Dysport
Powder for solution for injection
&
Botulinum Toxin Type A
Powder for solution for injection

(Clostridium botulinum type A toxin – haemagglutinin complex)

PL 34926/0014 & 0015

UKPAR

TABLE OF CONTENTS

- Lay summary P2
- Scientific discussion P3
- Steps taken for assessment P14
- Steps taken after assessment P15
- Summary of product characteristics P16
- Product information leaflet P41
- Labelling P52
- Annex 1 P57
Dysport
Powder for solution for injection
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(*Clostridium botulinum* type A toxin – haemagglutinin complex)

PL 34926/0014 & 0015

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Ispen Limited a Marketing Authorisation for the medicinal products Dysport (PL 34926/0014) and Botulinum Toxin Type A powder for solution for injection (PL 34926/0015) on 5th January 2011. These applications were submitted as an abridged complex national extension application and an abridged standard national application, respectively, in accordance with Article 8(3), known active substance, of Directive 2001/83/EC in order to introduce a 300U/Vial presentation. These medicines are subject to restricted medical prescription and are 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. Dysport and Botulinum Toxin Type A powder for solution for injection are also indicated for the following treatments: spasmodic torticollis in adults; blepharospasm in adults; and hemifacial spasm in adults.

The bulk active substance (BAS) drug substance is the same as the drug substance used in the licensed 125 U/Vial presentation of Azzalure, 10 Speywood units/0.05ml, powder for solution for injection (PL 06958/0031) and Dysport injection 500 Units (PL 34926/0001). *Clostridium botulinum* toxin Type A haemagglutinin complex BAS (CNT52120 BAS) is a complex composed of a 150 kDa polypeptide neurotoxin of 1296 amino acids, a 120 kDa non-toxin non-haemagglutinin protein (NTNH), and various haemagglutinin (HA) proteins ranging between 17 and 50 kDa in size.

Non-clinical and clinical data are not presented with these extension applications. Cross referral is made to the existing non-clinical and clinical data of the approved product Dysport injection 500 Units (PL 34926/0001). Botulinum Toxin Type A powder for solution for injection (PL 34926/0015) is not currently marketed in the UK.

A critical review of the data presented to the MHRA demonstrated that Dysport and Botulinum Toxin Type A powder for solution for injection are effective in the treatment of focal spasticity in the specified groups of patients. No new safety risks were identified and the safety profile of these medicines was considered to be acceptable. It was therefore judged that the benefits of using these products outweigh the risks, hence the application has been granted.
Dysport
Powder for solution for injection
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(Clostridium botulinum type A toxin – haemagglutinin complex)

PL 34926/0014 & 0015

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction P4
Pharmaceutical assessment P5
Pre-clinical assessment P11
Clinical assessment P12
Overall conclusions and risk benefit assessment P13
INTRODUCTION

Based on the review of data on safety and efficacy the UK granted a Marketing Authorisation to Ipsen Limited for the medicinal products Dysport (PL 34926/0014) and Botulinum Toxin Type A powder for solution for injection (PL 34926/0015) on 5th January 2011. These applications were submitted as an abridged complex national extension application and an abridged standard national application, respectively, in accordance with Article 8(3), known active substance, of Directive 2001/83/EC in order to market a new strength, a 300U/Vial presentation. These medicines are subject to restricted medical prescription and are 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. Dysport and Botulinum Toxin Type A powder for solution for injection are also indicated for the following treatments: spasmodic torticollis in adults; blepharospasm in adults; and hemifacial spasm in adults.

Dysport and Botulinum Toxin Type A powder for solution for injection are presented as white lyophilised powders for reconstitution with sodium chloride injection B.P. (0.9%) administered via intramuscular injection. The exact posology and administration is dependent on the indication. Dysport and Botulinum Toxin Type A powder for solution for injection are available in 3ml glass vials with 13 mm bromobutyl freeze-drying closures oversealed by 13 mm aluminium overseals with centre hole, crimped over. The powders must be reconstituted with sodium chloride injection B.P. (0.9%) prior to use.

The new strength is identical to the existing Dysport injection 500 U/Vial (PL 34926/0001) with the exception of the quantity of active pharmaceutical ingredient added to the vial.

The original licence for Dysport injection 500 Units (PL 06958/0005) was granted 22nd November 1995 and was transferred to PL 34926/0001 via change of ownership on 21st July 2010. These subsequent line extensions to add a new strength (300 U/Vial) were granted on 5th January 2011. Botulinum Toxin Type A powder for solution for injection (PL 34926/0015) is not currently marketed in the UK.
QUALITY ASSESSMENT

1 REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION
Not applicable.

2 INTRODUCTION
This Assessment Report covers submissions PL 34926/0014 and PL 34926/0015.

Ipsen have presented a MAA for Dysport 300 U/Vial strength. This is identical to the 500 U/Vial strength with the exception of the quantity of API added to the vial. Drug product information relevant to this change is also updated.

Dysport belongs to the pharmacotherapeutic group of 'other muscle relaxants, peripherally acting agents' (ATC code: M03AX01) and is presented as a powder for solution for injection.

2.1 LEGAL BASIS
Submitted as a national abridged complex application in accordance with Directive 2001/83/EC; Article 8(3): known active substance.

This is an extension application: addition of a new strength.

The applicant holds a market authorisation for Dysport injection 500 Units. This is a National UK license (PL 34926/0001).

2.2 USE
Dysport 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. Dysport is also indicated for the following treatments: spasmodic torticollis in adults; blepharospasm in adults; and hemifacial spasm in adults.

It is intended for intramuscular injection but may also be given subcutaneously depending on the indication.

2.3 SCIENTIFIC ADVICE
N/A

2.4 LEGAL STATUS
POM.

3 DRUG SUBSTANCE

3.1 GENERAL INFORMATION
The bulk active substance (BAS) drug substance is the same as drug substance used in the licensed 125U/Vial and 500 U/Vial presentations of Azzalure and Dysport, respectively.
The manufacturing site is the same, and has appropriate and up-to-date manufacturing licenses and GMP certificates. The specifications are also identical to the currently licensed presentations of Dysport BAS.

### 3.1.1 Nomenclature

**INN/BAN:** None  
**Chemical name:** Not applicable  
**Non-proprietary name:** Dysport  
CNT52120 500 LD$_{50}$ units  
**Other names:**  
- *C. botulinum* toxin Type A  
- *C. botulinum* toxin Type A – haemagglutinin neurotoxin complex  
- *C. botulinum* toxin Type A - conjugate toxin  
- *C. botulinum* toxin Type A - haemagglutinin complex

### 3.1.2 Structure

*Clostridium botulinum* toxin Type A haemagglutinin complex Bulk Active Substance (CNT52120 BAS) is a complex composed of a 150 kDa polypeptide neurotoxin of 1296 amino acids, a 120 kDa non-toxin non-haemagglutinin protein (NTNH), and various haemagglutinin (HA) proteins ranging between 17 and 50 kDa in size.

On a genetic level the toxin gene occurs in a cluster of genes which also encode for the NTNH protein, a regulator protein and the HA proteins (HA70, HA34 and HA17). The complete amino acid sequence, deduced from the nucleotide sequence published by the Sanger Institute, before nicking, consists of 1296 amino acids and 1295 amino acids after cleavage of the N-terminus methionine.

### 3.1.3 General properties

CNT52120 BAS is a clear colourless solution at room temperature in 0.1 M tris (hydroxymethyl) methylamine.

### 3.2 MANUFACTURE

#### 3.2.1 Manufacturers

The applicant has provided full details of the manufacturing and testing facilities used for the preparation of *C. botulinum* type A toxin - haemagglutinin complex BAS (CNT52120 BAS). The MAH has provided current Good Manufacturing Practice (GMP) certificates from the relevant competent supervising authorities for all manufacturing sites.

#### 3.2.2 Manufacturing process

Assessment of the manufacture of CNT52120 BAS has already been carried out for licensing of Dysport (500 U/vial, PL 34926/0001) and Azzalure, 10 Speywood units/0.05ml, powder for solution for injection (125 U/vial, PL 06958/0031) and no further assessment is required or described here.

### 4 DRUG PRODUCT

#### 4.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

The drug product is very closely related to existing approved drug products in the European Union (EU) containing *Clostridium botulinum* type A toxin haemagglutinin complex. These are CNT52120 500 LD$_{50}$ U/Vial, known as Dysport and 125 LD$_{50}$ U/Vial,
known as Azzalure. The formulation for the 300 LD$_{50}$ U/Vial is exactly the same as for CNT52120 500 LD$_{50}$ U/Vial, except that the proposed drug product contains 60% of the amount of C. botulinum toxin Type A.

The formulation is presented as a white lyophilised powder for injection.

Prior to use CNT52120 300 LD$_{50}$ U/Vial is reconstituted with 0.6 or 1.5 mL of sodium chloride for injection (0.9% w/v) to yield a solution containing 500 or 200 LD$_{50}$ Units/mL, respectively.

4.2 PHARMACEUTICAL DEVELOPMENT
CNT52120 300 LD$_{50}$ U/Vial is very closely related to two existing approved medicinal drug products known as CNT52120 500 LD$_{50}$ U/Vial and CNT52120 125 LD$_{50}$ U/Vial. The only difference between the products is the quantity of toxin present per vial. Experience gained with the manufacture and control of CNT52120 500 LD$_{50}$ U/Vial and CNT52120 125 LD$_{50}$ U/Vial has therefore been used as a basis for the development of CNT52120 300 LD$_{50}$ U/Vial.

Comment from Assessor
Since the only difference between this product and the licensed product is the amount of BAS per vial, and the amount is bracketed by the licensed presentations, then this is acceptable.

4.3 MANUFACTURE

4.3.1 Manufacturers
Details of the manufacturers and contract testing laboratories and their responsibilities have been provided.
Current GMP certificates for all the manufacturers have been provided and are satisfactory.

Comment from Assessor
The Drug Product manufacturing site is identical to the site already licensed for the other presentations of Ipsen’s Botulinum Toxin Type A products and the license is acceptable. Other aspects are discussed in the Manufacturing section of Drug Substance, above.

4.3.2 Batch Formula
The batch formula for the new presentation has been provided and is acceptable.

4.3.3 Description of Manufacturing Process
300 LD$_{50}$ U/Vial is based on an existing process that has been established and approved for the medicinal product CNT52120 500 LD$_{50}$ U/Vial for more than 17 years. Manufacture at the IBL site has been established since 1989. The process is therefore well-characterised and conventional for this type of product.

4.3.4 Control of Critical Steps
Control of the manufacturing process is maintained through a combination of tests on key in-process materials and adherence to validated operating parameters. The same controls are routinely applied to the manufacture of CNT52120 500 LD$_{50}$ U/Vial and CNT52120 125 LD$_{50}$ U/Vial, and are therefore very well established.
4.3.5 Process Validation
The manufacturing process for CNT52120 300 LD₅₀ U/Vial is identical to that used for CNT52120 500 LD₅₀ U/Vial, and CNT52120 125 LD₅₀ U/Vial except with respect to the amount of LD₅₀ units presented in each vial.

Data are provided for process validation batches of CNT52120 300 LD₅₀ U/Vial. Each step of the manufacturing process was monitored in terms of Operational Control Parameters (OCPs – parameters that are managed within defined limits), and/or Critical Control Parameters (CCPs – a process step, process condition, test result or other parameter that must be controlled within predetermined criteria in order to ensure that the drug product meets the specification).

The manufacturing procedures were validated with respect to each main step in the process. The overall results for the validation studies clearly demonstrated the consistency of the process.

Comment from Assessor
The manufacturing process is identical to the licensed presentations except for the quantity of BAS added. This amount is bracketed by the licensed processes. The descriptions and data provided for this section are acceptable and the process is acceptably validated.

4.4 CONTROL OF EXCIPIENTS
Excipients are identical to the already licensed presentations of this product and will not be assessed further. The PMF for albumin is provided.

4.5 CONTROL OF DRUG PRODUCT
4.5.1 Specifications
Drug product specification for the new presentation has been provided and is acceptable.

Comment from Assessor
The differences in specifications from the currently approved Dysport (500 U/Vial) have been adequately justified and are acceptable.

4.5.2 Analytical Procedures
Details of the analytical methods applied to control of the drug product have been provided. A range of well-established methods, most already approved for CNT52120 500 LD₅₀ U/Vial and CNT52120 125 LD₅₀ U/Vial are used to monitor the critical quality features of the drug product.

4.5.3 Validation of Analytical Procedures
Validation data has been supplied and are adequate.

4.5.4 Batch Analysis
Batch data has been provided for process validation batches and demonstrate consistency of manufacture.
Comment from Assessor
All results are within specifications.

4.5.5 Characterisation of Impurities
The applicant has demonstrated that process-related impurities in the product are well controlled.

4.5.6 Justification of the specification
The specifications have been adequately justified and are acceptable.

4.6 REFERENCE STANDARDS OR MATERIALS
The reference standards have been detailed and are satisfactory.

Comment from Assessor
The procedure for assigning reference standards for this product is well established and is the same as for the already licensed vial strengths and no further information (such as current reference standard batch number) is required.

4.7 CONTAINER CLOSURE SYSTEM
The container-closure system for CNT52120 300 LD$_{50}$ U/Vial is identical to that for CNT52120 500 LD$_{50}$ U/Vial, and CNT52120 125 LD$_{50}$ U/Vial.

CNT52120 300 LD$_{50}$ U/Vial is supplied in conventional Type I Ph Eur/USP neutral 3 mL glass vials, each of which is sealed with a 13 mm bromobutyl freeze-drying rubber closure and oversealed with a 13 mm polypropylene fliptop seal. The vials are supplied in a conventional boxboard carton.

Comment from assessor
The container closure system components are identical to the components already licensed for the other Dysport strengths.

4.8 STABILITY
Stability data are presented for batches of CNT52120 300 LD$_{50}$ U/Vial. All batches remained within specification.

The stability data presented support a shelf-life for the finished drug product of up to 24 months when stored at 2 to 8°C.

Stability After Reconstitution
In addition to the routine stability studies, additional studies have been conducted to assess the stability of reconstituted samples of CNT52120 300 LD$_{50}$ U/Vial when stored at 2 to 8°C for up to 8 hours after reconstitution.

The potency of all of the samples was within specification after storage for 8 hours. These data support a proposed shelf-life of 8 hours for reconstituted solutions of CNT52120 300U/Vial Drug Product at 2-8°C provided the product was reconstituted under aseptic conditions.
Post-Approval Stability Protocol and Stability Testing Commitment
At least one commercial scale batch of the proposed product will be set down on stability test annually.

Comment from assessor
The stability data is acceptable and the shelf-life for the product and reconstituted product is satisfactory.

5 APPENDICES

5.1 FACILITIES AND EQUIPMENT
Identical to licensed formulations

5.2 ADVENTITIOUS AGENTS SAFETY EVALUATION
Identical to licensed formulations

5.3 NOVEL EXCIPIENTS
N/A

6 REGIONAL INFORMATION

6.3 TSE ISSUES
Identical to licensed formulations.

Assessor's Overall Conclusions
All quality issues have been addressed and this application can be approved.
NON-CLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for applications of this type.
CLINICAL ASSESSMENT

No new clinical data have been supplied with this application and none are required for applications of this type.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Dysport and Botulinum Toxin Type A are well defined and controlled. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY AND SAFETY
No new clinical data were submitted and none are required for applications of this type.

The SmPC, PIL and labelling are acceptable.

BENEFIT-RISK ASSESSMENT
No pharmaceutical concerns have been identified. Sufficient clinical experience with Dysport and Botulinum Toxin Type A powder for solution for injection is considered to have demonstrated the therapeutic value of the new presentations. The benefit-risk balance is, therefore, considered to be positive.
Dysport
Powder for solution for injection
&
Botulinum Toxin Type A
Powder for solution for injection

(*Clostridium botulinum* type A toxin – haemagglutinin complex)

PL 34926/0014 & 0015

**STEPS TAKEN FOR ASSESSMENT**

1. The MHRA received the marketing authorisation application on 22\textsuperscript{nd} April 2010
2. Following standard checks the MHRA informed the applicant that its application was considered valid on 22\textsuperscript{nd} April 2010
3. Following assessment of the submitted data, a request for supplementary information was sent to the applicant on 4\textsuperscript{th} August 2010
4. The applicant submitted its response to the supplementary information request in a letter dated 1\textsuperscript{st} October 2010
5. Following assessment of the submitted data, a further request for supplementary information was sent to the applicant on 1\textsuperscript{st} November 2010
6. The applicant submitted its response to the supplementary information request in a letter dated 29\textsuperscript{th} November 2010
7. The application was finalised on 5\textsuperscript{th} January 2011
**Dysport**
**Powder for solution for injection**
&
**Botulinum Toxin Type A**
**Powder for solution for injection**

(*Clostridium botulinum* type A toxin – haemagglutinin complex)

**PL 34926/0014 & 0015**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>22.06.15</td>
<td>Type IB national variation</td>
<td>To update section 4.2 (posology and administration) and 4.8 (undesirable effects) of the SmPC to correct some discrepancies in the content and adjust the format. The patient information leaflet is unaffected by this correction variation.</td>
<td>Granted 15.07.15</td>
</tr>
</tbody>
</table>
Summary of Product Characteristics

Dysport
Powder for solution for injection
&
Botulinum Toxin Type A
Powder for solution for injection

(Clostridium botulinum type A toxin – haemagglutinin complex)

PL 34926/0014 & 0015
1 **NAME OF THE MEDICINAL PRODUCT**  
Dysport

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**  
*Clostridium botulinum* type A toxin-haemagglutinin complex 300 units*  

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

For a full list of excipients, see section 6.1.

3 **PHARMACEUTICAL FORM**  
Injection.

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**  
Dysport 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.

Dysport is also indicated for the following treatments:  
− Spasmodic torticollis in adults  
− Blepharospasm in adults  
− Hemifacial spasm in adults.

4.2 **Posology and method of administration**  
The units of Dysport are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.

Training: Dysport should only be administered by appropriately trained physicians.  
Ipsen can facilitate training in administration of Dysport 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**  
*Adults:* The recommended dose is 1000 units in total, distributed amongst the following five muscles:

<table>
<thead>
<tr>
<th>Biceps brachii (BB)</th>
<th>Flexor digitorum profundus (FDP)</th>
<th>Flexor digitorum superficialis (FDS)</th>
<th>Flexor carpi ulnaris (FCU)</th>
<th>Flexor carpi radialis (FCR)</th>
<th>Total Dose</th>
</tr>
</thead>
</table>
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 maximum dose administered must not exceed 1000 units.

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 Dysport in the treatment of arm spasticity in children have not been demonstrated.

**Method of administration**

When treating arm spasticity, Dysport 300U vial is reconstituted with 0.6 mL of sodium chloride injection B.P. (0.9%) to yield a solution with a concentration equivalent to 500 units per mL of botulinum toxin type A. Dysport 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, Dysport 300U vial is reconstituted with 0.6 mL of sodium chloride injection B.P. (0.9%) to yield a solution with a concentration equivalent to 500 units per mL of botulinum toxin type A.

Dysport 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. The maximum dose administered must not exceed 1000 units.
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 Dysport in the treatment of spasmodic torticollis in children have not been demonstrated.

**Method of administration**
When treating spasmodic torticollis Dysport 300U vial is reconstituted with 0.6 mL of sodium chloride injection B.P. (0.9%) to yield a solution with a concentration equivalent to 500 units per mL of botulinum toxin type A.

Dysport 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.

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 Dysport in the treatment of blepharospasm and hemifacial spasm in children have not been demonstrated.

Method of administration
When treating blepharospasm and hemifacial spasm, Dysport 300U vial is reconstituted with 1.5 mL of sodium chloride injection BP (0.9%) to yield a solution containing 200 units per mL of botulinum toxin type A.

Dysport 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.

4.3 Contraindications
Dysport is contraindicated in individuals with known hypersensitivity to any components of Dysport.

4.4 Special warnings and precautions for use
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, very rarely, in death. Patients treated with therapeutic doses may present with excessive muscle weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose and by not exceeding the recommended dose.

Dysport 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 Dysport 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 is a risk when treating patients who have a chronic respiratory disorder. Dysport 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.

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

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.

For the treatment of spasticity associated with cerebral palsy in children, Dysport should only be used in children over 2 years of age.

As with any intramuscular injection, Dysport should be used only where strictly necessary in patients with prolonged bleeding times, infection or inflammation at the proposed injection site.
Dysport 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).

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.

Antibody formation to botulinum toxin has been noted rarely in patients receiving Dysport. Clinically, neutralising antibodies might be detected by substantial deterioration in response to therapy and/or the need for consistent use of increased doses.

Careful consideration should be given before the injection of patients who have experienced a previous allergic reaction to a product containing botulinum toxin type A. The risk of a further allergic reaction must be considered in relation to the benefit of treatment.

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
Pregnancy:
There are limited data from the use of Clostridium botulinum type A toxin-haemagglutinin complex in pregnant women. Studies in animals have shown reproductive toxicity at doses causing maternal toxicity (see section 5.3).

Dysport should be used during pregnancy only if the benefit justifies any potential risk to the foetus. Caution should be exercised when prescribing to pregnant women.

Lactation:
It is not known whether Clostridium botulinum type A toxin-haemagglutinin complex is excreted in human milk. The excretion of Clostridium botulinum type A toxin-haemagglutinin complex in milk has not been studied in animals. The use of Clostridium botulinum type A toxin-haemagglutinin complex during lactation cannot be recommended.

4.7 Effects on ability to drive and use machines
There is a potential risk of muscle weakness or visual disturbances which, if experienced, may temporarily impair the ability to drive or operate machinery.

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 reactions were seen in patients treated across a 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 indications 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 Dysport 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 Dysport temporarily paralysing other nearby muscle groups.

**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. 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. dysphagia and dysphonia). 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. In the event of overdose the patient should be medically monitored for signs of excessive muscle weakness or muscle paralysis. Symptomatic treatment should be instigated if necessary.

Symptoms of overdose may not present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or muscle paralysis.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**
Pharmacotherapeutic Group: Other muscle relaxants, peripherally acting agents.  
ATC code: M03AX01

*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 I\(^{125}\) 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
Reproductive toxicity studies in pregnant rats and rabbits given \textit{Clostridium botulinum} type A toxin-haemagglutinin complex by daily intramuscular injection, at doses of 6.6 units/kg (79 units/kg total cumulative dose) and 3.0 units/kg (42 units/kg total cumulative dose) in rats and rabbits respectively, did not result in embryo/foetal toxicity. Implantation losses at maternally toxic doses were observed at higher doses in both species. \textit{Clostridium botulinum} type A toxin-haemagglutinin complex demonstrated no teratogenic activity in either rats or rabbits and no effects were observed in the pre- and postnatal study on the F1 generation in rats. Fertility of male and female rats was decreased due to reduced mating secondary to muscle paralysis at doses of 29.4 units/kg weekly in males and increased implantation loss at 20 units/kg weekly in females.

In a chronic toxicity study performed in rats up to 12 units/animal, there was no indication of systemic toxicity. Effects in chronic toxicity non-clinical studies were limited to changes on injected muscles related to the mechanism of action of \textit{Clostridium botulinum} type A toxin-haemagglutinin complex. There was no ocular irritation following administration of \textit{Clostridium botulinum} type A toxin-haemagglutinin complex into the eyes of rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Human albumin solution,
Lactose.

6.2 Incompatibilities
None known.

6.3 Shelf life
The shelf life of the packaged product is 24 months at 2-8\(^\circ\)C.

The product may be stored for up to 8 hours at 2-8\(^\circ\)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\(^\circ\)C and 8\(^\circ\)C.
Dysport 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 Dysport may be stored in a refrigerator (2-8\(^\circ\)C) for up to 8 hours prior to use. Dysport should not be frozen.

6.5 Nature and contents of container
\textit{Nature of container/closure:}
Type 1 glass vials 3 mL capacity. 13 mm bromobutyl 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 Dysport 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 Dysport 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
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 34926/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/01/2011

10 DATE OF REVISION OF THE TEXT
05/01/2011
1 NAME OF THE MEDICINAL PRODUCT
Botulinum Toxin Type A powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Clostridium botulinum type A toxin-haemagglutinin complex 300 units*

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

For a full list of excipients, see section 6.1.

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.

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:

<table>
<thead>
<tr>
<th>Biceps brachii (BB)</th>
<th>Flexor digitorum profundus (FDP)</th>
<th>Flexor digitorum superficialis (FDS)</th>
<th>Flexor carpi ulnaris (FCU)</th>
<th>Flexor carpi radialis (FCR)</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>300-400 units (0.6-0.8 mL)</td>
<td>150 units (0.3 mL)</td>
<td>150-250 units (0.3-0.5 mL)</td>
<td>150 units (0.3 mL)</td>
<td>150 units (0.3 mL)</td>
<td>1,000 units (2.0 mL)</td>
</tr>
</tbody>
</table>

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 maximum dose administered must not exceed 1000 units.

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 300U vial is reconstituted with 0.6 mL of sodium chloride injection B.P. (0.9%) %) to yield a solution with a concentration equivalent to 500 units per mL of Botulinum Toxin Type A.

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 300U vial is reconstituted with 0.6 mL of sodium chloride injection B.P. (0.9%) to yield a solution with a concentration equivalent to 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. The maximum dose administered must not exceed 1000 units.

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 300U vial is reconstituted with 0.6 mL of sodium chloride injection B.P. (0.9%) to yield a solution with a concentration equivalent to 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.
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 300U vial is reconstituted with 1.5 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 thelevator 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

Side effects related to spread of toxin distant from the site of administration have been reported (see section 4.8) which, in some cases, were associated with dysphagia, pneumonia and/or significant debility resulting, very rarely, in death. Patients treated with therapeutic doses may present with excessive muscle
weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose and by not exceeding the recommended dose.

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. 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.

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

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.

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

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

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).

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.

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

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.
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
Pregnancy:
There are limited data from the use of Clostridium botulinum type A toxin-haemagglutinin complex in pregnant women. Studies in animals have shown reproductive toxicity at doses causing maternal toxicity (see section 5.3).

Botulinum toxin type A should be used during pregnancy only if the benefit justifies any potential risk to the foetus. Caution should be exercised when prescribing to pregnant women.

Lactation:
It is not known whether Clostridium botulinum type A toxin-haemagglutinin complex is excreted in human milk. The excretion of Clostridium botulinum type A toxin-haemagglutinin complex in milk has not been studied in animals. The use of Clostridium botulinum type A toxin-haemagglutinin complex during lactation cannot be recommended.

4.7 Effects on ability to drive and use machines
There is a potential risk of muscle weakness or visual disturbances which, if experienced, may temporarily impair the ability to drive or operate machinery.

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 Botulinum Toxin Type A experienced an adverse event.

The following adverse reactions 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**

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Very Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Facial paresis (predominantly describes brow paresis)</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenopia, Ptosis, Eyelid oedema, Lacrimation increase, Dry eye, Muscle twitching (twitching of muscles around the eyes)</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Visual disturbances, Vision blurred, Diplopia</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Eye movement disorder</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus, Rash</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Very Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions (e.g. erythema, oedema, irritation, rash, pruritus, paraesthesia, pain, discomfort, stinging and bruising)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td></td>
</tr>
</tbody>
</table>

**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. 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. dysphagia and dysphonia). 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. In the event of overdose the patient should be medically monitored for signs of excessive muscle weakness or muscle paralysis. Symptomatic treatment should be instigated if necessary.

Symptoms of overdose may not present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or muscle paralysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Other muscle relaxants, peripherally acting agents. ATC code: M03AX01

*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 I\(^{125}\) 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

Reproductive toxicity studies in pregnant rats and rabbits given *Clostridium botulinum* type A toxin-haemagglutinin complex by daily intramuscular injection,
at doses of 6.6 units/kg (79 units/kg total cumulative dose) and 3.0 units/kg (42 units/kg total cumulative dose) in rats and rabbits respectively, did not result in embryo/foetal toxicity. Implantation losses at maternally toxic doses were observed at higher doses in both species. *Clostridium botulinum* type A toxin-haemagglutinin complex demonstrated no teratogenic activity in either rats or rabbits and no effects were observed in the pre- and postnatal study on the F1 generation in rats. Fertility of male and female rats was decreased due to reduced mating secondary to muscle paralysis at doses of 29.4 units/kg weekly in males and increased implantation loss at 20 units/kg weekly in females.

In a chronic toxicity study performed in rats up to 12 units/animal, there was no indication of systemic toxicity. Effects in chronic toxicity non-clinical studies were limited to changes on injected muscles related to the mechanism of action of *Clostridium botulinum* type A toxin-haemagglutinin complex. There was no ocular irritation following administration of *Clostridium botulinum* type A toxin-haemagglutinin complex into the eyes of rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Human albumin solution, 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 anti-microbial 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
Type 1 glass vials 3 mL capacity. 13 mm bromobutyl 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 34926/0015

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
05/01/2011

10 DATE OF REVISION OF THE TEXT
05/01/2011
Patient Information Leaflet

Dysport
Powder for solution for injection
&
Botulinum Toxin Type A
Powder for solution for injection

(Clostridium botulinum type A toxin – haemagglutinin complex)

PL 34926/0014 & 0015
Dysport

Clostridium botulinum type A toxoid-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 severe, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What Dysport is and what it is used for
2. Before you use Dysport
3. How Dysport is given
4. Possible side effects
5. How to store Dysport
6. Further information

1. WHAT DYSPORT IS AND WHAT IT IS USED FOR

Dysport is a toxin produced by the bacterium Clostridium botulinum. 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.

Dysport is used in adults to treat muscle spasms:
- around the eyes
- in the face
- in the neck and shoulders
- in the arm

Dysport is also used to treat spasms in the legs of children aged two years or older, with cerebral palsy, to improve their walking. You may also need to have physiotherapy.

2. BEFORE YOU USE DYSPORT

Do not use Dysport:
- If you are allergic to botulinum toxin or any of the ingredients (see section 6 for a list of ingredients).

Take special care with Dysport:
There are increased risks of having Dysport 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 an infection where the injection will be given or if that area is swollen.

Important information about one of the ingredients of Dysport:
Dysport 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. amoxicillin and penicillin) or muscle relaxant drugs. Some of these medicines may increase the effect of Dysport.

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:
Dysport is not recommended during pregnancy, unless clearly necessary.

Dysport is not recommended in breast-feeding women.

If you are pregnant or breast-feeding you should ask your doctor for advice before taking any medicine.

Dysport should normally be used in these situations.

Use in children:
Dysport should not be used in children younger than 2 years of age.

Driving and using machines:
Dysport 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 DYSPORT 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 Dysport should be used only for you and only for a single treatment occasion.

For treatment of muscle spasms in your arm:
The dose of Dysport will usually be 1000 units and should not exceed this dose. The doctor may divide the amount between the affected arm muscles. Your muscle spasm should normally improve within 2 weeks. Injections will usually be given every 12 to 16 weeks.

For treatment of muscle spasms in your neck and shoulder:
The first dose of Dysport will normally be 500 units. The doctor will divide the 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 spasm should improve in 1 week. Further injections (250-1000 units) will be given about every 12 weeks depending on how long the effect lasts. The maximum dose should not exceed 1000 units.

For treatment of muscle spasm around your eyes:
The first injection will usually be 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 Dysport around this eye. Injections will be given every 12 weeks depending on how long the effect lasts. The next visit the amount of Dysport 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 will usually be 120 units. Injections will be given about every 12 weeks depending on how long the effect lasts. Your next injections of Dysport 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 Dysport will be 20 units for each kg of the child's body weight. The doctor will decide the amount between both lower leg muscles. If only one leg is affected by spasm, the doctor will only give injections of 10 units per kg in this leg. Injections will be given every 12 to 16 weeks. The dose your doctor gives the child could change depending on how they respond. The maximum dose should not exceed 1000 units.

If you are given more Dysport than you should:
If you are given more Dysport than you need muscles other than the ones that were injected may begin to feel weak. This may not happen straightaway, if this does happen, speak to your doctor immediately. Seek urgent medical help if you have difficulty breathing, swallowing or speaking.
If you forget an injection of Dysport

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

If you stop taking Dysport

Your muscle spasms will return to the way they were before treatment

4. POSSIBLE SIDE EFFECTS

Like all medicines, Dysport 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 Dysport.

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

<table>
<thead>
<tr>
<th>How often it occurs</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Common</td>
<td>Occurs in more than 1 in 10 patients treated</td>
</tr>
<tr>
<td>Common</td>
<td>in less than 1 in 10 patients treated</td>
</tr>
<tr>
<td>Uncommon</td>
<td>in less than 1 in 100 patients treated</td>
</tr>
<tr>
<td>Rare</td>
<td>in less than 1 in 1000 patients treated</td>
</tr>
</tbody>
</table>

Some side effects may occur in any patient treated with Dysport whilst other side effects may depend on the condition being 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 rash and muscle weakness

Other side effects related to the spread of Dysport away from the site of administration have also been reported (worsened muscle weakness, difficulty with swallowing or breathing, in which 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 paresis

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 any 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
- Dry mouth
- Double or blurred vision
- Headache

Rare:
- Dysport 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

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

5. HOW TO STORE DYSPORT

Keep out of the reach and sight of children.

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

Dysport 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 Dysport contains

The active constituent of Dysport is Clostridium botulinum toxin-BoNT/A complex (200 units). Dysport also contains human albumin and lactose. Before it is injected, Dysport will be dissolved in sodium chloride for injection (a solution of salt).

What Dysport looks like and contents of the pack

Dysport is a white powder in a glass vial. It comes in a pack size of 1 or 2 vials, though not all pack sizes may be marketed.

Marketing Authorization Holder and manufacturer

The marketing authorization holder is:

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

Dysport is manufactured by:

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

This leaflet was last approved in September 2010.

Product licence number

PL 34926/0014
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 the legs of children (aged two years or older) with cerebral palsy, to improve their walking.

You may also need to 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 Botulinum Toxin Type A.
- 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 relaxing drugs. Some of these medicines may increase the effect of Botulinum toxin type A.

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**

Botulinum toxin type A is not recommended during pregnancy, unless clearly necessary.

Botulinum toxin type A is not recommended in breast-feeding women.

If you are pregnant or breast-feeding you should ask your doctor for advice before taking any medicine.
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 and should not exceed this dose. The doctor may divide the amount between the affected arm muscles. Your muscle spasms should normally improve within 2 weeks. Injections will usually be given about every 12 to 16 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. The maximum dose should not exceed 1000 units.

For treatment of muscle spasm around your eyes:
The first injection will usually be 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 will usually be 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 should not exceed 1000 units.

**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 spasms 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:

<p>| How often it occurs |</p>
<table>
<thead>
<tr>
<th>Very Common</th>
<th>Occurs in more than 1 in 10 patients treated</th>
</tr>
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<td>Common</td>
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<tr>
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<td>in less than 1 in 100 patients treated</td>
</tr>
<tr>
<td>Rare</td>
<td>in less than 1 in 1000 patients treated</td>
</tr>
</tbody>
</table>

Some side effects may occur in any patient treated with Botulinum toxin type A whilst other side effects may depend on the condition being 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 breathing 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 paralysis

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 become 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 \textit{Clostridium botulinum} toxin-haemagglutinin complex (300 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 vial. It comes in a pack size of 1 or 2 vials though not all pack sizes may be marketed.

**Marketing Authorisation Holder and manufacturer**

The marketing authorisation 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**

December 2010

**Product licence number**

PL 34926/0015
Labelling

Dysport
Powder for solution for injection
&
Botulinum Toxin Type A
Powder for solution for injection

(Clostridium botulinum type A toxin – haemagglutinin complex)

PL 34926/0014 & 0015
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARDBOARD BOX

1. **NAME OF THE MEDICINAL PRODUCT**
   
   Botulinum toxin type A

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**
   
   *Clostridium botulinum* type A toxin-haemagglutinin complex

3. **LIST OF EXCIPIENTS**
   
   Inactive ingredients: human albumin, lactose.

4. **PHARMACEUTICAL FORM AND CONTENTS**
   
   Powder for solution for injection 300 Units/Vial.
   1 vial.

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**
   
   For subcutaneous/intramuscular use.
   Read the package leaflet before use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**
   
   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**
   
   Use as directed by physician.

8. **EXPIRY DATE**
   
   EXP

9. **SPECIAL STORAGE CONDITIONS**
   
   Store between 2°C and 8°C.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**
Ipsen Ltd, 190 Bath Road, Slough, Berkshire, SL1 3XE, UK.
Tel: +44 (0)1753 627777
Fax: +44 (0)1753 627778

12. MARKETING AUTHORISATION NUMBER(S)

PL 34926/0015

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**VIAL**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><strong>NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
</tbody>
</table>
|   | Botulinum toxin type A  
**Clostridium botulinum** type A toxin-haemagglutinin complex |
| 2. | **METHOD OF ADMINISTRATION** |
|   | For subcutaneous/intramuscular use |
| 3. | **EXPIRY DATE** |
|   | Expiry date: |
| 4. | **BATCH NUMBER** |
|   | Batch: |
| 5. | **CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT** |
|   | 300 units/vial |
| 6. | **OTHER** |
|   | PL 34926/0015  
Ipsen Ltd  
190 Bath Road,  
Slough,  
SL1 3XE, UK. |
Annex 1

Our Reference: PL 34926/0015–0039
Product: PL 34926/0015–Botulinum Toxin Type A powder for solution for injection
Marketing Authorisation Holder: ALLERGAN LIMITED

Reason:
To update section 4.2 (posology and administration) and 4.8 (undesirable effects) of the SmPC to correct some discrepancies in the content and adjust the format. The patient information leaflet is unaffected by this correction variation.

Linked / Related Variation(s) or Case(s):
The Assessment Report refers to the Collection ID 15958770 and covers the following submissions PL 34926/0015–0039 & PL 34926/0009–0047.

Supporting Evidence
This variation is to correct section 4.2 of the SmPC for the glabellar lines indication only.

Evaluation
The MAH suggest the following changes to the SmPC.

Amendment 1:
Separating existing sub-heading ‘Posology and method of administration’ for 4.2 subsection for Glabellar Lines (GL), into two separate headings: ‘Posology’ and ‘Method of administration’.

Amendment 2:
Subsequent to amendment 1, introduction of new text under ‘Method of administration’ derived from existing approved text within the SPC.

Amendment 3:
Re-arranging the format of the existing instructions under ‘Posology’ for section 4.2 GL, for better clarity.

Amendment 4:
Subsequent to amendment 1 and 2, deletion of redundant text under the ‘Posology’ heading for section 4.2 GL.

Amendment 5:
Additional minor change to correct the subsection header 4.2 and 4.8 from “Glabellar lines” to “Moderate to severe glabellar lines” in line with approved indication in subsection 4.1.

Conclusion
These changes are acceptable and the MAH have provided adequate justification.

Decision - Approve
4 CLINICAL PARTICULARS

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.

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:

<table>
<thead>
<tr>
<th>Biceps brachii (BB)</th>
<th>Flexor digitorum profundus (FDP)</th>
<th>Flexor digitorum superficialis (FDS)</th>
<th>Flexor carpi ulnaris (FCU)</th>
<th>Flexor carpi radialis (FCR)</th>
<th>Total Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>300-400 units</td>
<td>150 units</td>
<td>150-250 units</td>
<td>150 units</td>
<td>150 units</td>
<td>1,000 units</td>
</tr>
<tr>
<td>(0.6-0.8mL)</td>
<td>(0.3mL)</td>
<td>(0.3-0.5mL)</td>
<td>(0.3mL)</td>
<td>(0.3mL)</td>
<td>(2.0mL)</td>
</tr>
</tbody>
</table>

The sites of injection should be guided by standard locations used for electromyography (EMG), 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 maximum dose administered must not exceed 1000 units.

The starting 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 for patients who require concomitant injections into other muscle groups. Clinical improvement may be expected within two weeks after injection. Injections may be repeated approximately every 16 weeks, or as required to maintain a response, but not more frequently than every 12 weeks.

*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**

When treating arm spasticity, Botulinum Toxin Type A is reconstituted with 1.0mL 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 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 body weight 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 30 units/kg or 1000 units/patient, whichever is the lower.

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 1.0mL 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**

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. Bilateral splenius 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. The maximum dose administered must not exceed 1000 units.

The relief of symptoms of torticollis may be expected within a week after the injection.

Injections may be repeated approximately every 16 weeks or as required to maintain a response, but not more frequently than every 12 weeks.

**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 1.0mL 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**

In a dose ranging clinical trial on the use of Botulinum Toxin Type A for the treatment of benign essential blepharospasm, a dose of 40 units per eye was significantly effective. Doses of 80 units and 120 units per eye resulted in a longer duration of effect. However, the incidence of local adverse events, specifically ptosis, was dose related. In the treatment of blepharospasm and hemifacial spasm, the maximum dose used must not exceed a total dose of 120 units per eye.

An injection of 10 units (0.05mL) medially and 10 units (0.05mL) laterally should be made into the junction between the preseptal and orbital parts of both the upper (3 and 4) and lower *orbicularis oculi* muscles (5 and 6) of each eye. In order to reduce the risk of ptosis, injections near the *levator palpebrae superioris* should be avoided.
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 twelve weeks or as required to prevent recurrence of symptoms but not more frequently than every twelve weeks. On such subsequent administrations, if the response from the initial treatment is considered insufficient, the dose per eye may need to be increased to 60 units: 10 units (0.05mL) medially and 20 units (0.1mL) laterally, 80 units: 20 units (0.1mL) medially and 20 units (0.1mL) laterally or up to 120 units: 20 units (0.1mL) medially and 40 units (0.2mL) laterally above and below each eye in the manner previously described. Additional sites in the frontalis muscle above the brow (1 and 2) may also be injected if spasms here interfere with vision.

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 2.5mL 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.

*Moderate to severe glabellar lines:*

**Posology**

The recommended dose is 50 units (0.25mL of reconstituted solution) of Botulinum Toxin Type A to be divided into 5 injection sites, 10 units (0.05mL 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.

![Diagram of injection sites](image)

Remove any make-up and disinfect the skin with a local antiseptic. 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. Intramuscular injections should be performed at right angles to the skin using a sterile 29-30 gauge needle. 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 supercili). Injections in the corrugator muscle must be made into the central part of that muscle, at least 1cm 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. The treatment interval should not be more frequent than once 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 Type A.

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

Method of administration

For moderate to severe glabellar lines, Botulinum Toxin Type A is reconstituted with sodium chloride injection BP (0.9% w/v) to yield a solution containing 200 units per ml of Botulinum Toxin Type A.

Botulinum Toxin Type A should be injected as described above when treating moderate to severe glabellar lines.
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 Botulinum Toxin Type A experienced an adverse event.

The following adverse reactions were seen in patients treated across a 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 indications 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

**Musculoskeletal and connective tissue disorders**

Common: Leg muscle weakness, muscle pain

**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 overweakening 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: Headache, dizziness, facial paresis

**Eye disorders**

Common: Blurred vision, visual acuity reduced

Uncommon: Diplopia, ptosis

**Respiratory, thoracic and mediastinal disorders**

Common: Dysphonia, dyspnoea

Rare: Aspiration
Gastrointestinal disorders

Very common: Dysphagia, dry mouth

Musculoskeletal and connective tissue disorders

Very Common: Muscle weakness

Common: Neck pain, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal stiffness

Uncommon: Muscle atrophy, jaw disorder

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 paralysis

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.

Moderate to severe glabellar lines

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