |
| Mean Change at Week 6b | Maximum Detrusor Pressure during 1st Involuntary Detrusor Contraction (cmH20) | 51.5 | 47.3 | <0.001 |
| Mean Baseline | -27.1 | -0.4 | <0.001 |
**Incontinence Quality of Life Total Score**

<table>
<thead>
<tr>
<th></th>
<th>Mean Baseline</th>
<th>Mean Change† at Week 6</th>
<th>Mean Change† at Week 12</th>
<th>Percentage of patients achieving full continence at Week 6 (dry patients over a 7 day diary)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>35.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 6</td>
<td>+23.6</td>
<td>+8.9</td>
<td>+7.1</td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 12</td>
<td>+26.9</td>
<td></td>
<td></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>
<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**

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</th>
<th>Placebo</th>
<th>BOTOX</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Investigator Assessment</td>
<td>Patient Assessment</td>
<td>Investigator Assessment</td>
<td>Patient Assessment</td>
</tr>
<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%* (106/306)</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®

50 Allergan Units
100 Allergan Units
200 Allergan Units
Powder for solution for injection
Botoxum toxoid type A

Please read this leaflet carefully before you start using this medicine.

1. What BOTOX is and what it is used for

BOTOX is a medication used to treat muscles that are too tight or too weak due to the underlying condition of the muscle. It works by weakening the muscles, which can help improve movement and function.

2. BEFORE YOU USE BOTOX

Do NOT use BOTOX:

- If you are allergic (hypersensitive) to botulinum toxin type A or any other of the ingredients in BOTOX.
- If you have a history of allergy or have had an allergic reaction to BOTOX in the past.

Take special care with BOTOX:

-†††††

3. HOW TO USE BOTOX

BOTOX is usually injected into the muscles by a specialist using a needle or a small syringe. The needle is inserted into the muscle, and the provider then injects the medicine into the muscle. The amount of medicine injected will vary depending on the condition being treated.

4. POSSIBLEADVERSE EFFECTS

The most common side effects of BOTOX are:

-†††††

5. HOW TO REPORT SUSPECTED ADVERSE REACTIONS

If you have any concerns about the use of BOTOX, please contact your doctor or pharmacist.

6. FURTHER INFORMATION

Please read the leaflet carefully before you start using this medicine. If you have any questions, please contact your doctor or pharmacist. This leaflet contains important information about the use of BOTOX.

†††††

6.3. General Information

BOTOX is a prescription medication. It should be used only by patients who have been properly diagnosed and have been prescribed BOTOX by a qualified healthcare provider. BOTOX is supplied in a vial or a prefilled syringe. It is important to keep this medicine out of reach of children.

†††††
The dosage of Botox and the duration of its effect will vary depending on the condition for which it is treated. Below are dosage instructions for each condition:

- **The safety and effectiveness of Botox in the treatment of premature muscular spasms of the eyelid, face, neck, and shoulder in children under 12 years of age are not established.**
- **The safety and effectiveness of Botox in the treatment of chronic strabismus in children** under 12 years of age is not established.**
- **The safety and effectiveness of Botox in the treatment of spasticity of the upper limb in children** is not established.**
- **The safety and effectiveness of Botox in the treatment of spasticity of the lower limb in children** is not established.**
- **The safety and effectiveness of Botox in the treatment of spasticity of the neck and shoulders in children** is not established.**
- **The safety and effectiveness of Botox in the treatment of spasticity of the face, neck, and shoulder in children** is not established.**

**For persistent release spasticity of the upper and lower limb:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.

**For premature release spasticity of the neck and shoulder:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.

**For persistent release spasticity of the face and neck:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.

**For persistent release spasticity of the face and neck:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.

**For premature release spasticity of the face and neck:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.

**For persistent release spasticity of the face and neck:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.

**For premature release spasticity of the face and neck:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.

**For persistent release spasticity of the face and neck:**

**Dosage:**
- The usual dose is 8-10 units, given subcutaneously over 4-6 weeks. The maximum dose is 50 units. The treatment is repeated every 3-6 months.
### Possible Side Effects

If you have received too much BOTOX®, you may have any of the following symptoms and you must consult your doctor immediately. You must consult your doctor or pharmacist if you notice any side effects:
- Difficulty in breathing, swallowing or speaking due to muscle paralysis.
- Fast or rapid breathing or paralysis of your legs which may cause unconsciousness (injection of the legs) due to muscle paralysis.
- Difficulty in swallowing.
- Double vision.
- Generalized weakness.

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

### Injections in the Neck and Shoulder

<table>
<thead>
<tr>
<th>Very common side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty in swallowing.</td>
</tr>
<tr>
<td>Paralysis of both arms.</td>
</tr>
<tr>
<td>Common side effects:</td>
</tr>
<tr>
<td>Shoulder crease.</td>
</tr>
</tbody>
</table>

### Injections for Excessive Sweating of the palms

<table>
<thead>
<tr>
<th>Very common side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient ( fazie skin).</td>
</tr>
<tr>
<td>Common side effects:</td>
</tr>
<tr>
<td>Headache.</td>
</tr>
</tbody>
</table>

### Injections in the Wrist and Hand of patients who have had a stroke

<table>
<thead>
<tr>
<th>Very common side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness.</td>
</tr>
<tr>
<td>Sensory symptoms (numbness, tingling)</td>
</tr>
</tbody>
</table>

### Injections in the legs of children in the neonatal period

<table>
<thead>
<tr>
<th>Very common side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient weakness (e.g., weakness of the bicep muscle).</td>
</tr>
<tr>
<td>Common side effects:</td>
</tr>
<tr>
<td>Sensory symptoms (numbness, tingling)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Very common side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient headache.</td>
</tr>
<tr>
<td>Common side effects:</td>
</tr>
<tr>
<td>Nausea.</td>
</tr>
</tbody>
</table>

### Injections in the bladder wall for overactive bladder with frequent urination

<table>
<thead>
<tr>
<th>Very common side effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient (fazie skin).</td>
</tr>
</tbody>
</table>

The side effects are arranged in the following categories:

- **Very common**
- **Common**
- **Uncommon**
- **Rare**

**Uncommon side effects**:

- Transient weakness (e.g., weakness of the bicep muscle).
- Sensory symptoms (numbness, tingling).

**Rare side effects**:

- Sensory symptoms (numbness, tingling).

**Side effects not listed in this leaflet**

Please tell your doctor or pharmacist if you notice any side effects not listed in this leaflet.

### Injections in the eyelid

- **Very common side effects**:
- Transient weakness (e.g., weakness of the bicep muscle).
- Sensory symptoms (numbness, tingling).

Please tell your doctor or pharmacist if you notice any side effects not listed in this leaflet.
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 CL INICAL PARTICULARS

4.1 T herapeutic 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
  - neurogenic 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</td>
<td>2 years</td>
</tr>
<tr>
<td>cerebral palsy</td>
<td></td>
</tr>
<tr>
<td>Upper and lower limb spasticity associated with</td>
<td>18 years</td>
</tr>
<tr>
<td>stroke</td>
<td></td>
</tr>
<tr>
<td>Blepharospasm/Hemifacial spasm/ Idiopathic</td>
<td>12 years</td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td></td>
</tr>
<tr>
<td>Chronic migraine (CM)</td>
<td>18 years</td>
</tr>
<tr>
<td>Overactive Bladder (OAB) and Neurogenic</td>
<td>18 years</td>
</tr>
<tr>
<td>Detrusor Overactivity (NDO)</td>
<td></td>
</tr>
<tr>
<td>Primary hyperhidrosis of the axillae</td>
<td>12 years</td>
</tr>
<tr>
<td>(limited experience in adolescents between 12</td>
<td></td>
</tr>
<tr>
<td>and 17 years, see sections 4.8 and 5.1)</td>
<td></td>
</tr>
<tr>
<td>Glabellar lines seen at maximum frown and/or</td>
<td>18 years</td>
</tr>
<tr>
<td>crow’s feet lines seen at maximum smile</td>
<td></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>Recommended Dose</th>
<th>Total Dosage; Number of Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrocnemius</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial head</td>
<td>75 Units; 3 sites</td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Lateral head</td>
<td>75 Units; 3 sites</td>
<td></td>
</tr>
<tr>
<td>Soleus</td>
<td>75 Units; 3 sites</td>
<td></td>
</tr>
<tr>
<td>Tibialis Posterior</td>
<td>75 Units; 3 sites</td>
<td></td>
</tr>
</tbody>
</table>

**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:

![Injection Sites Diagram](image_url)

**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>50 - 100 Units; at least 2 sites</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Levator scapulae</td>
<td>50 Units; 1 - 2 sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scalenae</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>

| Type II | Head rotation only | Sternomastoid | 25 - 100 Units; at least 2 sites if >25 Units given |

| 190 |

PL 00426/0118 Botox Injection 50 allergan units
<table>
<thead>
<tr>
<th>Type III</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head tilted toward side of shoulder elevation</td>
<td>Bilateral posterior cervical muscle spasm with elevation of the face</td>
</tr>
<tr>
<td><strong>Sternomastoid</strong></td>
<td><strong>Splenus capitis and cervicis</strong></td>
</tr>
<tr>
<td>Levator scapulae</td>
<td></td>
</tr>
<tr>
<td>Scalen</td>
<td></td>
</tr>
<tr>
<td>Trapezius</td>
<td></td>
</tr>
<tr>
<td>25 - 100 Units at posterior border; at least 2 sites if &gt;25 Units given</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>
<tr>
<td>25 - 100 Units; at least 2 sites</td>
<td></td>
</tr>
<tr>
<td>25 - 75 Units; at least 2 sites</td>
<td></td>
</tr>
<tr>
<td>25 - 100 Units; 1 - 8 sites</td>
<td></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.

**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:

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:

![Diagram of muscle groups]

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&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>Frontalis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 Units (4 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>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>Cervical Paraspinal Muscle Group&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20 Units (4 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>Total Dose Range:</td>
<td>155 Units to 195 Units</td>
</tr>
<tr>
<td></td>
<td>31 to 39 sites</td>
</tr>
</tbody>
</table>

<sup>a</sup>1 IM injection site = 0.1 ml = 5 Units BOTOX
<sup>b</sup>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.

![Image](image_url)

**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:** 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 1]

Figure 2: 

![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>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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site pain, pyrexia, influenza-like illness, injection site haemorrhage, injection site irritation</td>
<td>Common</td>
</tr>
<tr>
<td>Asthenia, pain, injection site hypersensitivity, malaise, peripheral oedema</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

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>General disorders and administration site conditions</td>
<td>Rash/dermatitis</td>
<td>Uncommon</td>
</tr>
<tr>
<td></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, hypoesthesia, 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

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Very common</td>
<td></td>
</tr>
<tr>
<td>Asthenia, influenza-like illness, malaise</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Uncommon</td>
<td></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>Eye disorders</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>Pain of skin</td>
<td></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>Pain in jaw</td>
<td></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>

*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**

<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>Muscular weakness, myalgia, arthropathy</td>
<td></td>
<td>Uncommon</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site pain</td>
<td>Very common</td>
</tr>
<tr>
<td>Pain, injection site oedema, injection site haemorrhage, injection site hypersensitivity, injection site irritation, asthenia, injection site reactions</td>
<td>Common</td>
<td></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</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Paraesthesia, dizziness</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eyelid ptosis</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Blepharitis, eye pain, visual disturbance</td>
<td>Uncommon</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>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>Muscle twitching</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Face pain</td>
<td>Common</td>
</tr>
<tr>
<td></td>
<td>Flu syndrome, asthenia, fever</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, hypoaesthesia, 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 Change † at Week 2</td>
<td>-2.66</td>
<td>-1.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean Change ‡ 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></th>
<th>Co-primary endpoints</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion with Positive Treatment Response using Treatment Benefit Scale (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>64.4</td>
<td>34.7</td>
</tr>
<tr>
<td>Week 6</td>
<td>68.1</td>
<td>32.8</td>
</tr>
<tr>
<td>Week 12</td>
<td>61.8</td>
<td>28.0</td>
</tr>
<tr>
<td>Daily Frequency of Micturition Episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>11.99</td>
<td>11.48</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-2.19</td>
<td>-0.82</td>
</tr>
<tr>
<td>Daily Frequency of Urgency Episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>8.82</td>
<td>8.31</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-3.08</td>
<td>-1.12</td>
</tr>
<tr>
<td>Incontinence Quality of Life Total Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>34.1</td>
<td>34.7</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>+21.3</td>
<td>+5.4</td>
</tr>
<tr>
<td>King’s Health Questionnaire: Role Limitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>65.4</td>
<td>61.2</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-24.3</td>
<td>-3.9</td>
</tr>
<tr>
<td>King’s Health Questionnaire: Social Limitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Baseline</td>
<td>44.8</td>
<td>42.4</td>
</tr>
<tr>
<td>Mean Change at Week 12</td>
<td>-16.1</td>
<td>-2.5</td>
</tr>
<tr>
<td>Percentage of patients achieving full continence at Week 12 (dry patients over a 3-day diary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27.1%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Percentage of patients achieving reduction from baseline in urinary incontinence episodes at Week 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at least 75%</td>
<td>46.0%</td>
<td>17.7%</td>
</tr>
<tr>
<td>at least 50%</td>
<td>60.5%</td>
<td>31.0%</td>
</tr>
</tbody>
</table>

† Least Squares (LS) mean changes are presented

‡ Co-primary endpoints

§ Secondary endpoints

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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 2</td>
<td>32.4</td>
<td>31.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Change† at Week 6</td>
<td>-16.8</td>
<td>-9.1</td>
<td></td>
</tr>
<tr>
<td>Mean Change† at Week 12</td>
<td>-20.0</td>
<td>-10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>-19.8</td>
<td>-9.3</td>
<td></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>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>
<tr>
<td>Percentage of patients achieving reduction from baseline in urinary incontinence episodes at Week 6 at least 75%</td>
<td>63%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† LS mean changes are presented

Secondary endpoints

I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all).

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.

<table>
<thead>
<tr>
<th>Clinical Study</th>
<th>Dose</th>
<th>BOTOX</th>
<th>Placebo</th>
<th>BOTOX</th>
<th>Placebo</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>
</tbody>
</table>

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)
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.

### 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.
Package leaflet: Information for the user

ALLERGAN®

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. See section 4.

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:
- obstructive bladder with leakage of urine, he 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 obstructive 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. 25% 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 30 episodes per week down to 10 after 10 weeks. 25% 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 when 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 corner 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 as vertical 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 have either a urinary tract infection or 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 neuron); and
- 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;
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, throat, tongue, lips, and sneezing;
• feeling faint and narrowing of vision (possible symptoms of severe allergic reaction).

General precautions

As with any injection, it is possible for the procedure to result in infection, pain, swelling, burning, stinging, increased sensitivity, tenderness, redness, and/or bleeding 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 it is not listed in this list, it could result in serious reactions, particularly in patients who already experience difficulty in swallowing or have significant dizziness.

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 ankel 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, or artificial tears or an ophthalmologist who checks 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 injections), or any medicines that affect the nerves that control muscles
• 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.
• you are using any antiplatelet (aspirin-like) products and/or anticoagulants (blood thinners).

If you have had problems in the past with previous botulinum toxin injections;
• if you have cardiovascular disease (disease of the heart or blood vessels);
• if you suffer from eye disease called closed-angle glaucoma (high pressure in the eyes) or were told you are at risk for developing this type of glaucoma;
• if you will have an operation soon;
• if you are taking any blood thinning medicine.

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicine.

Pregnancy and breast-feeding

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 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 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 data sets 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>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>2 years</td>
</tr>
<tr>
<td>Persistent muscle spasms</td>
<td>18 years</td>
</tr>
<tr>
<td>Persistent muscle spasms in the wrist, hand, and calf of patients who have suffered a stroke</td>
<td>12 years</td>
</tr>
<tr>
<td>Persistent muscle spasms in the eyelid, face</td>
<td>12 years</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 extremities</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 eyebrows and/or fan-shaped lines from the corner of the eyes</td>
<td>16 years</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.
## Dosage

<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 (hemiplegia) 6 Units/kg (diplegia)</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 per hand/wrist 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 per eye</td>
<td>3 months</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>The effects of more than four treatment sessions have not been evaluated.</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 frown</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 frown, 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 your urine (cystoscope). 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 urin 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 while 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.

For persistent muscle spasms in the legs of children who have cerebral palsy, the improvement is usually seen 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 leakage of urine due to overactive bladder, you will usually see an improvement within 2 weeks after the injection. The maximum effect is usually seen about 6 weeks after treatment.

For leakage of urine due to bladder problems associated with spinal cord injury or multiple sclerosis, you may be given a local or general anaesthetic before the procedure.

You will be observed for at least 30 minutes after the injection before you can leave. At the time of the injection, due to the procedure by which the injection is delivered into your bladder.

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.
For vertical lines between the eyebrows seen at a maximum frown, you will usually 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 fan-shaped 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
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 weeks.

If you have received too much BOTOX, you may have any of the following symptoms and you must contact your doctor immediately. 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
- Free 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.

4. Possible side effects

If you have any difficulty in 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.

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

As expected for any injection procedure, pain/burning/stinging, swelling and/or bruising may be associated with the injection.

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

- Very common: may affect more than 1 in 10 people
- Common: may affect up to 1 in 10 people
- Uncommon: may affect up to 1 in 100 people
- Rare: may affect up to 1 in 1,000 people
- Very rare: may affect up to 1 in 10,000 people

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 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

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness, increased muscle tension</td>
<td>Depression, difficulty in sleeping</td>
</tr>
<tr>
<td>Pain in the hand and fingers</td>
<td>(insomnia)</td>
</tr>
<tr>
<td>Bruising and bleeding under the skin</td>
<td>A fall in blood pressure on standing up</td>
</tr>
<tr>
<td>(causing rashespetes etc)</td>
<td>which causes dizziness, light-headedness</td>
</tr>
<tr>
<td>Bleeding, burning, pain where the injection was given</td>
<td>Nausea</td>
</tr>
<tr>
<td>Fever, flu manifestations</td>
<td>General weakness, feeling generally unwell</td>
</tr>
</tbody>
</table>

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

Injections in the legs of patients who have had a stroke

<table>
<thead>
<tr>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, joint pain or inflammation, stiff or sore muscles</td>
</tr>
<tr>
<td>Swelling of the extremities such as the hands and feet</td>
</tr>
</tbody>
</table>

Injections in the eyelid and face for muscle spasms

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drooping of the eyelid</td>
<td>Swelling of the face</td>
<td>Dizziness, weakness of the face muscles, drooping of the muscles on one side of the face</td>
</tr>
<tr>
<td></td>
<td>Pinpoint damage of the cornea (transparent surface covering the front of the eye)</td>
<td>Visual disturbance, blurred vision</td>
</tr>
<tr>
<td></td>
<td>Difficulty in completely closing the eye,</td>
<td>Double vision, inflammation of the cornea (transparent surface covering the front of the eye), abnormal burning of the eyelids outwards or inwards</td>
</tr>
<tr>
<td></td>
<td>overflow of tears, dry eyes, eye irritation and sensitivity to light</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bruising under the skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irritation</td>
<td></td>
</tr>
</tbody>
</table>

Injections in the neck and shoulder

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty in swallowing, pain, muscle weakness</td>
<td>Dizziness, sleepiness, headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feeling of weakness or generally unwell, flu manifestations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Feeling sick, dry mouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Muscle cramps, stiff or sore muscles, increased muscle tension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain where the injection was given</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td></td>
</tr>
</tbody>
</table>

Injections in the legs of children with cerebral palsy

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infection, ear infection</td>
<td>Sleepiness, problems with walking, numbness</td>
</tr>
<tr>
<td>Muscle pain, muscle weakness, pain of the extremities</td>
<td>Urinary incontinence (leakage of urine)</td>
</tr>
<tr>
<td>Feeling generally unwell or weak</td>
<td>Fell</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
</tr>
</tbody>
</table>

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with BOTOX.
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 0°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 Closunum 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
Castlebar 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 not 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 procedures 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 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 orolinguo-pharyngeal region, esophagus 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 cerebral palsy after treatment with botulinum toxin, including 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.

Refer to the Summary of Product Characteristics for complete information for BOTOX.

Reconstruction of the medial rectus muscle:

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

Reconstitute BOTOX only with sterile unpreserved normal saline (0.9% sodium chloride solution 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 vial size for all indications except bladder disorders:

<table>
<thead>
<tr>
<th>Vial Size</th>
<th>Amount of Diluent (sodium chloride 9 mg/ml) (0.9%) solution for injection added in a 100 ml vial</th>
<th>Amount of Diluent (sodium chloride 9 mg/ml) (0.9%) solution for injection added in a 200 ml vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 unit vial</td>
<td>0.25 ml</td>
<td>0.125 ml</td>
</tr>
<tr>
<td>100 unit vial</td>
<td>0.5 ml</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>200 unit vial</td>
<td>1 ml</td>
<td>0.25 ml</td>
</tr>
</tbody>
</table>

Since BOTOX is denatured by boiling 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 solution should be visibly 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, 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 - 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 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 8 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution into the 10 ml syringe and mix gently. The result will be 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.

If you 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 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.

If you 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 10 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.

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 vial of BOTOX with 8 ml of 9 mg/ml (0.9%) preservative-free sodium chloride solution for injection and mix 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.

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 6 ml from the 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 50 Unit vials of BOTOX, 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 vials into a second 10 ml syringe. 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 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.

This product is for single use only and any unused reconstituted product 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 spillages 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 on the top and bottom flaps of the BOTOX container and a holographic film on the vial label. In order to see this film,