

**Botulinum Toxin Type A Powder For Solution For Injection
(Clostridium botulinum toxin type A – Haemagglutinin complex)**

PL 06958/0028

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ipsen Limited a variation for the medicinal product Botulinum toxin type A powder for solution for injection (PL 06958/0028) on 22nd July 2010 to add the new indication of “The temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.”.

This medicine is subject to restricted medical prescription and is already indicated for arm symptoms associated with focal spasticity in conjunction with physiotherapy; and dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older, only to be administered in hospital specialist centres with appropriately trained personnel. Botulinum toxin type A is also indicated for spasmodic torticollis in adults, blepharospasm in adults, and hemifacial spasm in adults.

Botulinum toxin type A contains the active ingredient clostridium botulinum toxin type A – haemagglutinin complex. The type of injection, subcutaneous or intramuscular, and dose of Botulinum toxin type A given is dependent on the indication and should only be administered by appropriately trained physicians. Botulinum toxin type A is not recommended in the treatment of arm spasticity, spasmodic torticollis, blepharospasm and hemifacial spasm, or glabellar lines in individuals under 18 years of age.

A critical review of the clinical data presented to the MHRA demonstrated that Botulinum toxin type A powder for solution for injection is effective for the temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient. No new safety risks were identified and the safety profile of Botulinum toxin type A was considered to be acceptable. It was therefore judged that the benefits of using this product outweigh the risks, hence the variation has been granted.

Botulinum Toxin Type A Powder For Solution For Injection
(Clostridium botulinum toxin type A – Haemagglutinin complex)

PL 06958/0028

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of data on safety and efficacy the UK granted a variation to Ipsen Limited for the medicinal product Botulinum toxin type A powder for solution for injection (PL 06958/0028) on 22nd July 2010 to add the new indication of “The temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.”. This product is a restricted prescription only medicine. This variation application was submitted as a complex type II (extended) national variation. As Botulinum toxin type A powder for solution for injection (PL 06958/0028) is not currently marketed in the UK, the marketing authorisation holder (MAH) has not provided a mock-up of the patient information leaflet.

Botulinum toxin type A is already indicated for arm symptoms associated with focal spasticity in conjunction with physiotherapy; and dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older, only to be administered in hospital specialist centres with appropriately trained personnel. Botulinum toxin type A is also indicated for spasmodic torticollis in adults, blepharospasm in adults, and hemifacial spasm in adults.

Botulinum toxin type A is presented as a white lyophilised powder for reconstitution in a glass vial, with rubber stopper and aluminium seal. Following reconstitution with sterile saline Botulinum toxin type A is injected using a sterile needle, the size of which varies according to the indication.

The active constituent in Botulinum toxin type A is a *Clostridium botulinum* type A toxin-haemagglutinin complex. *Clostridium botulinum* toxin type A neurotoxin complex blocks peripheral acetyl choline release at presynaptic cholinergic nerve terminals thereby blocking impulse transmission and causing paralysis. Recovery of impulse transmission occurs gradually as new nerve terminals sprout and make contact with the post synaptic motor endplate.

The original licence (PL 06958/0028) for Botulinum toxin type A was granted on 4th May 2006 and this subsequent variation to extend the indication to include “The temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.” was granted on 22nd July 2010.

QUALITY ASSESSMENT

No new pharmaceutical data have been supplied with this application and none are required for applications of this type. Ipsen Limited Botulinum toxin A is marketed under the name Dysport, and therefore all trials using Dysport reflect the activity of Ipsen Limited Botulinum toxin A. Additional names used for Ipsen Limited Botulinum toxin A include Azzalure. Also the name Reloxin was used in clinical trials.

NON-CLINICAL ASSESSMENT

No new non-clinical data have been supplied with this application and none are required for applications of this type.

CLINICAL ASSESSMENT

INTRODUCTION

Botulinum toxin type A (PL 06958/0028) was initially licensed as a simple abridged Article 10c informed consent application cross referring to the applicant's (Ipsen Limited) existing product licence for Dysport (PL 06958/0005). The applicant has submitted this extended complex type II national variation for Botulinum toxin type A in order to add an indication for the treatment of the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.

Background

Assessor's comment: An important point to note in this application is the decentralised procedure (DCP) for Azzalure (which contains the same active substance as Dysport) and differs only by size of vials (500U for Dysport and 125U for Azzalure) both marketed by Ipsen Limited, who is also the MAH for Azzalure, however Azzalure is distributed by Galderma for the indication of

"for the temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient". The DCP procedure is now completed and the indication as written above is from the final summary of product characteristics (SmPC) for Azzalure.

The DCP procedure provided 2 pivotal trials that provided evidence of superiority of BTX-A-HAC 50U versus placebo in the reduction of moderate to severe glabellar lines, studies Y-97-52120-718 and Y-97-52120-719.

The dose finding study which preceded these pivotal trials was Study Y-97-52120-717. In addition a long-term open-label study (Study Y-97-52120-720) was provided which although primarily for safety also provided evidence of efficacy.

For the DCP procedure additional supportive studies were provided as follows:

Study 2-54-52120-046
Study A-94-52120-710
Study 2-54-52120-009 and
Study Y-97-52120-096

An additional retrospective post marketing survey (Study A-94-52120-728) was provided in the DCP procedure.

These studies were already assessed under the DCP procedure by the MHRA.

Therefore the current application is being assessed with consideration to this background information.

Supporting Evidence

For the addition of the indication "moderate to severe glabellar lines" for Botulinum toxin type A (PL 06958/0028) the following data was provided:

- Clinical overview
- Clinical summary

- **Study No. 2-54-52120 009** (A phase III, multicenter, randomised, double blind placebo controlled study of efficacy and safety of 3 total doses 25, 50 and 75 Speywood units of botulinum toxin A (Dysport) in the treatment of glabellar lines.)
- **Study No. 2-54-52120-046** (A phase III, multicentre, randomised, double blind, placebo controlled study of efficacy and safety of 2 injections of with 50 Speywood units botulinum toxin A (Dysport) in the treatment of glabellar frown lines.)
- **Study No. A-94-52120-710** (Multicentre, double-blind, placebo-controlled, randomised study to evaluate the efficacy and safety of two doses of botulinum toxin A (30 or 50 units Dysport) in the symptomatic treatment of glabellar wrinkles associated with idiopathic hypertonus of glabellar muscles)
- **Study No. Y-97-52120-717** (A phase II, Randomized, double-blind, placebo-controlled, dose-finding study to determine the optimal dose of 52120 in the treatment of glabellar lines).
- **Study No. Y-97-52120-720** (A phase III, open-label, multicentre study to assess the long-term safety of repeat administration of Reloxin in the treatment of glabellar lines: Interim analysis. April 2006.)
- **Study No. A- 8-52120-728** (Retrospective survey of the effectiveness and safety of repeated injections of botulinum toxin A Ipsen Limited (Dysport) in aesthetic medicine).
- In addition reports of post-marketing experience were also provided.

In addition the trials which supported the approval of the DCP procedure were submitted by the MAH

- **Study No. Y-97-52120-720** (A phase III, open-label, multicentre study to assess the long-term safety of repeat administration of Reloxin in the treatment of glabellar lines: Final report August 2007.)
- **Y-97-52120-718:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of 52120 (Reloxin) in the Treatment of Glabellar Lines. Study centers: 5 sites from the United States. July 2007)
- **Y-97-52120-719:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Reloxin in the Treatment of Glabellar Lines. July 2007)

Assessor's comment:

The data provided that support efficacy and safety of 50U Dysport in glabellar lines are accepted. A summary of the three main trials for the indication of glabellar line is provided under the efficacy section.

DESCRIPTION OF PROPOSED CHANGE(S)

To include the following indication:

Treatment of moderate to severe glabellar lines

Rationale

The vertical frown lines in the glabellar region are caused by contractions of the *corrugator supercilii*, *procerus* and *depressor supercilii* and *orbicularis oculi* muscles at the top of the nose. Excessive involuntary muscular contraction of these facial muscles causes deep mimetic lines that are apparent both at rest and at maximum expression. The rationale for using botulinum toxin A, injected into the hyperfunctional facial muscles, is to induce paralysis of the muscle and, in doing so, reduce the severity of the facial lines.

Background.

Dysport is a botulinum Type-A toxin-haemagglutinin complex isolated and purified from the bacterium *Clostridium botulinum*. Dysport was first licensed on 6th December 1990 in the United Kingdom for the treatment of blepharospasm and hemifacial spasm. Dysport has since been approved for use in paediatrics for cerebral palsy spasticity, and for use in adults for spasmodic torticollis and it is currently licensed for most of these indications in the European Union as well as in more than 73 additional countries worldwide.

The possible cosmetic applications of botulinum toxin A were discovered in 1987, when it was found that treatment of blepharospasm also resulted in a smooth and relaxed appearance of the glabellar area. The facial expressions involving the exaggeration of these lines indicate socially negative emotions such as anger, sadness, fear or anxiety. Individuals with exaggerated glabellar frown lines often complain to be considered by others as angry when they are not.

Assessor's comment: *For severe glabellar lines there could be a misinterpretation of affect by others as stated by the MAH:*

"Individuals with exaggerated glabellar frown lines often complain to be considered by others as angry when they are not".

This implies that some individuals may suffer from psychological ill effects from their glabellar lines.

As the indication for glabellar lines has already been approved for those in whom there is an important psychological impact this indication for Dysport is in line with other similar therapies.

Excessively prominent and cosmetically displeasing facial lines have been treated by a number of remedies: facelift, surgical excision, resurfacing procedures using laser, acid peels or dermabrasion or soft tissue fillers. **However, in order to choose the most appropriate therapy, distinction must be made between facial lines created by loss of collagen or elastic fibres within the dermis or volumetric loss of fat, and those caused by hyperfunctional facial muscles.**

The rationale for using botulinum toxin A, injected into the hyperfunctional facial muscles, is to induce temporary/reversible paralysis of the muscle and, in doing so, reduce the severity of the facial lines.

From the positive results obtained by anatomically-directed injections of botulinum toxin A reported in the literature, both in terms of relative ease of treatment, effectiveness in established treatment-refractory glabellar lines, and local and general safety, the MAH undertook a clinical development program to establish the efficacy and safety of botulinum toxin A, in the treatment of glabellar lines. Of note is that the glabellar lines indication has been approved in 18 countries including Germany, Australia, Russia, New

Zealand, Argentina, Belarus, Columbia, Honduras, Israel, Mexico, Republic of Moldova, Ukraine, Uruguay and Vietnam.

The clinical development program of botulinum toxin A in the cosmetic treatment of hyperkinetic glabellar lines comprises a total of six clinical studies conducted by Ipsen Limited. There were two phase II randomized, placebo-controlled, double-blind dose-ranging studies conducted in Europe and North-America for the glabellar line indication:

Study Y-97-52120-717 (**717**) was conducted in four centres in the USA and one centre in Canada, and comprised four parallel groups of patients receiving a single glabellar treatment of five injections with placebo or at a total dose of 20, 50 and 75 units of botulinum toxin A, respectively. Results of this study together with study **009** (which was a phase III dose finding study (see below)) led to the selection of the dose of 50 units in five glabellar injections as the recommended dose in the claimed indication.

- Study 2-54-52120-009 conducted in three centres in France evaluated a single treatment with 25, 50 and 75 units of Dysport or placebo
- Study Y-97-52120-717 was conducted in four centres in the USA and one centre in Canada, and comprised four parallel groups of patients receiving a single glabellar treatment of five injections with placebo or at a total dose of 20, 50 and 75 units of botulinum toxin A, respectively.

Results of these two studies led to the selection of the dose of 50 units in five glabellar injections as the recommended dose in the claimed indication.

There were also two Phase III efficacy studies:

- Study 2-54-52120-046 conducted in France, included a double-blind placebo controlled phase followed by an open-label phase. This study, which was carried out at the selected dose of 50 units, was specifically designed to determine, in a practical manner, the optimal interval between a first and a subsequent treatment of glabellar lines with Dysport.
- Study A-94-52120-710 was conducted in Germany and Austria. It comprised separate placebo-controlled evaluations of two doses: 30 units and 50 units. It differed from the three other studies by the different location of the glabellar injection sites and the different definition of the efficacy endpoints. Nevertheless, this supportive study confirmed the efficacy of Dysport in the cosmetic treatment of glabellar lines.

There was one pivotal phase III safety study

- Study Y-97-52120-720, an open-labelled multicentre study to assess the long-term safety of repeat administration of 50 units of botulinum toxin A across 5 injection sites, is currently ongoing at 21 centres in the USA. An interim report of this study is also included in this document which provides supportive efficacy data for the treatment of glabellar lines

Further safety data and supportive efficacy data has been generated from the following additional retrospective study:

- A German retrospective survey of the effectiveness and safety of repeat injections of repeated injections of botulinum toxin A (Dysport) in aesthetic medicine (A-28-5212-728).

Regulatory guidance and advice were sought from the scientific and regulatory agencies to design the French and North American trial protocols. For the two French trials, 2-54-52120-009 and 2-54-52120-046, scientific advice was obtained from the *Agence Française de Sécurité Sanitaire des Produits de Santé* (AFSSAPS) on 22 October 2001 and protocol approvals were obtained thereafter. For the North-American trial, Y-97-52120-717, an Investigational New Drug (IND) application was filed with the Division of Vaccines and Related Product Application of the Food and Drug Administration (FDA) on 06 October 2002 following a pre-IND meeting held on 21 April 2002 for scientific advice. Further scientific advice was obtained from the FDA on 19 December 2002.

All seven trial protocols were approved by the Independent Ethics Committees or Review Boards. All seven trials were conducted in accordance with the principles of the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH) and in keeping with the local legal requirements.

The seven clinical studies and the survey are supported by three other reports prepared by Ipsen following a review of the Company databases in 2004 and 2005;

- A review of the available data on neutralising antibody formation and testing to Dysport. The information sources reviewed include; (i) clinical trials conducted by Ipsen, (ii) published literature in which Dysport was clearly identified and (iii) post-marketing surveillance data. Report dated November 2004.
- An overview of Ipsen Limited prospective post-marketing studies and retrospective repeat dose Dysport studies which summarises the safety data collected from studies in order to help understand the effect of repeat exposure to Dysport. The studies predominantly collected data on high dose indications such as cervical dystonia and arm spasticity. In total the study reviews about 3000 patients exposed to 8205 cycles of Dysport treatment. Report dated January 2005.

Assessor's comment: *The limitation of this overview of post-marketing studies is in addressing the risk of muscle atrophy following injection in glabellar lines. Whereas muscle atrophy is less likely after Dysport administration into hypertrophied spastic muscles and some degree of atrophy may be a positive outcome, this is not the case for normal facial muscles – where even a small degree of atrophy is expected to affect the contours of the face. This question was put to the MAH. The MAH responded that there was no evidence of muscle atrophy in prospectively conducted clinical trials in the glabellar lines indication (009, 046, 717, 718, 719 and 720) including the long term repeated dose study 720 in which 1200 patients received up to 5 cycles of treatment. This response was accepted and the issue was considered resolved.*

- A cumulative review of skin tolerance and dermatological effects which specifically addresses skin tolerance of Dysport from the available data; clinical trials, published literature and post-marketing surveillance data. Report dated May 2005.

OVERVIEW OF CLINICAL PHARMACOLOGY

No clinical pharmacology studies were conducted with Dysport. However, despite the relative lack of information on the pharmacokinetics of the botulinum toxin A in human, there is a large body of published literature to document the pharmacodynamics, mechanisms of action and clinical potential of the toxin.

Pharmacokinetics

Rigorous pharmacokinetic studies of botulinum toxin A could not be conducted due to the technical difficulties involved in such studies: use of minute dose, difficulty of labelling the molecule with appropriate specific activity and thus difficulty in obtaining measurable plasma levels. However, established and probable/putative pathways of distribution, based on electrophysiological and electromyographic studies have been published (Moore 2003). Pathways may include haematogenous spread to distant muscle, trans-synaptic transfer at the same segmental or an adjacent segmental level within the cord, and anterograde spread to distant muscle.

From the clinical experience with the toxin, the clinical implications of such mechanisms are probably minimal and, if anything, limited to high doses (Gury 2002, Moore 1995, Klein 2003).

Assessor's comment: *These methods of action and spread are pertinent to the adverse events that follow treatment for glabellar lines.*

The fate of the toxin molecule within the nerve cell is unknown. The recovery of the nerve terminal function presumably depends on the rate at which the toxin is cleared from or metabolized by nerve endings and the rate at which the nerve cell repairs damaged SNAP-25 (Klein 2003, Frampton et al 2003).

Pharmacodynamics

Briefly summarized, the mechanism of the neurotoxic action of botulinum toxin A involves three steps:

- (i) the irreversible binding of the toxin to presynaptic acceptors;
- (ii) the subsequent internalisation of the neurotoxin through an acceptor-mediated endocytosis which is a complex process: the toxin is first encapsulated in an endosome which migrates into the cytoplasm of the neurone; the lipophilic sites of the heavy chain enables the passage of the di-chain toxin through the endosomal membrane;
- (iii) the neuromuscular blockade: once liberated into the cytoplasm of the neurone terminal, the disulphide bond of the toxin di-chain is cleaved, and the light chain which contains a highly specific zinc endopeptidase concentrates at the terminal; it cleaves one of the SNARE protein isoforms (SNAP-25) which is involved in the exocytosis of acetylcholine vesicle into the synaptic cleft, thus preventing acetylcholine release (Huang et al 2000, Gury 2002).

Binding and internalisation of the toxin at the presynaptic nerve end is a rapid process which may take as little as 30 to 60 minutes and is enhanced in neurones of actively contracting muscle. Thus, patients treated with botulinum toxin A are often instructed to exercise the injected muscle(s) for up to one hour after injection (Huang et al 2000).

The toxin does not inhibit acetylcholine synthesis or storage, nor does it affect the excitability or conductivity of nerves or the contractility of muscles. The blockade of acetylcholine release into the neuromuscular junction causes a chemical denervation of the muscle, with possible atrophy as a result.

Assessor's comment: Possible atrophy following repeated injections raises concern. Publications draw attention to the observation that long-term use is affected by the balance between hypertrophy of untreated muscles and atrophy of treated muscles (Moriarty, 2005). Other publications on atrophy of muscles following Botulinum toxin have been published (Guyuron et al, 2004, Lee et al 2007). In a paper by Kim et al (2005) the authors propose that Dysport injection can replace surgical masseter reduction. The evidence for muscle atrophy from these papers raises concern that the short-term treatment of a non-medical condition could lead to significant facial re-contouring. This question was posed to the MAH who responded with information demonstrating that muscle atrophy for the proposed indication is extremely rare. The response was considered adequate but muscle atrophy may pose a problem for those who have frequent repeated use. The recommendation in section 4.4 of the SPC that the recommended posology and frequency of administration must not be exceeded with a reference to section 4.2 of the SmPC is considered satisfactory to advise the treating physician regarding safe use. Note that section 4.2 of the SmPC states that treatment intervals should not be more frequent than every three months. In addition the MAH has included the following comment in section 4.4 of the SmPC regarding caution with muscle atrophy "Caution should be taken when the targeted muscle shows excessive weakness or atrophy".

However, studies in human muscle fibres of treated patients as well as in a rabbit model have shown that both denervation and atrophy are reversible and, after four to five months, recovery from denervation occurs by neuroneogenesis (Huang et al 2000, Gury 2002).

Data submitted by the MAH suggest that the incidence of muscle atrophy in patients injected with Dysport in the glabellar area at the doses approved is extremely low and is not clinically considered as a matter for concern.

Assessor's comment: This information that denervation and atrophy are reversible and recovery from denervation occurs after 4-5 months by neuroneogenesis is relevant in consideration of the minimum time interval for re-treatment. What are the time-frames for full recovery from muscle atrophy? In addition if frequent re-treatment occurs at the minimum interval specified in the SmPC (3 months) is there any evidence that smaller doses of Dysport are required in subsequent cycles? Are there any reports of irreversible muscle atrophy/fibrosis after excessive cosmetic use? The MAH is asked to comment.

The applicant has provided a recently completed three-month intramuscular toxicity study with 13- and 26-week follow-up in the rat, results of which suggest that the effects of 3 repeated monthly treatments of Dysport, at high doses compared to the recommended doses at each injection site in humans, are fully reversible clinically (locomotor activity) after 17 weeks and appear to cause no long-term impairment of the neuromuscular junctions.

In addition, the applicant conducted a search of the database of the applicant-sponsored studies 009, 046, 717, 718, 719 and 720 (the long term repeated dose study in which 1200 patients received up to 5 cycles of treatment) which revealed no reports of muscle atrophy or fibrosis.

Assessor's comment and conclusion,
The position that a dose-reduction is not required over successive treatments is accepted. Point resolved.

The pharmacodynamic mechanism of action of botulinum toxin A is the basis of its therapeutic applications and of its expected adverse effects. According to the Company Core Safety Information, the toxin must be used with caution in patients with subclinical or clinical evidence of marked defective neuromuscular transmission disorders such as Lambert-Eaton syndrome or myasthenia gravis which are likely to enhance its paralysing effect. Likewise, botulinum toxin A should be used with care in the presence of drugs interfering either directly or indirectly with the neuromuscular function (e.g. curare-like non-depolarising blockers, aminoglycosides, etc) (Huang et al 2000, Gury 2002, Vartanian et al 2003).

Supportive data on safety

A-94-52120-728 was a retrospective survey of the effectiveness and safety of repeated injections of Botulinum toxin A Ipsen Limited (Dysport) in aesthetic medicine performed at 21 centres in Austria and Germany. The objectives were to evaluate the effectiveness and safety of Dysport in aesthetic medicine as experienced in actual use in a large number of patients with particular reference to the effects of repeated doses. This was a retrospective, anonymised survey of patient records and 945 patient records were analysed.

Diagnosis and main criteria for inclusion were:

Receipt of at least three consecutive documented aesthetic treatment cycles with Dysport in the upper third of the face.

Criteria for evaluation:

- Effectiveness
- Structured questionnaire;
- physician and patient rating of treatment success of each cycle as recorded in patients' records.
- Final assessment at end of treatment period covered by the survey.

Concomitant treatment: record of previous and concomitant other aesthetic treatments

Safety

Structured questionnaire; particularly concentrating on (but not restricted to) known adverse events (AE) after facial/aesthetic injections: local pain, haematoma, ptosis, skin reactions, dry eye and vision disturbances.

Exploratory/descriptive (non-interventional).

Effectiveness results:

Data was collected from 4103 treatment cycles in 945 patients. All the patients had three treatments with Dysport, 76% four treatments and 59% five treatments. Most of the patients were women (94%) of middle age (30-59 years: 85%, 40-49 years: 36%).

The satisfaction with the treatment expressed by both patients and physicians was very high (88-99%) throughout the treatment cycles recorded, showing a slight increase in later cycles. At the end of the treatment period studied, 77% of the patients expressed a wish to continue with treatment, 21 % were undecided or had lost contact and only 2% definitely decided not to continue with treatment. None explicitly decided to discontinue treatment because of lack of effectiveness or AE.

Nearly half of the patients had no previous aesthetic treatment before (48%) or concomitant aesthetic treatment during (43%) the Dysport treatment. For those patients

that did have other aesthetic treatment, the use of fillers was the most frequent intervention (before: 28%, during: 37% of patients).

Average doses of Dysport were in agreement with published guidelines and remained constant throughout treatment cycles.

Table 1. Recorded Dysport dose (median, mean±SD) in units for the three areas in the upper face

Area	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
Glabella	60, 60 \pm 21	50, 59 \pm 21	50, 58 \pm 21	50, 55 \pm 18	50, 53 \pm 16
Frontalis	53, 55 \pm 23	50, 54 \pm 23	50, 53 \pm 23	50, 52 \pm 23	50, 53 \pm 25
Lateral Periorbital*	50, 53 \pm 21	50, 54 \pm 22	50, 53 \pm 20	50, 51 \pm 18	50, 49 \pm 17

*Sum of both sides

The most frequently injected area was the glabella (94% of patients) but the majority (81.5%) of patients received treatment in more than one area of the upper face. Injections in frontalis+glabella+lateral periorbital (i.e. all three areas of the upper face) were the most common (31%) followed by frontalis+glabella (18%) and glabella+lateral periorbital (16%). In those patients where only one area was treated, this was usually the glabella (15%), followed by lateral periorbital (3%) and frontalis (1%). Other areas of the face were also treated in 17% of the patients. The median time between injections remained constant at approximately 6-7 months throughout the cycles.

Table 2. Time interval (months) between cycles (median, mean±SD)

Cycle 1-Cycle 2	Cycle 2-Cycle 3	Cycle 3-Cycle 4	Cycle 4-Cycle 5
5.9, 6.8 \pm 4.2	6.2, 7.3 \pm 4.3	6.2, 7.0 \pm 3.7	6.5, 7.4 \pm 3.5

Shorter (< 2 weeks) injection intervals were associated with “touch up” injections to correct unsatisfactory results.

Safety results:

No serious adverse events (SAE) were reported. Nearly all AEs reported were mild or moderate and a specific treatment for the AE was only recorded in 7 cases (from 4103 treatment cycles). The most common AE was local haematoma (1.25% of treatment cycles), followed by brow or lid ptosis (0.46% of treatment cycles, 0.51% of treatment cycles after injections to glabella and/or frontalis). Local pain was reported in 0.37% of treatment cycles, local skin irritation in 0.24%, other skin changes in 0.12% and dry eye or vision disturbance in 0.12%. The haematoma and ptosis rates were similar to those reported in four Ipsen sponsored controlled clinical trials of Dysport injections for glabella frown lines (haematoma: 0.65-0.88% per treatment cycle [including placebo injections]; ptosis: 0.59% per verum treatment cycle). The somewhat higher haematoma rates in this study are probably due to the larger number of injection cycles per treatment.

There was no evidence of any cumulative, unexpected or long term effects. The overall AE rate per cycle decreased with repeated treatments: 4.1%, 2.1%, 2.3%, 1.7% and 2.0% for cycles 1, 2, 3, 4 and 5 respectively. There was little apparent effect of dosage on AE rate. When the dose administered for patients showing an AE at any cycle, was analysed over cycles, there was no clear change compared with those showing no such AE.

There was also no obvious effect of site of injection on AE rate. There was some evidence that injections in the frontalis were associated with a slightly higher incidence of

AE but the numbers of reports in any one category were too small to allow a statistical analysis.

Conclusions:

This survey provides a representative picture of the effectiveness and safety of the actual practice of use of repeated Dysport treatments in aesthetic medicine in Germany and Austria and complements the information obtained from controlled clinical trials. The efficacy and safety profile of Dysport in this indication, as demonstrated in controlled clinical trials was confirmed. There was no indication of any loss of effectiveness with repeated cycles. The same conclusion can be made for the safety data. The AEs reported were nearly all mild or moderate and the rate decreased somewhat for cycles subsequent to cycle 1. The most frequent AE was local haematoma in 1.25 % of cycles. Mild or moderate ptosis was the next most frequent AE in 0.46% of cycles. There was no indication of unexpected or cumulative effects.

Assessor's comments: *The retrospective study summary (A-94-52120-728) provides some reassuring information on the safety of repeated treatment courses for aesthetic indications.*

Pivotal Efficacy Studies

Study Y-97-52120-718

A Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of 52120 (Reloxin) in the treatment of glabellar lines. Study centres: 5 sites from the United States

Objectives:

The primary objective of this study was to demonstrate the efficacy of a single treatment of Reloxin (50 units) compared with placebo in the treatment of glabellar lines. This objective was evaluated 30 days post-treatment (Day 30) using the co-primary endpoints of the Investigator's assessment of glabellar lines at maximum frown (using a validated 4-point Photographic Scale of Glabellar Line Severity [Study Photographic Scale]) and the patient's assessment of glabellar lines at maximum frown (using a static 4-point categorical scale).

The safety of a single treatment of Reloxin (50 units) compared with placebo was also assessed.

Secondary objectives were:

- To determine efficacy with respect to independent panel reviewers' (IPRs') assessment of photographs of the patient's glabellar lines at maximum frown at Day 30, using the Study Photographic Scale.
- To determine efficacy with respect to the Investigator's live assessment of glabellar lines at maximum frown at Days 14, 60, 90, 120, and 150 (using the Study Photographic Scale) (for Day 14 only, this assessment was performed using photographs rather than live evaluations).
- To determine efficacy with respect to the Investigator's live assessment of glabellar lines at rest at Days 14, 30, 60, 90, 120, and 150 (using the Study Photographic Scale) (for Day 14 only, this assessment was performed using photographs rather than live evaluations).
- To determine efficacy with respect to the patient's self-assessment of glabellar lines at maximum frown at Days 14, 60, 90, 120, and 150 (using a static 4 point categorical scale).
- To determine efficacy with respect to the patient's global self-assessment of the change in appearance of glabellar lines at Days 14, 30, 60, 90, 120, and 150 (using a 9-point dynamic scale).

- To determine onset of treatment response based on the patient's assessment of glabellar lines, as recorded on a diary card from Days 1 to 7.
- To determine duration of treatment response based on the Investigator's assessment of glabellar lines at maximum frown (using the Study Photographic Scale) and the patient's assessment of glabellar lines at maximum frown (using a 4-point categorical scale).

Methodology: Randomized double-blind placebo-controlled study
Number of patients (planned and analyzed): 300

Criteria for inclusion and exclusion:

Inclusion Criteria

Male and female patients who met all of the following criteria were eligible.

- Eighteen years of age or older.
- Moderate to severe vertical glabellar lines (score of [2] or [3]) at maximum frown by the patient's assessment, using a static 4-point categorical scale. The patient's static assessment must have been performed prior to, and independent of, the Investigator's live assessment at maximum frown.
- Moderate to severe vertical glabellar lines (score of [2] or [3]) at maximum frown by the Investigator's assessment, using a Study Photographic Scale.
- Negative pregnancy test result for women of childbearing potential.
- Time and ability to complete the study and comply with instructions.
- Understanding of the study and the contents of the informed consent.

Exclusion Criteria

Patients who met any of the following criteria were not eligible.

- Previous treatment with Reloxin or other botulinum toxin.
- Inability to substantially lessen glabellar lines by physically spreading them apart.
- Soft tissue augmentation of the glabella (e.g., collagen-type implants, such as Zyderm or Zyplast) within the previous 12 months.
- Permanent or semi-permanent dermal fillers in the glabellar area.
- Ablative skin resurfacing on the glabellar area within the previous 12 months.
- Non-ablative dermal treatment of the glabellar area (e.g., light-emitting diodes, intermittent pulse light, laser, and radio-frequency treatments) within the previous 12 months.
- Upper eyelid blepharoplasty or brow lift within 12 months of the study.
- Retinoid, microdermabrasion, or glycolic acid treatments to the glabellar area within 2 weeks prior to study participation.
- Concurrent therapy that, in the Investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study medication.
- Active infection in the glabellar area (e.g., acute acne lesions or ulcers).
- Pregnant women, nursing mothers, or women who were planning pregnancy during the study, or think they might have been pregnant at the start of the study. Throughout the study, women of childbearing potential were to use reliable forms of contraception (e.g., abstinence, oral contraceptives for >12 consecutive weeks, or spermicide and condoms).
- Current history of chronic drug or alcohol abuse.
- Enrolment in any active study involving the use of investigational devices or drugs.
- History of facial palsy.
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.

- Neuromuscular junctional disorders (e.g., myasthenia gravis).
- Known allergy or hypersensitivity to any botulinum toxin or any component of Reloxin.
- Clinically diagnosed anxiety disorder, or any other significant psychiatric disorder (e.g., depression) that, in the opinion of the Investigator, might interfere with the patient's participation in the study.
- Concurrent use of medications that affect neuromuscular transmission, such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases, and aminoglycoside antibiotics.

Test product, dose and mode of administration, batch number:

Reloxin was administered at 5 injection points in the glabellar region (0.25 mL total; 0.05 mL [10 units] per injection point).

Reference therapy, dose and mode of administration, batch number:

Placebo Lot Number 034 (0.25 mL total; 0.05 mL per injection point) administered at 5 injection points in the glabellar region (n=100).

Duration of treatment: One treatment on Day 0

Criteria for evaluation:

Efficacy:

The patient's self assessment of appearance of glabellar lines at maximum frown on Day 30, using a four point categorical scale (no wrinkles [0], mild wrinkles [1], moderate wrinkles [2], or severe wrinkles [3]). The patient's self assessment had to be made prior to, and independent of, the Investigator's live assessment at each visit. The Investigator's live assessment of glabellar lines at maximum frown on Day 30, using a validated four point Photographic Scale (Study Photographic Scale) of Glabellar Line Severity (none [0], mild [1], moderate [2], or severe [3]). A written description of each photograph was included to help standardize the Investigator's application of the Study Photographic Scale. For each scale, a responder was defined as having a severity grade of none [0] or mild [1] at maximum frown on Day 30 and a severity grade of moderate [2] or severe [3] at maximum frown at Baseline (Day 0, pre treatment). The efficacy endpoint was the proportion of responders at Day 30.

Safety:

Monitoring of adverse events (AEs) throughout the study, vital signs at screening, Day 0, 7, 14, 30 and at every monthly visit, clinical laboratory parameters at screening and Day 150, and presence of neutralizing antibodies to Clostridium botulinum type A toxin at Day 0 and Day 150.

Statistical methods:

The analysis of safety data was generally descriptive in nature. Patient data were summarized by treatment group using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum). Categorical data were summarized by treatment group using frequency tables (frequencies and percentages). In summaries of the efficacy data, 95% confidence intervals (95% CIs) were constructed for the proportions of responders in each group and overall, and for the differences between treatment groups. All summaries of safety data were based on the Safety population, which was defined as all treated patients. All summaries of efficacy data were based on the intent-to-treat (ITT) population which was defined as all randomized patients who received any study treatment and the modified intent-to-treat population (MITT), which excludes site 05 from the analysis. Patients from this center (20% of the ITT population) were excluded from the ITT population due to protocol deviations such as unavailability

of original source documentation, study documentation not completed in real-time, and study activities completed in an incorrect sequence. Despite these problems, all patients at Center 05 were treated per the protocol and there were no important protocol violations. The statistical analysis plan also allowed for analyses using the perprotocol (PP) population, which was defined as all randomized patients who received any study medication and who were not major protocol violators. In the Safety, ITT, and PP populations no major protocol violations occurred and all randomized patients received study medication, therefore the populations were identical.

Summary - conclusions:

Efficacy results:

A single dose of 50 units of Reloxin was shown, by multiple measures, to be effective compared with placebo using accepted and clinically meaningful measures. Both co-primary endpoints were met, thus meeting the definition of clinical success. At Day 30, the proportion of responders was statistically greater in the Reloxin treated group compared to placebo based on the Investigator assessment at maximum frown ($p < 0.001$) and the patient's self-assessment ($p < 0.001$).

These results were supported by greater response rates at Day 30 in the Reloxin versus placebo group as assessed by independent reviewers (0.959 vs 0.026) and further by Investigator's assessment of glabellar line severity at rest (0.727 vs. 0.100).

The median time to onset of response in the Reloxin treatment group was two days and by seven days, the cumulative percent of responders was 90.0% whereas, in placebo treated patients, 9.0% were responding at seven days. In the Reloxin group, the median duration of response was 117 days for both the Investigator and patient assessments. The duration of response in the placebo group was calculated to be 33 days from Investigator assessments at maximum frown ($n=6$ responders), and 150 days from the patient assessments ($n=7$ responders). However, these calculations were made on a very small number of responders and are not considered to be clinically meaningful. Had the placebo patients who did not respond to treatment been included with a duration value of 0 days, the median duration for both assessments would have been 0 days.

The proportion of responders exhibiting a response to treatment was statistically significantly greater at every time point in the Reloxin group throughout the 150 day study by Investigator's assessments at maximum frown, patient self-assessment and Investigator assessment at rest.

The patient's global self-assessments showed a maximum proportion of responders in the Reloxin treatment group at Day 14 of 0.932 versus 0.02 in the placebo group. At every visit thereafter, the proportion of patients exhibiting a response to treatment was greater in the Reloxin group than in the placebo group. The results of each of the MITT analyses confirmed the results of the analysis of the ITT population.

Safety results:

A single treatment with 50 units of Reloxin was well-tolerated.

The percentages of patients experiencing one or more TEAEs were similar in the Reloxin treatment and placebo groups (52% and 43%, respectively). The Reloxin treated patients experienced more eye disorder TEAEs than the placebo group (8% versus 0%). The majority of all TEAEs reported were mild or moderate in intensity, and severe TEAEs were experienced by only 4% of Reloxin treated patients and 3% of placebo treated patients.

The majority of TEAEs were considered by the Investigator to be unrelated or unlikely to be related to study medication. However, more TEAEs reported by the Reloxin treated patients than the placebo patients (50 [0.25 events per patient versus 15 [0.15 events per patient]) were considered to be probably or possibly related to study medication. There were two cases of mild ptosis reported in the Reloxin treatment group, both

occurring at the same center, considered by the Investigator to be probably and possibly related to study medication.

There were no deaths during the study. Five patients experienced serious TEAEs, four in the Reloxin treatment group and one in the placebo group. None of the serious TEAEs was considered to be related to study medication, and no patient withdrew from the study because of a serious TEAE.

No clinically significant changes were observed in the hematology, clinical chemistry or vital signs during the study. Additionally, no patients produced neutralizing antibodies to Reloxin.

Conclusions:

A single treatment with 50 units of Reloxin, when compared with placebo, is highly efficacious in ameliorating moderate or severe glabellar lines at 30 days after injection, as assessed both by Investigators and patients. The median time to onset of effect of 50 units of Reloxin is two days. The median duration of response was 117 days for both the Investigator and patient assessments. A single treatment with 50 units of Reloxin is well-tolerated. The safety profile of the Reloxin is very similar to placebo in terms of type, frequency, severity, and relatedness, except for TEAEs occurring around the eyes, where a higher frequency was observed in the Reloxin treatment group.

Assessor's comment: Efficacy was clearly demonstrated from Study Y-97-52120-718 and was assessed in the DCP procedure for Reloxin.

Y-97-52120-719 Study report

Title of study: A phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of Reloxin in the treatment of glabellar lines

Study centres: 3 sites in the USA

Study period: 180 days for each patient

Date of first patient enrolled: November 18, 2005

Date last patient completed: July 28, 2006

Objectives:

The primary objective of this study was to demonstrate the safety and efficacy of a single treatment of Reloxin (50 units) compared with placebo in the treatment of glabellar lines at 30 days post-treatment. This objective was evaluated using the co-primary endpoints of the Investigator's live assessment of glabellar lines at maximum frown (using a validated 4-point Study Photographic Scale of Glabellar Line Severity [Study Photographic Scale]) and the patient's self-assessment of glabellar lines at maximum frown (using a static 4-point categorical scale). These data are presented both individually and as a Composite Response at Day 30. For each scale, a responder was defined as having a severity grade of moderate [2] or severe [3] at maximum frown at Baseline and a severity grade of none [0] or mild [1] at maximum frown at Day 30.

The safety of a single treatment of Reloxin (50 units) compared with placebo was also assessed throughout the study by the monitoring of AEs, vital sign measurements and clinical laboratory parameters. Serum samples were collected and will be analyzed for presence of antibodies to Reloxin (Clostridium botulinum type A toxin-hemagglutinin complex) and presented in a separate report with data captured across the entire Reloxin clinical program.

Supportive objectives were:

- To determine efficacy with respect to Independent Reviewer's assessment of photographs of the patient's glabellar lines at maximum frown at Day 30 (using the Study Photographic Scale).
- By USA FDA request, to determine response rate where a response is defined as a glabellar line severity score of [0] or [1] but with a minimum of a 2- grade improvement from the Baseline score of [2] or [3] at Day 30 by:
 - a. the Investigator's live assessment
 - b. the patient's self-assessment
 - c. the Composite Response of 2-grade improvement on both Investigator's live assessment and patient's self-assessment.
- To determine efficacy with respect to the Investigator's live assessment of glabellar lines at maximum frown at Days 14, 60, 90, 120, 150, and 180 (using the Study Photographic Scale) (for Day 14 only, this assessment was performed using photographs rather than live evaluations).
- To determine efficacy with respect to the Investigator's live assessment of glabellar lines at rest at Days 14, 30, 60, 90, 120, 150, and 180 (using the Study Photographic Scale) (for Day 14 only, this assessment was performed using photographs rather than live evaluations).
- To determine efficacy with respect to the patient's self-assessment of glabellar lines at maximum frown at Days 14, 60, 90, 120, 150, and 180 (using a static 4-point categorical scale).
- To determine efficacy with respect to the patient's global self-assessment of the change in appearance of glabellar lines at Days 14, 30, 60, 90, 120, 150, and 180 (using a 9-point dynamic scale).
- To determine onset of treatment response based on the patient's assessment recorded on a diary card from Day 1 through Day 7 or based on a score of none [0] or mild [1] using Investigator's assessment at maximum frown on Day 14 (visit 2) or a score of no wrinkles [0] or mild wrinkles [1] based on patient's self-assessment at maximum frown on Day 14 (visit 2).
- To determine duration of response, defined as the time (number of days) from onset of response as recorded on the patient's diary card or by Investigator's assessment at maximum frown on Day 14 or patient's self-assessment at maximum frown on Day 14, to reappearance of a severity grade of [2] or [3], based on the Investigator's live assessment at maximum frown. Patients who do not respond by Day 14 are included in the analysis with a zero duration. Patients who did not return to a score of [2] or [3] following onset of response were censored at the time of study completion/withdrawal.
- To determine duration of response, defined as the time (number of days) from onset of response as recorded on the patient's diary card or by Investigator's assessment at maximum frown on Day 14 or patient's self-assessment at maximum frown on Day 14, to reappearance of a severity grade of [2] or [3], based on the patient's self-assessment at maximum frown. Patients who do not respond by Day 14 are included in the analysis with a zero duration. Patients who did not return to a score of [2] or [3] following onset of response were censored at the time of study completion/withdrawal.

Methodology

Multi-center, Phase 3, randomized, parallel-group, placebo-controlled, double-blinded study

Number of patients:

158 patients were enrolled in the study; 105 were treated with Reloxin and 53 were treated with placebo. Of the 158 patient enrolled, 143 completed the study.

Criteria for inclusion and exclusion:

Inclusion Criteria

- Eighteen years of age or older.
- Moderate to severe vertical glabellar lines (score of [2] or [3]) at maximum frown by the patient's assessment, using a static 4-point categorical scale. The patient's static assessment must have been performed prior to, and independent of, the Investigator's live assessment at maximum frown.
- Moderate to severe vertical glabellar lines (score of [2] or [3]) at maximum frown by the Investigator's assessment, using a Study Photographic Scale.
- Negative pregnancy test result for women of childbearing potential.
- Time and ability to complete the study and comply with instructions.
- Understanding of the study and the contents of the informed consent.

Exclusion Criteria

Patients who met any of the following criteria were not eligible:

- Previous treatment with Reloxin or other botulinum toxin or toxin treatment (other than study treatment) to any areas of the body at any time (prior to or during the study) (i.e., patients were naïve to therapeutic botulinum toxin complex).
- Inability to substantially lessen glabellar lines by physically spreading them apart.
- Soft tissue augmentation of the glabella (e.g., collagen-type implants, such as Zyderm or Zyplast) within the previous 12 months or during the study.
- Permanent or semi-permanent dermal fillers in the glabellar area at any time.
- Ablative skin resurfacing on the glabellar area within 12 months or during the study.
- Upper eyelid blepharoplasty or brow lift within 12 months of the study or during the study.
- Non-ablative treatments in the glabellar area for skin dyschromias (e.g., Intense Pulsed Light, light-emitting diodes) within the previous 12 months or during the study.
- Non-ablative dermal treatment in the glabellar area for skin tightening (e.g., radio-frequency treatments) within the previous 12 months or during the study.
- Retinoid, microdermabrasion, or prescription level glycolic acid treatments to the glabellar area within two weeks prior to study participation or during the study.
- Concurrent therapy that, in the Investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study medication.
- Active infection in the glabellar area (e.g., acute acne lesions or ulcers).
- Pregnant women, nursing mothers, or women who are planning pregnancy during the study, or think they may be pregnant at the start of the study. Throughout the course of the study, women of childbearing potential must use reliable forms of contraception (e.g., abstinence, oral contraceptives for more than 12 consecutive weeks prior to enrolment, or spermicide and condoms).
- Current history of chronic drug or alcohol abuse.
- Enrollment in any active study involving the use of investigational devices or drugs.
- Current facial palsy.
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.
- Neuromuscular junctional disorders (e.g., myasthenia gravis).

- Known allergy or hypersensitivity to any botulinum toxin or any component of Reloxin.
- Clinically diagnosed anxiety disorder, or any other significant psychiatric disorder (e.g., depression) that, in the opinion of the Investigator, might interfere with the patient's participation in the study.
- Concurrent use of medications with Reloxin treatment that affect neuromuscular transmission, such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases affecting the striated muscle, and aminoglycoside antibiotics.
- Presence of any other condition (e.g., neuromuscular disorder or other disorder that could interfere with neuromuscular function) or circumstance that, in the judgment of the Investigator, might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.

Test product, dose and mode of administration, batch number:

Reloxin (50 units total [0.25 mL]; 10 units [0.05 mL] per injection point) administered at 5 injection points in the glabellar region.

Reference therapy, dose and mode of administration, batch number:

Placebo (0.25 mL total; 0.05 mL per injection point) administered at 5 injection points in the glabellar region.

Duration of treatment: One treatment on Day 0

Criteria for evaluation:

Efficacy

Patient's static self-assessment of appearance of glabellar lines at maximum frown at Day 30 using a 4-point categorical scale (no wrinkles [0], mild wrinkles [1], moderate wrinkles [2], or severe wrinkles [3]). The patient's self-assessment had to be complete prior to, and independent of the Investigator's live assessment at each visit.

Investigator's live assessment of glabellar lines at maximum frown at Day 30 using a validated 4-point Study Photographic Scale of Glabellar Line Severity (none [0], mild [1], moderate [2], or severe [3]). A written description of each photograph was included to help standardize the Investigator's application of the Study Photographic Scale. For each scale, a responder was defined as having a severity grade of moderate [2] or severe [3] at maximum frown at Baseline and a severity grade of none [0] or mild [1] at maximum frown at Day 30. The primary efficacy endpoint was the proportion of responders at Day 30.

Safety

Safety was assessed through the monitoring of AEs throughout the study (including a telephonic visit at Day 7 and live evaluation at all other study visits), vital signs at screening, Day 0, 14, and each monthly visit; clinical laboratory parameters at screening, Day 30 and Day 180 or earlier discontinuation. Sera samples were collected to assess the presence of antibodies to *Clostridium botulinum* type A toxin at Day 0 and Day 180 or, if earlier discontinuation, at study end.

Statistical methods:

Data were summarized based on the pooled data from the individual study centres. Data summaries consist of summary statistics (counts, means, standard deviations, medians, and minimum and maximum values) or frequencies and percentages, as appropriate. Ninety five percent confidence intervals (CIs) are constructed for proportions.

The primary population for the efficacy analysis was the intent-to-treat (ITT) population, which was identical to the per protocol (PP) and Safety populations in this study. For dichotomous and ordinal endpoints, between-treatment group comparisons are

presented using the Mantel-Haenszel Chi-square test (using modified ridits for ordinal endpoints), stratified by age group (≤ 50 years, > 50 years).

Sub-group analyses were performed to compare response rates by age, race, gender, study center, and Baseline severity. Logistic regression using backward elimination was performed to determine the relative effects of these predisposing factors on response. Statistical tests comparing treatment to placebo are two-sided and conducted at the 0.05 significance level.

Baseline is defined as the last measurement occurring before treatment administration. For analyses of duration of response, as detailed in the reporting and analysis plan, subjects without a response were censored. Additional analyses were conducted ad hoc and subjects without a response were coded as zero.

Durational assessments included conventions to ensure that all patients are included in the denominator and to deal with potential missing data in a conservative manner (e.g., patients with non-response are coded as zero duration; when missed visits followed by a visit with relapse, duration was censored at the last date of known activity plus 30 days).

Summary - conclusions:

Efficacy results:

A single treatment in patients with moderate to severe glabellar lines with 50 units of Reloxin is highly and statistically significantly more effective compared to placebo as measured by both predefined co-primary endpoints using a categorical scale of glabellar line severity at Day 30. Investigator's live assessment and patient's self-assessment of glabellar lines at maximum frown on Day 30 demonstrated a significantly higher proportion of responders compared to placebo ($p < 0.001$ for the Investigator's assessment, and $p < 0.001$ for the patient's assessment, respectively). The Composite Response where subjects had to be a responder by both the Investigator and patient assessment also demonstrated a statistically significant treatment effect ($p < 0.001$). These results are supported by comparative efficacy assessments at each time-point from Day 14 through Day 120, by assessment that defines efficacy as a 2-grade improvement in glabellar line severity score, by 2-grade Composite Response, and by global assessment of improvement by the patient. Thus, efficacy is persuasive and robust.

The median time to onset of effect based on patient's diary cards was three days. The median duration of effect was approximately 85 days by Investigator's assessment and patient's self-assessment.

The results of sub-group analysis performed to assure the absence of non-response in relevant subsets, including a logistic regression, suggested that no factor (gender, race, Baseline severity or center) had substantial impact on the underlying product efficacy with all subsets showing significant response. Older patients had a lower degree of response than patients under 50 years. However, the response rate in older patients treated with Reloxin was still significantly greater than in placebo ($p = 0.008$).

Correlation of Investigator's live assessments with Independent Photographic Reviewer (IPR) assessments demonstrated that, although IPR confirmed significant efficacy, exact agreement between the assessments deteriorates with increased wrinkle severity supporting the sponsor's original hypothesis that two-dimensional photography will not accurately demonstrate three-dimensional physical findings.

Findings with regard to the response in the subset of subjects with lines at rest after a single therapeutic intervention demonstrated that Reloxin is also effective in the subgroup of enrolled patients who have moderate to severe glabellar lines at rest.

Safety results:

A single dose (50 units) of Reloxin administered in equally divided doses in five protocol specified sites was well-tolerated.

The percent of patients with Treatment Emergent Adverse Events (TEAEs) was similar between the Reloxin and the placebo group, 47% versus 40% respectively. The majority of TEAEs were of mild or moderate severity. The number and percent of severe TEAEs was low overall. Slightly more patients with severe TEAEs were in the Reloxin group (9%) than in the placebo group (4%).

The most frequent TEAEs – those experienced by $\geq 3\%$ of patients – were (by preferred term) blepharospasm (verbatim: eyelid twitching), eyelid ptosis, vomiting, injection site reaction, injection site pain, nasopharyngitis, influenza and headache. Differences between placebo and Reloxin appear to occur for injection site reaction (0% versus 8%) and possibly for eyelid ptosis (0% versus 3%). The 8 injection site reactions in the Reloxin group may possibly reflect injection site reactogenicity or neurotoxin activity.

The majority of TEAEs were considered unlikely or not related to treatment. Of those considered probably or possibly related to treatment, the percentages of patients affected were higher in the Reloxin group compared to the placebo group (23% versus 15%, respectively). These were primarily injection site problems and problems around the eyes. There were six SAEs in two patients, all occurring in the Reloxin group. None of these events (i.e., vomiting, malignant melanoma, squamous cell carcinoma of skin, parotidectomy, skin neoplasm excision) was considered related to study treatment. There were no deaths and no patients required discontinuation of the study due to adverse events. No clinically significant changes were observed in the hematological or biochemical parameters measured, nor were there any clinically significant abnormalities or changes in vital signs.

Conclusion:

A single treatment with Reloxin 50 units is highly efficacious in the treatment of moderate to severe glabellar lines when compared with placebo and assessed by both Investigators and patients at Day 30, with onset of effect within 3 days, a median duration of 85 days and statistically significant efficacy through Day 120.

A single treatment with Reloxin (50 units) is well-tolerated. The safety profile of Reloxin was comparable to placebo in terms of type, frequency, severity and relatedness, with the exception of ptosis (2.9% v. 0%) and injection site reactions (8% v. 0%).

<p>Assessor's comment: <i>Efficacy has been demonstrated for the treatment of glabellar line in Study Y-97-52120-719 and no new safety concerns have been identified.</i></p>
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Safety of repeated treatments:

Study Y-97-52120-720: Phase III, open-label, multicenter study to assess the long-term safety of repeat administrations of Reloxin in the treatment of glabellar lines: interim analysis.

This study was carried out in 21 sites in the USA.

Objectives:

The primary objective was to evaluate the long-term safety of repeat administrations of Reloxin in the treatment of glabellar lines.

Secondary objectives were to demonstrate the effectiveness (efficacy) of Reloxin (50 units) in the treatment of glabellar lines after each treatment, and to evaluate the duration of effect (time to re-treatment).

Exactly 1200 patients were enrolled and analyzed: 1200 patients were treated in Cycle 1, 1145 in Cycle 2, 1031 in Cycle 3, 661 in Cycle 4, and 177 in Cycle 5.

Methodology:

This was an open-label study, with up to five repeat treatments over 13 months. Patients were contacted by telephone 7 days post-injection to check for adverse events and concomitant medications. Follow-up clinic visits occurred on Days 14, 30, and monthly until re-treatment, study completion or early termination.

At each study visit, patients performed a static self-assessment of their glabellar lines at maximum frown using a 4-point categorical scale. Investigators performed a live (face-to-face) assessment of the patient's glabellar lines at maximum frown and at rest using a validated 4-point Photographic Scale. Patients exhibiting moderate [2] or severe [3] glabellar lines at maximum frown after treatment with Reloxin (on both the Investigator's live assessment and the patient's static self-assessment) were to be re-treated, provided that at least 85 days had elapsed since any previous treatment with Reloxin.

The study was designed with a fixed maximum study duration, which means that a subject's final cycle had an observation window determined by his or her prior response durations. This, coupled with the study design of a minimum of 85 days between treatments, resulted in Cycles 4 and 5 duration necessarily being truncated for every patient who had those cycles. Thus, the analysis of duration of effect in these cycles was influenced more by reaching the study end than true durational effect.

Diagnosis and criteria for inclusion

Male or female patients who met all of the following criteria were eligible:

- Eighteen years of age or older.
- Moderate to severe vertical glabellar lines at maximum frown (score of [2] or [3] by the patient's static self-assessment using a 4-point categorical scale (no wrinkles [0], mild wrinkles [1], moderate wrinkles [2], or severe wrinkles [3]). The patient's static self-assessment had to be performed before, and independent of, the Investigator's live assessment of glabellar lines.
- Moderate to severe vertical glabellar lines at maximum frown (score of [2] or [3] by the Investigator's live assessment using a validated 4-point Photographic Scale of none [0], mild [1], moderate [2], or severe [3]).
- Negative pregnancy test result for females of childbearing potential.
- Time and ability to complete the study and comply with instructions.
- Understanding of the study and the contents of the informed consent.

Criteria for exclusion:

Patients who met any of the following criteria were not eligible for this study:

- Previous treatment with 52120 or other botulinum toxin within 85 days of entry into the study or treatment to areas other than the glabellar area during the study.
- Patients who enrolled in either the 52120 Phase II Study Y-97-52120-717 or the Phase III Study Y-97-52120-718 and who did not complete all follow-up visits.
- Inability to substantially lessen glabellar lines by physically spreading them apart.
- Soft tissue augmentation of the glabellar (e.g., collagen-type implants, such as Zyderm or Zyplast) within the previous 6 months or during the study.
- Permanent or semi-permanent dermal fillers in the glabellar area.
- Ablative skin resurfacing on the glabellar area within the previous 6 months or during the study.
- Upper eyelid blepharoplasty or brow lift within 3 months of the study or during the study.
- Non-ablative treatments in the glabellar area for skin dyschromias (e.g., Intense Pulsed Light, light-emitting diodes) within the previous month or during the study.
- Non-ablative dermal treatment in the glabellar area for skin tightening (e.g., radio-frequency treatments) within the previous 6 months or during the study.

- Retinoid, microdermabrasion, or prescription level glycolic acid treatments to the glabellar area within 2 weeks prior to study participation or during the study.
- Concurrent therapy that, in the investigator's opinion, would interfere with the evaluation of the safety or efficacy of the study medication.
- Active infection in the glabellar area (e.g., acute acne lesions or ulcers).
- Pregnant women, nursing mothers, or women who were planning pregnancy during the study, or thought they might be pregnant at the start of the study. Throughout the course of the study, women of childbearing potential had to use reliable forms of contraception (e.g., abstinence, oral contraceptives for more than 12 consecutive weeks prior to enrolment, or spermicide and condoms).
- Current history of chronic drug or alcohol abuse.
- Enrolment in any active study involving the use of investigational devices or drugs.
- Current facial palsy.
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.
- Neuromuscular junctional disorders (e.g., myasthenia gravis).
- Known allergy or hypersensitivity to any botulinum toxin or any component of 52120.
- Clinically diagnosed anxiety disorder, or any other significant psychiatric disorder (e.g., depression) that, in the opinion of the investigator, might interfere with the patient's participation in the study.
- Concurrent use of medications that affect neuromuscular transmission, such as curare-like depolarizing agents, lincosamides, polymyxins, anticholinesterases affecting the striated muscle, and aminoglycoside antibiotics.
- Presence of any other condition (e.g., neuromuscular disorder or other disorder that could interfere with neuromuscular function) or circumstance that, in the judgment of the investigator, might increase the risk to the patient or decrease the chance of obtaining satisfactory data to achieve the objectives of the study.

Test product, dose and mode of administration, batch number:

Reloxin, *Clostridium botulinum* type A toxin-hemagglutinin complex, 50 units administered at 5 designated injection points in the glabellar region.

Duration of treatment:

Each patient enrolled in the study could be re-treated every 85 days and thus could receive up to 5 treatments over approximately 13 months

Criteria for evaluation:

Efficacy:

- The Investigator's live assessment of glabellar lines at maximum frown and at rest at every visit following treatment using the validated 4-point Photographic Scale (none [0], mild [1], moderate [2], or severe [3]). A written description of each photograph was included to help standardize the application of the Photographic Scale.
- The patient's static self-assessment of glabellar lines at maximum frown at every visit following treatment using the 4-point categorical scale (no wrinkles [0], mild wrinkles [1], moderate wrinkles [2], or severe wrinkles [3]).
- The patient's assessment of onset of treatment response as documented on a diary card on Days 1 through 7 of each treatment cycle.
- Duration of response after each treatment cycle, based on the time of onset as recorded on the patient diary and on the Investigator's live assessment of

- glabellar lines and patient's static self-assessment of glabellar lines at maximum frown.
- Two-grade improvement in the Investigator's live assessment of glabellar lines at maximum frown between Day 0 and Day 30 of each cycle.

Safety:

Safety endpoints were adverse events and changes in vital sign measurements. The effect on clinical safety or efficacy of the presence of anti-toxin antibodies to *Clostridium botulinum* type A toxin will be evaluated in a separate report, the summary of which is provided below.

In this study, 1200 patients received repeated treatment with Reloxin (50 units) up to a maximum of five treatment cycles. Serum samples were obtained from each patient on Day 0 (pre-treatment) of each treatment cycle and at the end of the study (or at early discontinuation). The first and last serum samples for each patient were analyzed. A total of 2369 samples were analyzed using the radioimmunoprecipitation assay (RIPA) screening assay to detect the presence of antibodies to botulinum toxin (BTX). Two hundred and fifty-five samples, from 181 patients were found positive by the RIPA screening assay and were subsequently analyzed by the confirmatory assay. Of these 255 samples, four samples, from four different patients, were found positive by the confirmatory assay. These four samples were further analyzed using the mouse protection assay. None of the samples tested positive for neutralizing antibodies.

Statistical methods:

For the Investigator's live assessment of glabellar lines at maximum frown, a responder was defined as having a severity grade of none [0] or mild [1] at any scheduled post-treatment time point of the given treatment cycle.

For the Investigators' live assessments of glabellar lines at rest, a responder was defined as a patient who improved from a Baseline score of moderate [2] or severe [3] in glabellar lines at rest to a rating of none [0] or mild [1] at rest at any scheduled post-treatment time point of the given treatment cycle. This result was analyzed first excluding patients with a Baseline score of none [0] or mild [1] in glabellar lines at rest, and again including them (as non-responders) to maintain a population comparable with other endpoints.

For the patient's static self-assessment of glabellar lines at maximum frown, a responder is defined as having a severity grade of no wrinkles [0] or mild wrinkles [1] at any scheduled post-treatment time point of the given treatment cycle.

Duration of response was evaluated using three different endpoints:

- Duration of response of each treatment cycle from the patient's diary assessment of onset to the date of the next occurrence of a score of [2] or [3] based on the Investigator's live assessment of glabellar lines at maximum frown.
- Duration of response of each treatment cycle, from the patient's diary assessment of onset to the date of the next occurrence of a score of [2] or [3] based on the patient's static self-assessment of glabellar lines at maximum frown.
- Duration of response of each treatment cycle, from the patient's diary assessment of onset to the date of the next re-treatment visit.

Summary - conclusions:

Efficacy results:

Multiple treatments in patients with moderate to severe glabellar lines with 50 units of Reloxin (up to five repeat treatments over 13 months) were highly efficacious as measured by both Investigator and patient self-assessments of glabellar line severity. By Investigator assessment, up to 93% of patients responded to Reloxin treatment, with up

to 73% of patients achieving at least a 2-grade improvement across treatment cycles. As evaluated at each visit by both Investigator and patient self-assessment at maximum frown and at rest, the majority of patients were responding through Day 60, with no indication of loss of efficacy upon repeat dosing.

The median time to onset of effect based on patient's diary cards was 3 days for all cycles and the cumulative proportion of responders in all cycles ranged from 93% to 95% by 7 days. For the first 3 cycles, the median duration of effect was approximately 88 days by Investigator's assessment and 84 days according to patient's self-assessment. For the corresponding time to re-treatment (rather than relapse) the median duration was 104 days for these 3 cycles.

Safety results:

Repeat administrations of 50 units of Reloxin in equally divided doses were well tolerated over the course of 13 months in the treatment of glabellar lines. There was no evidence of cumulative safety issues.

Overall, 73% of patients experienced TEAEs; the majority of these events were of mild or moderate severity. Of the 74 (6%) patients who experienced 124 severe TEAEs, only 8 TEAEs were possibly or probably related to treatment across all cycles.

The majority of all TEAEs (2034/2838; 72%) were considered unlikely or not related to treatment. During the study, 36% of patients had TEAEs that were considered possibly or probably related to treatment. These were primarily injection site events, events around the eyes, or headaches. The incidence of ptosis decreased over repeat cycles of therapy, from 2.4% in Cycle 1 to 0.6% in Cycle 5. Across all cycles, ptosis was reported by 4% of patients in the study and all episodes of ptosis were considered to be possibly or probably related to treatment.

TEAEs considered possibly or probably related to treatment experienced by the greatest number of patients (>3%) occurred in the system organ classes of eye disorders (12%), administration site conditions (21%), and nervous system disorders (20%). A total of 45 (4%) patients had a total of 55 events of ptosis across all cycles. In most patients reporting injection site pain (79/83), the events were considered possibly or probably related to treatment. Possibly or probably related injection site hemorrhage (bruising) occurred in 5% of patients. Headache was also often attributed to treatment (178/1200 patients reported headaches; 138 of these patient reports were considered treatment related).

There were 72 SAEs in 43 patients (including one death by gunshot); all were considered unrelated to study treatment. Twenty-seven events that were coded as SAEs were procedures used to treat SAEs. Eight patients discontinued from the study due to adverse events, but only one patient discontinued due to treatment-related incidents. Most reported cases of hypertension were in patients who had hypertensive systolic or diastolic readings pre-treatment. No clinically significant mean changes from Baseline in vital signs were observed

Conclusion:

Multiple cycles of treatment with Reloxin at the dose of 50 units are well-tolerated. There was no evidence of cumulative safety issues since the incidence of TEAEs decreases over time. Multiple cycles of treatment with Reloxin are highly efficacious in the treatment of moderate to severe glabellar lines as assessed by both Investigators and patients, with onset of effect within 3 days for all cycles and a median duration of 88 days overall for the first 3 cycles.

Assessor's conclusions: *Safety of repeated treatments for Reloxin for glabellar lines has been demonstrated. No new safety concerns have been identified.*

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

No new quality data were submitted with this application. Ipsen Limited Botulinum toxin A is also marketed under the name Dysport, and therefore all trials using Dysport reflect the activity of Ipsen Limited Botulinum toxin A. Additional names used for Ipsen Limited Botulin toxin A include Azzalure. Also the name Reloxin was used in clinical trials of Azzalure.

NON-CLINICAL

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

EFFICACY AND SAFETY

Significant improvements have been shown with Botulinum toxin type A in comparison with placebo for the temporary improvement in the appearance of moderate to severe glabellar lines seen at frown, in adult patients under 65 years.

The safety profile of Botulinum toxin type A is well known and no new or unexpected safety concerns arose from these applications.

The changes to the SmPC, and PIL are acceptable.

BENEFIT-RISK ASSESSMENT

No new clinical safety concerns have been identified. Sufficient clinical experience with Botulinum toxin type A is considered to have demonstrated the therapeutic value of the compound in this new indication. The benefit-risk balance is, therefore, considered to be positive.

Botulinum Toxin Type A Powder For Solution For Injection
(Clostridium botulinum toxin type A – Haemagglutinin complex)

PL 06958/0028

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application on 13th February 2007
- 2 Following standard checks the MHRA informed the applicant that its application was considered valid on 14th March 2007
- 3 Following assessment of the submitted data, a request for supplementary information was sent to the applicant on 13th July 2007
- 4 The applicant submitted its response to the supplementary information request in a letter dated 23rd November 2007
- 5 Following assessment of the submitted data, a further request for supplementary information was sent to the applicant on 13th March 2009
- 6 The applicant submitted its response to the supplementary information request in a letter dated 13th July 2009
- 7 Following assessment of the submitted data, a further request for supplementary information was sent to the applicant on 3rd December 2009
- 8 The applicant submitted its response to the supplementary information request in a letter dated 12th June 2010
- 9 The application was finalised on 22nd July 2010

Botulinum Toxin Type A Powder For Solution For Injection
(Clostridium botulinum toxin type A – Haemagglutinin complex)

PL 06958/0028

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics

Botulinum Toxin Type A Powder For Solution For Injection

(Clostridium botulinum toxin type A – Haemagglutinin complex)

PL 06958/0028

1 NAME OF THE MEDICINAL PRODUCT

Botulinum Toxin Type A powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

	<u>Per Vial</u>
Active Constituent	
<i>Clostridium botulinum</i> type A toxin-haemagglutinin complex	500U *
Other Constituents	
Albumin solution	125 MCG
Lactose	2.5 MG

* One unit (U) is defined as the median lethal intraperitoneal dose in mice.

3 PHARMACEUTICAL FORM

Injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Botulinum Toxin Type A is indicated for focal spasticity, including the treatment of:

- arm symptoms associated with focal spasticity in conjunction with physiotherapy;
- and
- dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older, only in hospital specialist centres with appropriately trained personnel.

Botulinum Toxin Type A is also indicated for the following treatments:

- Spasmodic torticollis in adults
- Blepharospasm in adults
- Hemifacial spasm in adults
- The temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) seen at frown, in adult patients under 65 years, when the severity of these lines has an important psychological impact on the patient.

4.2 Posology and method of administration

The units of Botulinum Toxin Type A are specific to the preparation and are not interchangeable with other preparations of botulinum toxin type A.

Training: Botulinum Toxin Type A should only be administered by appropriately trained physicians.

Ipsen can facilitate training in administration of Botulinum Toxin Type A injections.

The exposed central portion of the rubber stopper should be cleaned with alcohol immediately prior to piercing the septum. A sterile 23 or 25 gauge needle should be used.

Arm spasticity:

Posology

The recommended dose is 1000 units in total, distributed amongst the following five muscles:

Biceps brachii (BB)	Flexor digitorum profundus (FDP)	Flexor digitorum superficialis (FDS)	Flexor carpi ulnaris (FCU)	Flexor carpi radialis (FCR)	Total Dose
300-400 units (0.6-0.8 mL)	150 units (0.3 mL)	150-250 units (0.3-0.5 mL)	150 units (0.3 mL)	150 units (0.3 mL)	1,000 units (2.0 mL)

The sites of injection should be guided by standard locations used for electromyography, although actual location of the injection site will be determined by palpation. All muscles except the biceps brachii (BB) should be injected at one site, whilst the biceps should be injected at two sites.

The dose should be lowered if there is evidence to suggest that this dose may result in excessive weakness of the target muscles, such as for patients whose target muscles are small, where the BB muscle is not to be injected or patients who are to be administered multi-level injections. Clinical improvement may be expected within two weeks after injection. Data on repeated and long term treatment are limited.

Children: The safety and effectiveness of Botulinum Toxin Type A in the treatment of arm spasticity in children have not been demonstrated.

Method of administration

The exposed central portion of the rubber stopper should be cleaned with alcohol immediately prior to piercing the septum. A sterile 23 or 25 gauge needle should be used.

When treating arm spasticity, Botulinum Toxin Type A is reconstituted with 1.0 mL of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per mL of .

Botulinum Toxin Type A is administered by intramuscular injection into the five muscles detailed above when treating arm spasticity.

Paediatric cerebral palsy spasticity:

Posology

The initial recommended dose is 20 units/kg body weight given as a divided dose between both calf muscles. If only one calf is affected, a dose of 10 units/kg bodyweight should be used. Consideration should be given to lowering this starting dose if there is evidence to suggest that this dose may result in excessive weakness of the target muscles, such as for patients whose target muscles are small or patients who require concomitant injections to other muscle groups. Following evaluation of response to the starting dose subsequent treatment may be titrated within the range 10 units/kg and 30 units/kg divided between both legs. The maximum dose administered must not exceed 1000 units/patient.

Administration should primarily be targeted to the gastrocnemius, although injections of the soleus and injection of the tibialis posterior should also be considered.

The use of electromyography (EMG) is not routine clinical practice but may assist in identifying the most active muscles.

Clinical improvement may be expected within two weeks after injection. Injections may be repeated approximately every 16 weeks or as required to maintain response, but not more frequently than every 12 weeks.

Method of administration

When treating paediatric cerebral palsy spasticity, Botulinum Toxin Type A is reconstituted with 1.0 mL of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per mL of Botulinum Toxin Type A. Botulinum Toxin Type A is administered by intramuscular injection into the calf muscles when treating spasticity.

Spasmodic torticollis:

Posology

Adults and elderly: The doses recommended for torticollis are applicable to adults of all ages providing the adults are of normal weight with no evidence of low neck muscle mass. A reduced dose may be appropriate if the patient is markedly underweight or in the elderly, where reduced muscle mass may exist.

The initial recommended dose for the treatment of spasmodic torticollis is 500 units per patient given as a divided dose and administered to the two or three most active neck muscles.

- For rotational torticollis distribute the 500 units by administering 350 units into the splenius capitis muscle, ipsilateral to the direction of the chin/head rotation and 150 units into the sternomastoid muscle, contralateral to the rotation.
- For laterocollis, distribute the 500 units by administering 350 units into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternomastoid muscle. In cases associated with shoulder elevation the ipsilateral trapezoid or levator scapulae muscles may also require treatment, according to visible hypertrophy of the muscle or electromyographic (EMG) findings. Where injections of three muscles are required, distribute the 500 units as follows, 300 units splenius capitis, 100 units sternomastoid and 100 units to the third muscle.
- For retrocollis distribute the 500 units by administering 250 units into each of the splenius capitis muscles. This may be followed by bilateral

trapezius injections (up to 250 units per muscle) after 6 weeks, if there is insufficient response. Bilateral splenii injections may increase the risk of neck muscle weakness.

- All other forms of torticollis are highly dependent on specialist knowledge and EMG to identify and treat the most active muscles. EMG should be used diagnostically for all complex forms of torticollis, for reassessment after unsuccessful injections in non complex cases, and for guiding injections into deep muscles or in overweight patients with poorly palpable neck muscles.

On subsequent administration, the doses may be adjusted according to the clinical response and side effects observed. Doses within the range of 250-1000 units are recommended, although the higher doses may be accompanied by an increase in side effects, particularly dysphagia. Doses above 1000 units are not recommended.

The relief of symptoms of torticollis may be expected within a week after the injection. Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms.

Children: The safety and effectiveness of Botulinum Toxin Type A in the treatment of spasmodic torticollis in children have not been demonstrated.

Method of administration

When treating spasmodic torticollis Botulinum Toxin Type A is reconstituted with 1.0 mL of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per mL of Botulinum Toxin Type A. Botulinum Toxin Type A is administered by intramuscular injection as above when treating spasmodic torticollis.

Blepharospasm and hemifacial spasm

Posology

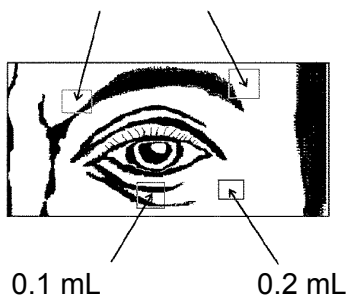
Adults and elderly: In the treatment of bilateral blepharospasm the recommended initial dose is 120 units per eye.

Injection of 0.1 mL (20 units) should be made medially and of 0.2 mL (40 units) should be made laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of each eye.

For injections into the upper lid the needle should be directed away from its centre to avoid the levator muscle. A diagram to aid placement of these injections is provided. The relief of symptoms may be expected to begin within two to four days with maximal effect within two weeks.

Injections should be repeated approximately every 12 weeks or as required to prevent recurrence of symptoms. On such subsequent administrations the dose may need to be reduced to 80 units per eye - viz -: 0.1 mL (20 units) medially and 0.1 mL (20 units) laterally above and below each eye in the manner previously described. The dose may be further reduced to 60 units per eye by omitting the medial lower lid injection.

0.1 mL 0.2 mL



In cases of unilateral blepharospasm the injections should be confined to the affected eye. Patients with hemifacial spasm should be treated as for unilateral blepharospasm. The doses recommended are applicable to adults of all ages including the elderly.

Children: The safety and effectiveness of Botulinum Toxin Type A in the treatment of blepharospasm and hemifacial spasm in children have not been demonstrated.

Method of administration

When treating blepharospasm and hemifacial spasm Botulinum Toxin Type A is reconstituted with 2.5 mL of sodium chloride injection BP (0.9%) to yield a solution containing 200 units per mL of Botulinum Toxin Type A. Botulinum Toxin Type A is administered by subcutaneous injection medially and laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of the eyes.

Glabellar Lines:

Posology and method of administration

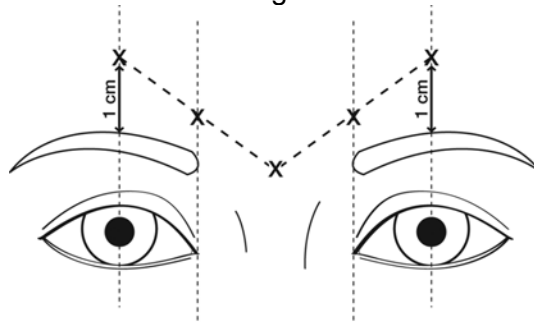
Once reconstituted, Botulinum Toxin Type A should only be used to treat a single patient, during a single session.

Prior to injection, the product should be reconstituted, instructions for which are given in Section 6.6.

Remove any make-up and disinfect the skin with a local antiseptic.

Intramuscular injections should be performed at right angles to the skin using a sterile 29-30 gauge needle.

The recommended dose is 50 Speywood units (0.25 ml of reconstituted solution) of Botulinum Toxin Type A to be divided into 5 injection sites, 10 Speywood units (0.05 ml of reconstituted solution) are to be administered intramuscularly into each of the 5 sites: 2 injections into each corrugator muscle and one into the procerus muscle near the nasofrontal angle as shown below:



The anatomical landmarks can be more readily identified if observed and palpated at maximal frown. Before injection, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be pointed upward and medially during the injection. In order to reduce the risk of ptosis, avoid injections near the levator palpebrae superioris muscle, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections in the corrugator muscle must be made into the central part of that muscle, at least 1 cm above the orbital rim.

The treatment interval depends on the individual patient's response after assessment. In clinical studies, an optimal effect was demonstrated for up to 4 months after injection. Some patients were still responders at 5 months. Treatment interval 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 treatment failure after the first treatment session, the following approaches may be considered:

- Analysis of the causes of failure, e.g. incorrect muscles injected, injection technique, and formation of toxin-neutralising antibodies;
- Re-evaluation of the relevance of treatment with botulinum toxin A

Use in children

The safety and effectiveness of Botulinum Toxin Type A in treating glabellar lines in individuals under 18 years of age have not been demonstrated.

4.3 Contraindications

Botulinum Toxin Type A is contraindicated:

In individuals with known hypersensitivity to any components of Botulinum Toxin Type A or to any of the excipients of the formulation.

In the presence of infection at the proposed injection sites;

In the presence of myasthenia gravis, Eaton Lambert syndrome or Amyotrophic lateral sclerosis.

4.4 Special warnings and precautions for use

Botulinum Toxin Type A should only be used with caution and under close supervision in patients with subclinical or clinical evidence of marked defective neuro-muscular transmission (e.g. myasthenia gravis). Such patients may have an increased sensitivity to agents such as Botulinum Toxin Type A which may result in excessive muscle weakness with therapeutic doses. Patients with underlying neurological disorders are at increased risk of this side effect.

Patients with a history of dysphagia and aspiration should be treated with extreme caution. Swallowing or breathing disorders can worsen due to the spread of toxin distant from the site of administration. Aspiration has occurred in rare cases and this is a risk when treating patients who have a chronic respiratory disorder. Botulinum Toxin Type A should be used under specialist supervision in all such patients and should only be used if the benefit of treatment is considered to outweigh the risk.

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

Patients and their care-givers must be warned of the necessity of immediate medical treatment in case of problems with swallowing, speech or respiratory disorders.

Antibody formation to botulinum toxin has been noted rarely in patients receiving Botulinum Toxin Type A. Clinically, neutralising antibodies have been detected by a substantial deterioration in response to therapy and /or a need for consistently increasing doses.

For the treatment of cerebral palsy in children, Botulinum Toxin Type A should only be used in children over 2 years of age.

The recommended posology and frequency of administration for must not be exceeded (see section 4.2).

Botulinum Toxin Type A should only be used to treat a single patient, during a single session. Specific precautions must be taken for the preparation and administration of the product (see section 4.2) and for the inactivation and disposal of any unused reconstituted solution (see section 6.6).

When treating glabellar lines, it is essential to study the patient's facial anatomy prior to administering. Facial asymmetry, ptosis, excessive dermatochalasis, scarring and any alterations to this anatomy, as a result of previous surgical interventions should be taken into consideration. Caution should be taken when the targeted muscle shows excessive weakness or atrophy.

The effect of administering different botulinum neurotoxins during the course of treatment with Botulinum Toxin Type A is unknown and must be avoided.

As with any intramuscular injection, Botulinum Toxin Type A should be used only where strictly necessary in patients with prolonged bleeding times.

This product contains a small amount of human albumin. The risk of transmission of viral infection cannot be excluded with absolute certainty following the use of human blood or blood products.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of botulinum toxin may be enhanced by drugs interfering directly or indirectly with the neuromuscular function (e.g. aminoglycosides, curare-like non-depolarising blockers) and such drugs should be used with caution in patients treated with botulinum toxin.

4.6 Pregnancy and lactation

Teratological and other reproductive studies have not been performed with Botulinum Toxin Type A. The safety of its use in pregnant or lactating women has not been demonstrated.

Botulinum Toxin Type A should not be used in pregnant or lactating women, unless clearly necessary.

4.7 Effects on ability to drive and use machines

Botulinum Toxin Type A may impair the ability to drive or operate machinery in case of adverse reactions such as muscle weakness and eye disorders (diplopia, blurred vision, eyelid ptosis).

4.8 Undesirable effects

Very common >1/10: Common >1/100, <1/10: Uncommon >1/1000, <1/100: Rare >1/10 000, < 1/1000: Very rare <1/10 000.

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

General

In the clinical trial programme, approximately 28% of the patients treated with Dysport experienced an adverse event.

The following adverse reaction were seen in patients treated across variety of indications including blepharospasm, hemifacial spasm, torticollis and spasticity associated with either cerebral palsy or stroke:

Nervous system disorders

Rare: Neuralgic amyotrophy

Skin and subcutaneous tissue disorders

Uncommon: Itching

Rare: Skin rashes

General disorders and administration site conditions

Common: Generalised weakness, fatigue, flu-like syndrome, pain / bruising at injection site.

In addition, the following adverse reactions specific to individual indication were reported:

Arm spasticity

Gastrointestinal disorders

Common: Dysphagia

Musculoskeletal and connective tissue disorders

Common: Arm muscle weakness

Injury, poisoning and procedural complications

Common: Accidental injury/falls

Paediatric cerebral palsy spasticity

Gastrointestinal disorders

Common: Diarrhoea, vomiting

Musculoskeletal and connective tissue disorders

Common: Leg muscle weakness

Renal and urinary disorders

Common: Urinary incontinence

General disorders and administration site conditions

Common: Abnormal gait

Injury, poisoning and procedural complications

Common: Accidental injury due to falling

Accidental injury due to falling and abnormal gait may have been due to the over-weakening of the target muscle and/or the local spread of Botulinum Toxin Type A to other muscles involved in ambulation and balance.

Spasmodic torticollis

Nervous system disorders

Common: Dysphonia

Uncommon: Headache

Eye disorders

Uncommon: Diplopia, blurred vision

Respiratory, thoracic and mediastinal disorders

Rare: Respiratory disorders

Gastrointestinal disorders

Very common: Dysphagia

Uncommon: Dry mouth

Musculoskeletal and connective tissue disorders

Common: Neck muscle weakness

Dysphagia appeared to be dose related and occurred most frequently following injection into the sternomastoid muscle. A soft diet may be required until symptoms resolve.

These side effects may be expected to resolve within two to four weeks.

Blepharospasm and hemifacial spasm

Nervous system disorders

Common: Facial muscle weakness

Uncommon: Facial nerve paresis

Eye disorders

Very common: Ptosis
Common: Diplopia, dry eyes, tearing
Rare: Ophthalmoplegia

Skin and subcutaneous tissue disorders

Common: Eyelid oedema
Rare: Entropion

Side effects may occur due to deep or misplaced injections of Botulinum Toxin Type A temporarily paralysing other nearby muscle groups.

Glabellar Lines

Nervous system disorders	<u>Very Common</u> Headache <u>Common</u> Facial paresis (predominantly describes brow paresis) <u>Uncommon</u> Dizziness
Eye disorders	<u>Common</u> Asthenopia, Ptosis, Eyelid oedema, Lacrimation increase, Dry eye, Muscle twitching (twitching of muscles around the eyes) <u>Uncommon</u> Visual disturbances, Vision blurred, Diplopia <u>Rare</u> Eye movement disorder
Skin and subcutaneous tissue disorders	<u>Uncommon</u> Pruritus, Rash <u>Rare</u> Urticaria
General disorders and administration site conditions	<u>Very Common</u> Injection site reactions (e.g. erythema, oedema, irritation, rash, pruritus, paraesthesia, pain, discomfort, stinging and bruising)
Immune system disorders	<u>Uncommon</u> Hypersensitivity

Post-marketing experience

The profile of adverse reactions reported to the Company during post-marketing use reflects the pharmacology of the product and those seen during clinical trials. In addition, hypersensitivity reactions have been reported.

4.9 Overdose

Excessive doses may produce distant and profound neuromuscular paralysis. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised. Overdose could lead to an increased risk of the neurotoxin entering the bloodstream and may

cause complications associated with the effects of oral botulinum poisoning (e.g. deglutition and dysphonia).

Symptomatic treatment should be instituted if necessary. In the event of an overdose the patient should be medically monitored for several weeks for symptoms of systemic weakness or muscle paralysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca^{2+} which culminate in transmitter release. It does not affect postganglionic cholinergic transmission or postganglionic sympathetic transmission.

The action of toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly, there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally the toxin inhibits the release of acetylcholine by disrupting the Ca^{2+} mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis.

Recovery of impulse transmission occurs gradually as new nerve terminals sprout and contact is made with the post synaptic motor endplate, a process which takes 6 - 8 weeks in the experimental animal.

5.2 Pharmacokinetic properties

Pharmacokinetic studies with botulinum toxin pose problems in animals because of the high potency, the minute doses involved, the large molecular weight of the compound and the difficulty of labelling toxin to produce sufficiently high specific activity. Studies using ^{125}I labelled toxin have shown that the receptor binding is specific and saturable, and the high density of toxin receptors is a contributory factor to the high potency. Dose and time responses in monkeys showed that at low doses there was a delay of 2 - 3 days with peak effect seen 5 - 6 days after injection. The duration of action, measured by changes of ocular alignment and muscle paralysis varied between 2 weeks and 8 months. This pattern is also seen in man, and is attributed to the process of binding, internalisation and changes at the neuromuscular junction.

5.3 Preclinical safety data

There is no further pre-clinical information relevant to the prescribing physician that has not been included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Albumin and Lactose.

6.2 Incompatibilities

None known.

6.3 Shelf life

The shelf life of the packaged product is 24 months at 2-8°C.

The product may be stored for up to 8 hours at 2-8°C following reconstitution.

Since the product does not contain an antimicrobial agent, from a microbiological point of view, it is recommended that the product should be used immediately following reconstitution.

6.4 Special precautions for storage

Unopened vials must be maintained at temperatures between 2°C and 8°C. Botulinum Toxin Type A must be stored in a refrigerator at the hospital where the injections are to be carried out and should not be given to the patient to store. Reconstituted Botulinum Toxin Type A may be stored in a refrigerator (2-8°C) for up to 8 hours prior to use. Botulinum Toxin Type A should not be frozen.

6.5 Nature and contents of container

Nature of container/closure:

Type 1 glass vials 3 mL capacity. 13 mm chlorbutyl freeze-drying closures oversealed by 13 mm aluminium overseals with centre hole, crimped over.

Contents of container:

A white lyophilised powder for reconstitution.

6.6 Special precautions for disposal

Immediately after treatment of the patient, any residual Botulinum Toxin Type A which may be present in either vial or syringe should be inactivated with dilute hypochlorite solution (1% available chlorine). Thereafter, all items should be disposed of in accordance with standard hospital practice.

Spillage of Botulinum Toxin Type A should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.

7 MARKETING AUTHORISATION HOLDER

Ipsen Limited

190 Bath Road, Slough
Berkshire, SL1 3XE

8 MARKETING AUTHORISATION NUMBER(S)

PL 06958/0028

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

First Authorisation: 04 May 2006

10 DATE OF REVISION OF THE TEXT

22/07/2010

Patient Information Leaflet

Botulinum Toxin Type A Powder For Solution For Injection

(Clostridium botulinum toxin type A – Haemagglutinin complex)

PL 06958/0028

PACKAGE LEAFLET: INFORMATION FOR THE USER
BOTULINUM TOXIN TYPE A[®]
***C. botulinum* type A toxin-haemagglutinin complex**

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 further questions, ask your doctor.
- 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 become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:

- 1. What Botulinum toxin type A is and what it is used for**
- 2. Before you use Botulinum toxin type A**
- 3. How Botulinum toxin type A is given**
- 4. Possible side effects**
- 5. How to store Botulinum toxin type A**
- 6. Further information**

1. What Botulinum toxin type A is and what it is used for

Botulinum toxin type A is a toxin produced by *Clostridium botulinum* bacteria. The toxin works by stopping muscles contracting. It does this by preventing the release of a chemical in between the nerves and muscles which would normally make the muscles contract. This helps to reduce some of the abnormal muscle contractions known as spasms.

Botulinum toxin type A is used in adults to treat muscle spasms

- around the eyes
- in the face
- in the neck and shoulders
- in the arm

Botulinum toxin type A is also used to treat spasms in legs of children (aged two years or older) with cerebral palsy, to improve their walking.

You may also have physiotherapy

Botulinum toxin type A can also be used to prevent the muscles which cause frown lines from contracting. This muscle relaxation is temporary and gradually wears off. Some people are distressed when lines appear on their face. Botulinum toxin type A can be used in adults under 65 years to temporarily improve the appearance of any moderate to severe glabellar lines (these are the vertical frown lines between the eyebrows).

2. Before you use Botulinum toxin type A

Do not use Botulinum toxin type A if:

- you are aware you are allergic (hypersensitive) to *Clostridium botulinum* toxin A or to any of the ingredients of Azzalure
- you have an infection at the proposed site of injection.
- you have myasthenia gravis, Eaton Lambert syndrome or amyotrophic lateral sclerosis

Take special care with Botulinum toxin type A

There are increased risks of having Botulinum toxin type A injections under any of these circumstances.

Tell your doctor if:

- you have problems swallowing.
- you have any history of bronchitis, pneumonia or problems with breathing
- you have had an allergic reaction to a botulinum toxin in the past
- you have other problems or diseases that affect your muscles e.g. myasthenia gravis
- you bleed easily
- you have had surgery on your face, or are likely to undergo facial surgery or other types of surgery soon (if you are considering treatment for glabellar lines)
- you had no significant improvement of your lines after your last treatment (if you are considering treatment for glabellar lines)

Important information about one of the ingredients of botulinum toxin type A

Botulinum toxin type A contains a small amount of albumin which has been obtained from human blood. The risk of passing on infections from blood cannot be eliminated completely when using human blood or products made from human blood.

Taking other medicines:

Please tell your doctor if you are taking any antibiotics for an infection (e.g. aminoglycosides such as gentamicin or amikacin) or muscle relaxant drugs.

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

Pregnancy and Breast-feeding

If you are pregnant or breast-feeding you should ask your doctor for advice before taking any medicine. Botulinum toxin type A should not normally be used.

Use in children

Botulinum toxin type A should not be used in children younger than 2 years of age. Botulinum toxin type A is not suitable for the treatment of glabellar lines in patients under the age of 18.

Driving and using machines

Botulinum toxin type A may cause muscle weakness or problems with your vision. If you experience any of these effects, do not drive or use any machines.

3. How Botulinum toxin type A is given

Your doctor will give you your injection and decide how often you need treatment. This will depend on what you are being treated for.

A vial of Botulinum toxin type A should be used only for you and only for a single treatment session.

For treatment of muscle spasms in your *arm*:

The dose of Botulinum toxin type A will normally be 1000 units. The doctor may divide the amount between the affected arm muscles. Your muscle spasms should normally improve within 2 weeks.

For treatment of muscle spasms in your *neck and shoulder*:

The first dose of Botulinum toxin type A will normally be 500 units. The doctor will divide this amount into a number of places in the neck, probably into 2 or 3 of the neck muscles most affected by the condition. A smaller amount may be given to very underweight or elderly patients. Your muscle spasms should improve within 1 week. Further injections (250-1000 units) will be given about every 12 weeks depending on how long the effect lasts.

For treatment of muscle spasm around your *eyes*:

The first injection may be about 120 units per eye. The medicine will be injected just under the skin at various sites around the eye. If only one eye is affected the doctor will only give injections of Botulinum toxin type A around this eye. Injections will be given about every 12 weeks depending on how long the effects last. On the next visits the amount of Botulinum toxin type A given may be reduced to 80 or 60 units per eye.

For treatment of muscle spasm in your *face*:

The doctor will give you injections on the side of your face that is affected. The first injection may be about 120 units. Injections will be given about every 12 weeks depending on how long the effects last. Your next injections of Botulinum toxin type A may be reduced to 80 or 60 units.

For treatment of a child with cerebral palsy with muscle spasms in their *legs*:

The first dose of Botulinum toxin type A will be 20 units for each kg of the child's body weight. The doctor will divide the amount between both lower leg muscles. If only one leg is affected by spasms, the doctor will only give injections of 10 units per kg in this leg. Injections will be given about every 12 to 16 weeks. The dose your doctor gives the child could change depending on how they respond. The maximum dose is 1000 Units per patient each time.

For temporary improvement of *glabellar lines*:

Botulinum toxin type A should only be administered by physicians with appropriate qualifications and expertise in this treatment and having the required equipment.

Your doctor will prepare and give the injections. A vial of Botulinum toxin type A should be used only for you and only for a single treatment session.

The recommended dose is 50 units, injected as 10 units at each of 5 injection sites in your forehead in the area above your nose and eyebrows.

The units used for different botulinum toxin products are not the same.

The effect of the treatment on the severity of your glabellar lines should be noticeable in 2 to 3 days.

The interval between treatments with Botulinum toxin type A will be decided by your doctor. You should not have treatment more often than every 12 weeks.

If you are given more Botulinum toxin type A than you should

If you are given more Botulinum toxin type A than you need, muscles other than the ones that were injected may begin to feel weak. This may not happen straightaway. If this happens, speak to your doctor immediately. Seek urgent medical help if you have difficulty breathing, swallowing or speaking.

If you forget an injection of Botulinum toxin type A

Nothing will happen if an injection is missed other than some of the spasm or muscle stiffness may return. Tell your doctor and he will decide when the next injection is needed.

If you stop taking Botulinum toxin type A

Your muscle movements will return to the way they were before treatment.

4. Possible Side Effects

Like all medicines, Botulinum toxin type A can cause side effects, although not everybody gets them.

Tell your doctor **immediately** if:

- you have any problems swallowing, breathing or with your speech
- you develop difficulty in breathing with or without swelling of the face, lips, tongue and /or throat, redness of the skin or an itchy lumpy rash (urticaria). This may mean you are having an allergic reaction to Botulinum toxin type A.

The chance of having a side effect is described by the following groups:

	How often it occurs
Very Common	Occurs in more than 1 in 10 patients treated
Common	In less than 1 in 10 patients treated
Uncommon	In less than 1 in 100 patients treated
Rare	In less than 1 in 1000 patients treated

Some side effects may occur in any patient treated with Botulinum toxin type A whilst other side effects may depend on the condition treated. Make sure you read all the sections that apply to you.

Treatment of any condition (*all patients*)

Side effects that have occurred include:

Common:

- Bruising, or pain around the site where the injection was given or a burning sensation at the time the injection is given
- Generalised weakness
- Tiredness
- Flu-like symptoms

Uncommon: Itching

Rare: Skin rashes and muscle weakness

Other side effects related to the spread of Botulinum toxin type A away from the site of administration have also been reported (worsened muscle weakness, difficulty with swallowing or inhalation of foreign material which in very rare cases have been fatal).

Treatment of muscle spasms in the *arm*:

Side effects that have occurred include:

Common:

- Arm muscle weakness
- Accidental injury/falls
- Difficulty in swallowing

Treatment of muscle spasms in the *eyes or face*

Side effects that have occurred include:

Very common:

- Drooping eyelids

Common:

- Dry eyes
- Double vision
- More tears than usual
- Swelling of the eyelid
- Facial muscle weakness

Uncommon:

- Facial nerves may become paralysed

Rare:

- Difficulty in moving the eye
- The edge of the eyelid may turn in towards the eyeball and the eye muscles may become paralysed

Tell your doctor **immediately** if you notice very dry eyes.

Treatment of muscle spasms in the *neck or shoulders*:

Side effects that have occurred include:

Very common:

- Difficulty in swallowing. This side effect may be expected to resolve within 2 to 4 weeks.

Common:

- Neck muscle weakness
- A change to the tone of the voice

Uncommon:

- Dry mouth
- Double or blurred vision
- Headache

Rare:

- Botulinum toxin type A may cause breathing difficulties

Treatment of children with muscle spasms in the *leg*:

Side effects that have occurred include:

Common:

- The muscles of the lower leg may be weakened too much. This may change the way you walk or make you fall over more
- Urinary incontinence
- Diarrhoea
- Vomiting

Temporary improvement of *glabellar lines*:

Side effects that have occurred include:

Very common:

- Redness, swelling, irritation, rash, itching, tingling, pain, discomfort, stinging or bruising at the site of injection
- Headache

Common:

- Tired eyes or dim vision, drooping of the upper eyelid, swelling of the eyelid, watering eyes, dry eye, twitching of muscles around the eyes
- Facial paralysis

Uncommon:

- Disturbed, blurred or double vision
- Dizziness

Rare:

- Eye movement disorder

Usually these side effects, after treatment for glabellar lines, have occurred within the first week following injections and did not last long. They were usually mild to moderate in severity.

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

5. How to store Botulinum toxin type A

Keep out of the reach and sight of children.

Do not use after the expiry date shown on the box.

Botulinum toxin type A will be stored in a refrigerator (2°C-8°C) at the place where the injections are carried out. This medicine should not be given to patients to store.

6. Further Information

What Botulinum toxin type A contains

The active constituent of Botulinum toxin type A is *Clostridium botulinum* complex (500 units). Botulinum toxin type A also contains human albumin and lactose. Before it is injected Botulinum toxin type A will be dissolved in sodium chloride for injection (a solution of salt).

What Botulinum toxin type A looks like and contents of the pack

Botulinum toxin type A is a white powder in a glass container called a vial. Each pack contains 2 vials of Botulinum toxin type A

Marketing Authorisation Holder and manufacturer

The marketing authorization holder is:

Ipsen Limited, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK.

Botulinum toxin type A is manufactured by:

Ipsen Biopharm Limited, Ash Road, Wrexham Industrial Estate, Wrexham LL13 9UF.

This leaflet was last approved in

July 2010

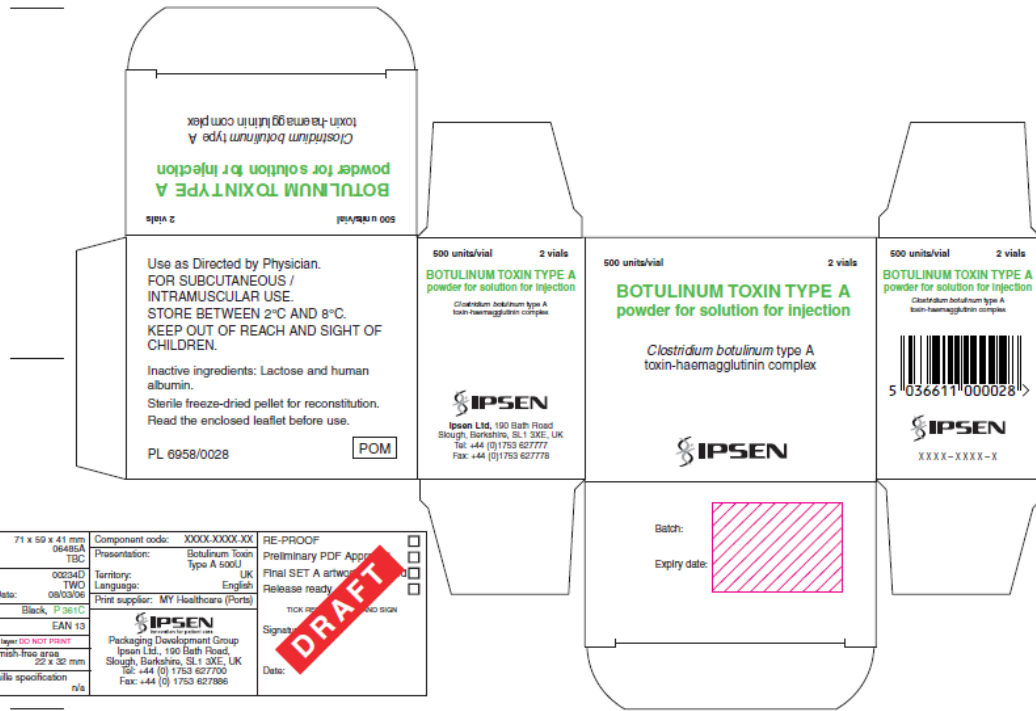
Product licence number

PL 06958/0028

Labelling

**Botulinum Toxin Type A Powder For Solution For Injection
(Clostridium botulinum toxin type A – Haemagglutinin complex)**

PL 06958/0028



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Specification ref:	TBC	Territory:	UK	Final SET A artwork	<input type="checkbox"/>
ICN:	00294D	Language:	English	Release ready	<input type="checkbox"/>
Draft No.:	TWO	Print supplier:	MY Healthcare (Ports)	TICK REVISION NO SIGN	<input type="checkbox"/>
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Varnish-free area	22 x 32 mm				
Braille specification	n/a				

