**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0583/001/002**
Case No: 2047433

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Ipsen Limited**

**190 Bath Road**, **Slough**, **Berkshire SL1 3XE**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Dysport, powder for solution for injection**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **19/12/2008** until **07/12/2013**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Dysport, powder for solution for injection

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

| | |
|---|---|
| *Clostridium botulinum* type A toxin-haemagglutinin complex | 500 U * |

* U = Unit of Activity = 1 mouse LD50 (MLD50) which is the quantity of material that kills 50% of mice when injected intraperitoneally.

During the development of botulinum type A toxin haemagglutinin complex, the activity was commonly expressed in terms of a nominal weight, based upon a standard specific activity of $4 \times 10^7$ units/mg.

Any reference to this product expressed in nanograms, whether in the literature or elsewhere, may therefore be readily converted into units using the formula 1 ng = 40 U.

For full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for Solution for Injection
Uncoloured Type I glass vial containing a sterile white lyophilised powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Dysport is indicated for the treatment of:

- Spasticity of the arm in patients following a stroke.
- Dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older
- Spasmodic torticollis
- Blepharospasm
- Hemifacial spasm
- Persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment.

### 4.2 Posology and method of administration

Dysport should only be administered by physicians who have experience in the diagnosis and treatment of the conditions indicated and who have received appropriate training in the administration of Dysport.

The units of Dysport are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.

*Axillary hyperhidrosis*
Posology
*Adults and elderly:* The recommended initial dosage is 100 units per axilla. If the desired effect is not attained, up to 200 units per axilla can be administered for subsequent injections.
The maximum effect should be seen by week two after injection. In the majority of cases, the recommended dose will provide adequate suppression of sweat secretion for approximately one year. The time point for further applications should be determined on an individual basis, when the patient's sweat secretion has returned to normal, but not more often than every 16 weeks. There is some evidence for a cumulative effect of repeated doses so the time of each treatment for a given patient should be assessed individually.
*Children:* The safety and effectiveness of Dysport in the treatment of primary axillary hyperhidrosis has not been investigated in children and adolescents under 18 years.

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.
Dysport is reconstituted with 2.5ml of sodium chloride solution (0.9%) to yield a solution containing 200 units per ml of Dysport. Dysport is administered by intradermal injection at ten sites when treating axillary hyperhidrosis.
The area to be injected should be determined beforehand using the iodine-starch test. Both axillae should be cleaned and disinfected. Intradermal injections at ten sites, each site receiving 10 units (0.05ml) i.e. 100 units (0.5ml) per axilla, are then administered. The injection should be administered in an even distribution within the hyperhidrotic area (delineated with the iodine-starch test and using ten injection points).

The use of Dysport in spasmodic torticollis and adult post-stroke spasticity is restricted to hospital-based specialist units. For the treatment of spasmodic torticollis, paediatric cerebral palsy spasticity and adult post-stroke spasticity, Dysport should only be injected by specialists experienced in the diagnosis and management of this condition and who have received training on the administration of Dysport.

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.

***Adult spasticity of the arm post-stroke:***

Posology
The recommended dose is 1000 units, distributed amongst the following five muscles: flexor digitorum profundus (FDP), flexor digitorum superficialis (FDS), flexor carpi ulnaris (FCU), flexor carpi radialis (FCR) and biceps brachii (BB). 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. It is recommended that the administration of the injection should also be under electromyography guidance. All muscles except the biceps brachii will be injected at one site, whilst the biceps will be injected at two sites. The recommended distribution of dose is given below:

| | BB (units) | FDP (units) | FDS (units) | FCU (units) | FCR (units) | Total Dose (units) |
|---|---|---|---|---|---|---|
| Dysport | **300-400** | **150** | **150-250** | **150** | **150** | **1,000** |

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 patients who are to be administered multi-level injections. 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 twelve weeks.

***Children:*** The safety and effectiveness of Dysport in the treatment of arm spasticity in children has not been demonstrated.

Method of administration

Dysport is reconstituted with 1.0ml of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per ml of Dysport. 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 twelve weeks.

Method of administration

When treating paediatric cerebral palsy spasticity, Dysport is reconstituted with 1.0ml of sodium chloride injection B.P. (0.9%) to yield a solution containing 500 units per ml of Dysport. 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 is appropriate if the patient is markedly underweight and in the elderly where reduced muscle mass may exist.

The initial recommended dose for the treatment of spasmodic torticollis is 500 units (1 ml) 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. Dose ranges from 250-1000 units are recommended, although the higher doses may be accompanied by increase in side effects, particularly dysphagia. Doses above 1000 units are not recommended**.**

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

Injections should be repeated approximately every **twelve** weeks or as required to prevent recurrence of symptoms.

*Children:* The safety and effectiveness of Dysport in the treatment of spasmodic torticollis in children has not been demonstrated.

Method of administration

When treating spasmodic torticollis Dysport is reconstituted with 1 ml Sodium Chloride Injection BP (0.9% w/v) to yield a solution containing 500 units per ml of Dysport. Dysport is administered by intramuscular injection as above when treating spasmodic torticollis.

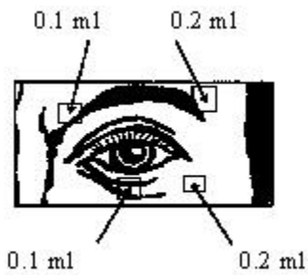
***Blepharospasm and hemifacial spasm:***

Posology

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

After the skin around each eye has been cleaned, injections 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 twelve weeks or as required to prevent recurrence of symptoms. On such subsequent administration 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 has not been demonstrated.

Method of administration

When treating blepharospasm and hemifacial spasm Dysport is reconstituted with 2.5 ml Sodium Chloride Injection BP (0.9% w/v) at to yield a solution containing 200 units per ml of Dysport. 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 contra-indicated in individuals with known hypersensitivity to any component of Dysport. Dysport is contraindicated in pregnancy and lactation.

## 4.4 Special warnings and precautions for use

Dysport should be administered with caution to patients with existing problems in swallowing or breathing as these problems can worsen following the distribution of the effect of toxin into the relevant muscles. Aspiration has occurred in rare cases, and is a risk when treating patients with spasmodic torticollis who have a chronic respiratory disorder.

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.

Dysport should only be used with caution 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.

There are no reports of any immune response after the local administration of *Clostridium botulinum* Type A toxin-haemagglutinin complex in accordance with the doses recommended when treating hemifacial spasm. Antibody formation to botulinum toxin has been noted rarely in a small number of torticollis patients receiving Dysport. Clinically, neutralizing antibodies have been detected by substantial deterioration in response to therapy or a need for consistently increasing doses.

For the treatment of 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.

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

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

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported (see section 4.8). Patients treated with therapeutic doses may present 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.

Very rare cases of death, occasionally in a context of dysphagia, pneumopathy and/or in patients with significant asthenia have been reported after treatment with botulinum toxin A or B.

Patients with disorders resulting in defective neuro-muscular transmission, difficulty in swallowing or breathing are more at risk of experiencing these effects. In these patients, treatment must be administered under the control of a specialist and only if the benefit of treatment outweighs the risk.

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.

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

The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or any other drugs that interfere with neuromuscular transmission, eg. tubocurarine-type muscle relaxants. These drugs should be used with caution. Polymyxins, tetracyclines and lincomycin should be used with caution in the botulinum toxin treated patient.

Muscle relaxants should also be used with caution, perhaps reducing the starting dose of relaxant or using an intermediate-action drug, such as vecuronium or atracurium, rather than those with longer lasting effects.

## 4.6 Pregnancy and lactation

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

## 4.7 Effects on ability to drive and use machines

None known.

## 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

Adverse effects resulting from distribution of the effects of the toxin to sites remote from the site of injection have been very rarely reported (excessive muscle weakness, dysphagia, aspiration pneumonia that may be fatal) (see section 4.4).

***General***
A total of approximately 7800 patients were treated with Dysport during a series of clinical trials in patients suffering blepharospasm, hemifacial spasm, torticollis or spasticity associated with either cerebral palsy or stroke or axillary hyperhydrosis.

Approximately 2200 patients included in these trials experienced an adverse event.

***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 and pain / bruising at injection site

***Axillary Hyperhidrosis***

In 4 clinical trials involving approximately 217 patients treated with Dysport the following adverse reactions were reported:

***Skin and subcutaneous tissue disorders***
Common: Compensatory sweating
Uncommon: Paraesthenia

***Adult spasticity of the arm post-stroke***

In 14 clinical trials involving 141 patients treated with Dysport the following adverse reactions were reported:

***Gastrointestinal disorders***

Common: Dysphagia
***Musculoskeletal and connective tissue disorders***

Common: Arm muscle weakness

***Injury, poisoning and procedural complications***

Common: Accidental injury / falls

Dysphagia was reported when doses in excess of 2700 units were used either as a single or divided dose.

***Paediatric cerebral palsy spasticity***

In 14 clinical trials involving approximately 900 patients treated with Dysport, the following adverse reactions were reported:

***Gastrointestinal disorders***

Common**:** Diarrhoea

***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***

In 21 clinical trials involving approximately 4100 patients the following adverse reactions were reported:

***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.

***Blepharospasm and hemifacial spasm***

In 13 clinical trials involving approximately 1400 patients the following adverse reactions were reported:

***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.

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.

## 4.9 Overdose

Excessive local doses may produce distant and profound neuromuscular paralysis. Respiratory support may be required where excessive doses cause paralysis of **respiratory muscles.** There is no specific antidote; antitoxin should not be expected to be beneficial. Overdose could lead to an increased risk of the neurotoxin entering the bloodstream, which may cause complications associated with the effects of oral botulinum poisoning. (e.g.: deglutition and phonation).

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:**

**Other Dermatological Preparation ATC code: D11AX**

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 on or in the nerve ending to antagonise those events that are triggered by calcium and that culminate in transmitter release. It does not affect 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 Ca2+ 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 to produce sufficiently high specific activity. Studies using I125 labelled toxin have shown that the receptor binding is specific and saturable, and the high density of toxin receptors is a contributory factor in 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

N/A

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Human albumin solution 200g/l
Composed of:
Human plasma protein (of which at least 95% is human albumin)
Sodium caprylate,
N-Acetyltryptophan/sodium acetyltryptophanate
Sodium chloride
Lactose monohydrate

## 6.2 Incompatibilities

Do not admix with other medicinal products.

## 6.3 Shelf Life

Unopened product: 24 months when stored at 2 – 8 $^{o}$C.

Reconstituted product: Chemical and physical in –use stability has been demonstrated for 8 hours at 2-8 °C.
From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbiological contamination,the product should be used immediately.

If not used immediately, in –use storage times and conditions prior to use are the responsibility of the user and should not be longer than 8 hours at 2-8 °C, the opening/ reconstitution of the product having taken place in controlled and validated aseptic conditions.

## 6.4 Special precautions for storage

Store unopened vials in a refrigerator at 2°C and 8°C. Do not freeze.

## 6.5 Nature and contents of container

***Nature of container/closure:***
Dysport is contained in 3 ml white neutral glass vials (Ph. Eur./BP Type I), injection sulphate treated to reduce the surface alkalinity, with 13 mm neck.
The vial is sealed with a 13 mm special butyl freeze drying stopper and 13 mm Type I aluminium overseal.

***Contents of container:***
Boxes of 1 or 2 vials of Dysport are available. Each vial of Dysport contains 500 units of the toxin complex.

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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.

Spillages 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,
UK.

## 8 MARKETING AUTHORISATION NUMBER

PA 583/1/2

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

Date of First Authorisation: 8th December 2008

## 10 DATE OF REVISION OF THE TEXT

June 2008