

SUMMARY OF PRODUCT CHARACTERISTICS

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DYSPO[®]

Clostridium botulinum type A toxin-haemagglutinin complex

1. Name of the Medicinal Product

Dysport.

2. Qualitative and Quantitative Composition

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

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

3. Pharmaceutical Form

Injection.

Clinical Particulars

4.1 Therapeutic indications

Dysport is indicated for the treatment of:

- Spasticity of the arm in adult patients following a stroke;
- Dynamic equinus foot deformity due to spasticity in paediatric cerebral palsy patients, two years of age or older.
- Spasmodic torticollis in adults
- Blepharospasm in adults
- Hemifacial spasm in adults
- Axillary hyperhidrosis
- Treatment of moderate to severe glabellar li

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.

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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.

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 (in units) is given below.

BB	FDP	FDS	FCU	FCR	Total
300-400	150	150-250	150	150	1000

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 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 response, but not more frequently than every 12 weeks.

Children: The safety and effectiveness of Dysport in the treatment of arm spasticity in children have 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 12 weeks.

Method of administration

When treating paediatric cerebral palsy spasticity, Dysport is reconstituted with 1.0 ml 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 may be appropriate if the patient is markedly underweight or in the elderly, where reduced muscle mass may exist.

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

For rotational torticollis distribute the 500 units by administering 350 units into the splenius capitis muscle, ipsilateral to the direction of the chin/head rotation and 150 units into the sternomastoid muscle, contralateral to the rotation.

For laterocollis, distribute the 500 units by administering 350 units into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternomastoid muscle. In cases associated with shoulder elevation the ipsilateral trapezoid or levator scapulae muscles may also require treatment, according to visible hypertrophy of the muscle or electromyographic (EMG) findings. Where injections of three muscles are required, distribute the 500 units as follows, 300 units splenius capitis, 100 units sternomastoid and 100 units to the third muscle.

For retrocollis distribute the 500 units by administering 250 units into each of the splenius capitis muscles. This may be followed by bilateral trapezius injections (up to

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

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

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

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

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

Method of administration

When treating spasmodic torticollis Dysport is reconstituted with 1.0 ml 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 as above when treating spasmodic torticollis.

Blepharospasm and hemifacial spasm

Posology

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

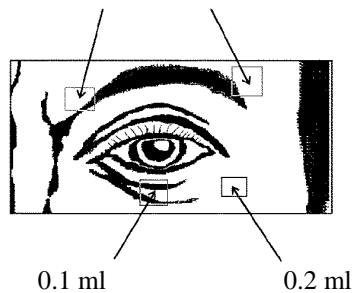
Injection of 0.1 ml (20 units) should be made medially and of 0.2 ml (40 units) should be made laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of each eye.

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

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

0.1 ml

0.2 ml



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

Children: The safety and effectiveness of 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 is reconstituted with 2.5ml of sodium chloride injection BP (0.9%) 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.

Axillary hyperhidrosis

Posology

Adults and the elderly: The recommended initial dose 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 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, 100 units per axilla, are then administered. 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 48 weeks. 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 12 weeks. There is some evidence for a cumulative effect of repeat 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 axillary hyperhidrosis in children has not been demonstrated.

Method of administration: 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.

Moderate to severe glabellar lines

Posology

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Adults:

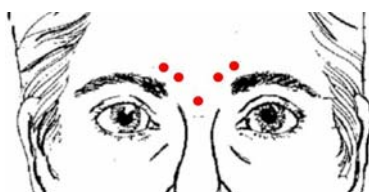
Remove the make-up and disinfect the skin with a local antiseptic.

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

The recommended dose is 50 Units (0.25 ml) of DYSPORT to be divided into 5 injection sites.

10 Units are to be administered intramuscularly into each 5 site: 2 injections into each *corrugator* muscle at 5 mm intervals and one into the *procerus* muscle near the naso frontal angle. The most internal point *corrugator* is localised 8 mm out of point which is in the *procerus* and 8 mm of the upper side of the orbit. Patients are asked to frown regularly in order to help these injection points to be localized.

In order to avoid the complication of ptosis, injection near the *levator palpebrae superioris* must be avoided. Lateral *corrugator* injections should be placed at least 1cm above the bony supraorbital ridge.



Injections may be repeated approximately every 16 weeks. The interval of injection should not be less than 3 months.

Children:

Use of DYSPORT is not recommended in children.

Method of administration

Prior to injection, the product should be reconstituted using 2.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. This provides a clear solution containing 200 Units of active substance (see 6.6 Instructions for use/ handling).

4.3 Contra-indications

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

4.4 Special warnings and special precautions for use

Dysport should be administered with caution to patients with existing problems in swallowing or breathing as these problems can worsen if toxin spreads to 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.

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 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 viral infection cannot be excluded with absolute certainty following the use of human blood or blood products.

4.5 Interaction with other medicaments and other forms of interaction

Drugs which affect neuromuscular transmission, such as aminoglycoside antibiotics, should be used with caution.

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.

General

A total of approximately 7400 patients were treated with Dysport during a series of clinical trials in patients suffering blepharospasm, hemifacial spasm, torticollis, spasticity associated with cerebral palsy or severe to moderate glabellar lines, in which the following adverse events were noted.

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.

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.

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

Blepharospasm and hemifacial spasm

In 13 clinical trials involving approximately 1400 patients treated with Dysport, 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

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

Moderate to severe glabellar lines

Among 800 patients with moderate to severe glabellar lines 626 were treated with DYSPORT doses ranging 20 U to 75 U during 4 clinical trials. Patients receiving the recommended dose of 50 Units experienced the following adverse events.

Eye disorders

Uncommon: Eyelid ptosis, keratoconjunctivitis sicca.

Common: Eye oedema.

General disorders and administration site conditions

Uncommon: Injection site pain, pruritis, stinging and warmth.

Nervous system disorders

Common: Headache, facial paresis

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

5. Pharmacological Properties**5.1 Pharmacodynamic properties**

Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca²⁺ 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 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 toxin 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 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 Pre-clinical safety data

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

6. Pharmaceutical Particulars

6.1. List of excipients

Albumin and Lactose.

6.2 Incompatibilities

None known.

6.3 Shelf life

The shelf life of the packaged product - 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. 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°C) for up to 8 hours prior to use. Dysport should not be frozen.

6.5 Nature and contents of container

Nature of container/closure:

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

Contents of container:

A white lyophilised powder for reconstitution.

6.6 Instructions for use/handling

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. Name and address of the holder of the marketing authorisation

Ipsen Limited

190 Bath Road, Slough
Berkshire, SL1 3XE

8. Marketing Authorisation Number

PL 6958/0005

9. Date of Approval/Revision of SPC

14/06/2005

Importer:

Medison Pharma

10 Hashiloach St. POB 7090
Petach Tikva 49170

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