Dysport

Clostridium botulinum type A toxin-haemagglutinin complex

INFORMATION FOR THE DOCTOR

1. NAME OF THE MEDICINAL PRODUCT

Dysport

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clostridium botulinum type A toxin-haemagglutinin complex 500 units*
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

Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dysport is indicated for symptomatic treatment of focal spasticity of:

- Upper limbs in adults
- Lower limbs in adults affecting the ankle joint due to stroke or traumatic brain injury (TBI)
- Dynamic equinus foot deformity in ambulant paediatric cerebral palsy patients, two years of age or older
- Upper limbs in paediatric cerebral palsy patients, two years of age or older

Dysport is indicated in adults for symptomatic treatment of:

- Spasmodic torticollis
- Blepharospasm
- Hemifacial spasm
- Axillary hyperhidrosis

Dysport is indicated for the temporary improvement in the appearance of moderate to severe:

- Glabellar lines (vertical lines between the eyebrows) seen at maximum frown and/or
- Lateral canthal lines (crow's feet lines) seen at maximum smile

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 Dysport are specific to the preparation and are not interchangeable with other

preparations of botulinum toxin.

Dysport should only be administered by appropriately trained physicians.
For the treatment of focal spasticity, Dysport can also be administered by healthcare professionals having received appropriate training and qualification in accordance with national guidelines (e.g., Royal College of Physicians).

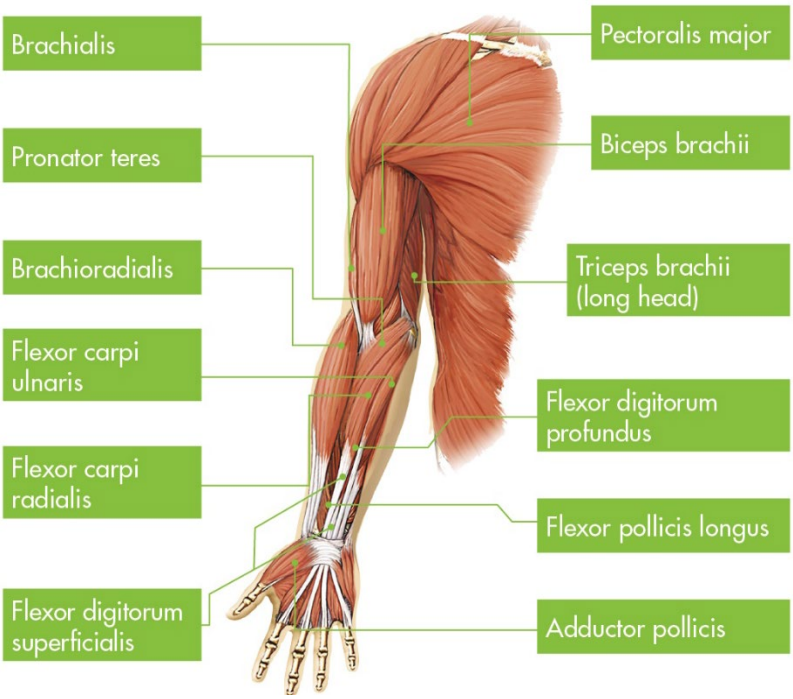
For instructions on reconstitution of the powder for solution for injection, handling and disposal of vials, please refer to section 6.6.

Focal spasticity in adults

Upper limb

Posology
Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with Dysport. In clinical trials, doses of 500 units and 1000 units were divided among selected muscles at a given treatment session as shown below. No more than 1 mL should generally be administered at any single injection site. The total dose should not exceed 1000 units at a given treatment session.

Muscles Injected	**Recommended Dose Dysport (U)**
Flexor carpi radialis (FCR)	100 – 200U
Flexor carpi ulnaris (FCU)	100 – 200U
Flexor digitorum profundus (FDP)	100 – 200U
Flexor digitorum superficialis (FDS)	100 – 200U
Flexor Pollicis Longus	100 – 200U
Adductor Pollicis	25 – 50U
Brachialis	200 – 400U
Brachioradialis	100 – 200U
Biceps Brachii (BB)	200 – 400U
Pronator Teres	100 – 200U
Triceps Brachii (long head)	150 – 300U
Pectoralis Major	150 – 300U
Subscapularis	150 – 300U
Latissimus Dorsi	150 – 300U



Although actual location of the injection sites can be determined by palpation, the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound is recommended to target the injection sites.

Clinical improvement may be expected one week after injection and may last up to 20 weeks. Injections may be repeated every 12 – 16 weeks or as required to maintain response, but not more frequently than every 12 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport and muscles to be injected.

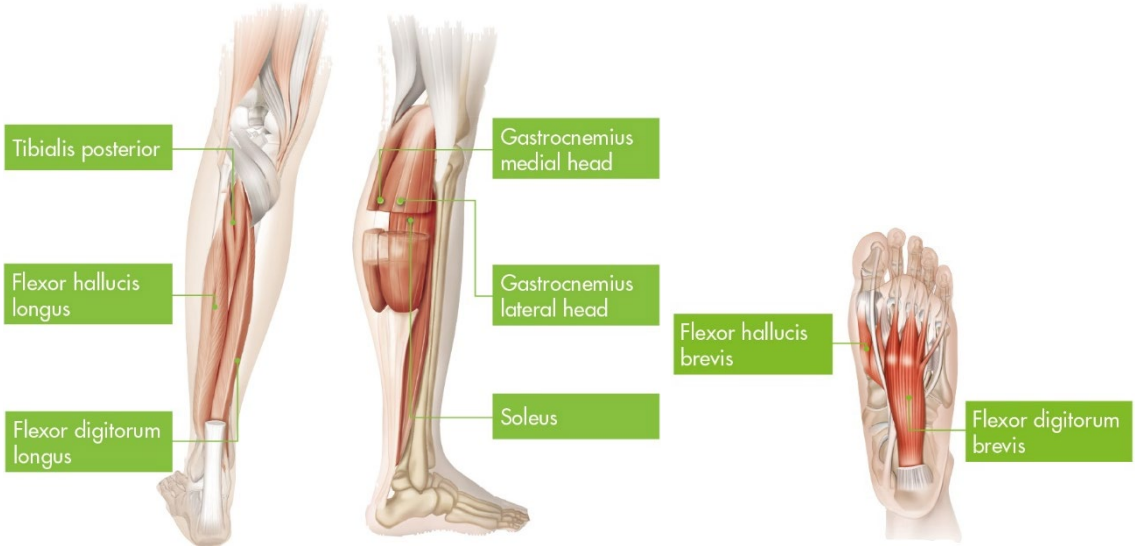
Lower limb spasticity affecting the ankle joint

Posology
In clinical trials, doses of 1000U and 1500U were divided among selected muscles.
The exact dosage in initial and sequential treatment sessions should be tailored to the individual based on the size and number of muscles involved, the severity of the spasticity, also taking into account the presence of local muscle weakness and the patient's response to previous treatment. However, the total

dose should not exceed 1500U.

No more than 1 mL should generally be administered at any single injection site.

Muscle	Recommended Dose Dysport (U)	Number of Injection Sites per Muscle
Primary target muscle		
Soleus muscle	300 – 550U	2 – 4
Gastrocnemius:		
Medial head	100 – 450U	1 – 3
Lateral head	100 – 450U	1 – 3
Distal muscles		
Tibialis posterior	100 – 250U	1 – 3
Flexor digitorum longus	50 – 200U	1 – 2
Flexor digitorum brevis	50 – 200U	1 – 2
Flexor halluces longus	50 – 200U	1 – 2
Flexor hallucis brevis	50 – 100U	1 – 2



The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport and muscles to be injected.

Although actual location of the injection sites can be determined by palpation, the use of injection guiding techniques, e.g. electromyography, electrical stimulation or ultrasound are recommended to help accurately target the injection sites.

Repeat Dysport treatment should be administered every 12 to 16 weeks, or longer as necessary, based on return of clinical symptoms but no sooner than 12 weeks after the previous injection.

Upper and lower limbs

If treatment is required in the upper and lower limbs during the same treatment session, the dose of Dysport to be injected in each limb should be tailored to the individual's need according to the relevant posology and without exceeding a total dose of 1500U.

Elderly patients (≥65 years): Clinical experience has not identified differences in response between the elderly and younger adult patients. In general, elderly patients should be observed to evaluate their tolerability of Dysport, due to the greater frequency of concomitant disease and other drug therapy.

Method of administration
When treating focal spasticity affecting the upper and lower limbs in adult, Dysport is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing either 100 units per mL, 200 units per mL or 500 units per mL of Dysport (see section 6.6).

Dysport is administered by intramuscular injection into the muscles as described above.

Focal spasticity in paediatric cerebral palsy patients, two years of age or older

Dysport maximum total doses per treatment session and minimum times before retreatment

Limb	**Maximum total dose of Dysport to be administered per treatment session**	**Minimum time before retreatment should be considered**
Single lower limb Both lower limbs	15 units/kg or 1000 units* 30 units/kg or 1000 units*	No sooner than 12 weeks
Single upper limb Both upper limbs	16 units/kg or 640 units* 21 units/kg or 840 units *	No sooner than 16 weeks
Upper and lower limbs	30 units/kg or 1000 units*	No sooner than 12 – 16 weeks

*whichever is lower

Please see below for full posology and method of administration by treatment indication.

Dynamic equinus foot deformity due to focal spasticity in ambulant paediatric cerebral palsy patients, two years of age or older

Posology
Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins. For treatment initiation, consideration should be given to start with a lower dose.

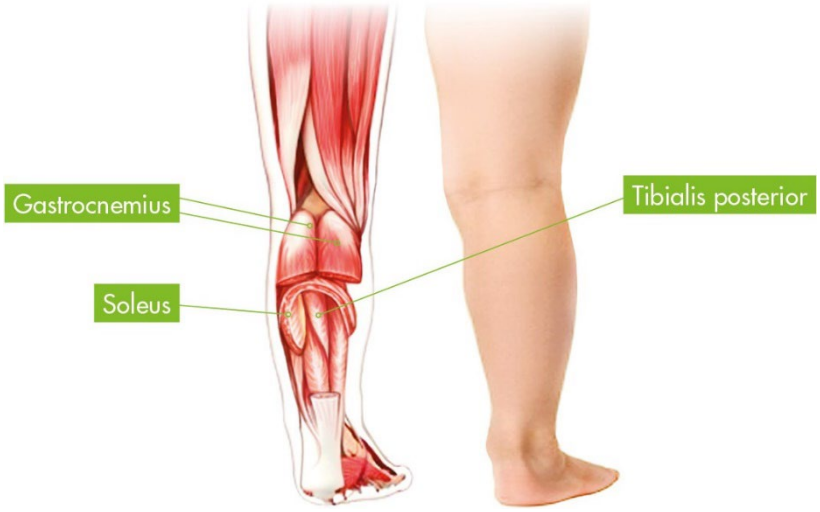
The maximum total dose of Dysport administered per treatment session must not exceed 15 units/kg for unilateral lower limb injections or 30 units/kg for bilateral injections. In addition, the total Dysport dose per treatment session must not exceed 1000 units or 30 units/kg, whichever is lower. The total dose administered should be divided between the affected spastic muscles of the lower limb(s). When possible, the dose should be distributed across more than 1 injection site in any single muscle.

No more than 0.5 mL of Dysport should be administered in any single injection site. See below table for recommended dosing:

Muscle	**Recommended Dose Range per muscle per leg (U/kg Body Weight)**	**Number of injection sites per muscle**
Gastrocnemius	5 to 15 U/kg	Up to 4

Soleus	4 to 6 U/kg	Up to 2
Tibialis posterior	3 to 5 U/kg	Up to 2
Total Dose	**Up to 15 U/kg in a single lower or 30 U/kg if both lower limbs injected and not exceeding 1000 U* Note: For concomitant treatment of upper and lower limbs, the total dose should not exceed 30 U/kg or 1000 U***	

*whichever is lower



Although actual location of the injection sites can be determined by palpation, the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound is recommended to target the injection sites.

Repeat Dysport treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection. A majority of patients in clinical studies were retreated between 16 – 22 weeks; however some patients had a longer duration of response, i.e. 28 weeks. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport and muscles to be injected.

Clinical improvement may be expected within two weeks after injection.

Method of administration

When treating lower limb spasticity associated with cerebral palsy in children, Dysport is reconstituted with sodium chloride injection B.P. (0.9% w/v) (see also section 6.6) and is administered by intramuscular injection as detailed above.

Focal spasticity of upper limbs in paediatric cerebral palsy patients, two years of age or older

Posology

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins. For treatment initiation, consideration should be given to start with a lower dose.

The maximum dose of Dysport administered per treatment session for unilateral upper limb injections must

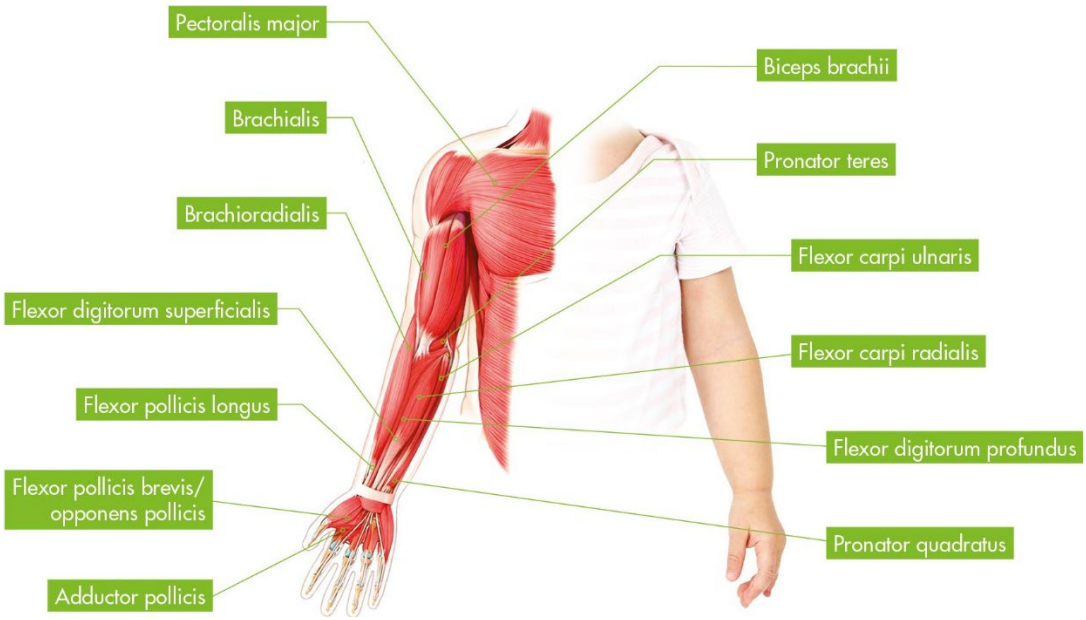
not exceed 16 U/kg or 640 U whichever is lower. When injecting bilaterally, the maximum Dysport dose per treatment session must not exceed 21 U/kg or 840 U, whichever is lower.

The total dose administered should be divided between the affected spastic muscles of the upper limb(s). No more than 0.5 ml of Dysport should be administered in any single injection site. See table below for recommended dosing:

Dysport Dosing by Muscle for Paediatric Upper Limb Spasticity

Muscle	**Recommended Dose Range per muscle per upper limb (U/kg Body Weight)**	**Number of injection sites per muscle**
Brachialis	3 to 6 U/kg	Up to 2
Brachioradialis	1.5 to 3 U/kg	1
Biceps brachii	3 to 6 U/kg	Up to 2
Pronator teres	1 to 2 U/kg	1
Pronator quadratus	0.5 to 1 U/kg	1
Flexor carpi radialis	2 to 4 U/kg	Up to 2
Flexor carpi ulnaris	1.5 to 3 U/kg	1
Flexor digitorum profundus	1 to 2 U/kg	1
Flexor digitorum superficialis	1.5 to 3 U/kg	Up to 4
Flexor pollicis longus	1 to 2 U/kg	1
Flexor pollicis brevis/ opponens pollicis	0.5 to 1 U/kg	1
Adductor pollicis	0.5 to 1 U/kg	1
Pectoralis major	0.5 to 1 U/kg	Up to 2
Total dose	**Up to 16 U/kg or 640 U*in a single upper limb (and not exceeding 21 U/kg or 840 U*if both upper limbs injected)** **Note: For concomitant treatment of upper and lower limbs the total dose should not exceed 30 U/kg or 1000 U***	

*whichever is lower



Although actual location of the injection sites can be determined by palpation, the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound is recommended to target the injection sites.

Repeat Dysport treatment should be administered when the effect of a previous injection has diminished, but no sooner than 16 weeks after the previous injection. A majority of patients in the clinical study were retreated between 16 – 28 weeks; however some patients had a longer duration of response, i.e. 34 weeks or more. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of Dysport and muscles to be injected.

Method of administration
When treating upper limb spasticity associated with cerebral palsy in children, Dysport is reconstituted with sodium chloride injection (0.9% w/v) (see section 6.6) and is administered by intramuscular injection as detailed above.

Focal spasticity of upper and lower limbs in paediatric cerebral palsy patients, two years of age or older

Posology
When treating combined upper and lower spasticity in children aged 2 years or older, refer to the posology section for the individual indications above. The dose of Dysport to be injected for concomitant treatment should not exceed a total dose per treatment session of 30 U/kg or 1000 U, whichever is lower.
Retreatment of the upper and lower limbs combined should be considered no sooner than a 12 to 16-week window after the previous treatment session. The optimal time to retreatment should be selected based on individuals progress and response to treatment.

Method of administration
When treating combined upper and lower spasticity associated with cerebral palsy in children refer to the method of administration section for the individual indications above.

Spasmodic torticollis

Posology
The doses recommended are applicable to adults of all ages provided the adults are of normal weight with no evidence of reduced neck muscle mass. A lower dose may be appropriate if the patient is markedly underweight or in the elderly, where a reduced muscle mass may exist.

The initial recommended initial dose for the treatment of spasmodic torticollis is 500 units per patient given as a divided dose and administered into 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 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 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 Dysport in the treatment of spasmodic torticollis in children have not been demonstrated.

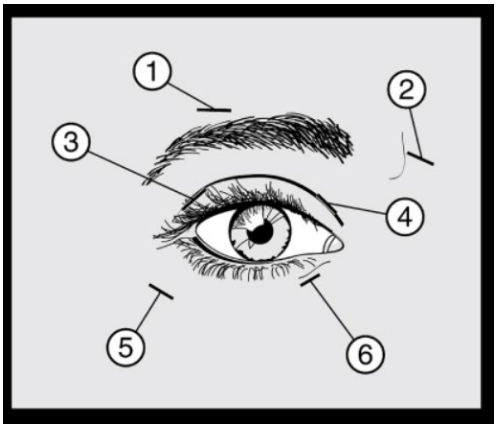
Method of administration
When treating spasmodic torticollis, Dysport is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing 500 units per mL of Dysport (see section 6.6).

Dysport is administered by intramuscular injection as described above.

Blepharospasm and hemifacial spasm

Posology
In a dose ranging clinical trial on the use of Dysport 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 (0.05 mL) medially and 10 units (0.05 mL) 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 above. 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 but not more frequently than every 12 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 (0.05 mL) medially and 20 units (0.1 mL) laterally
- 80 units: 20 units (0.1 mL) medially and 20 units (0.1 mL) laterally
- or up to 120 units: 20 units (0.1 mL) medially and 40 units (0.2 mL) 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 Dysport in the treatment of blepharospasm and hemifacial spasm in children have not been demonstrated.

Method of administration

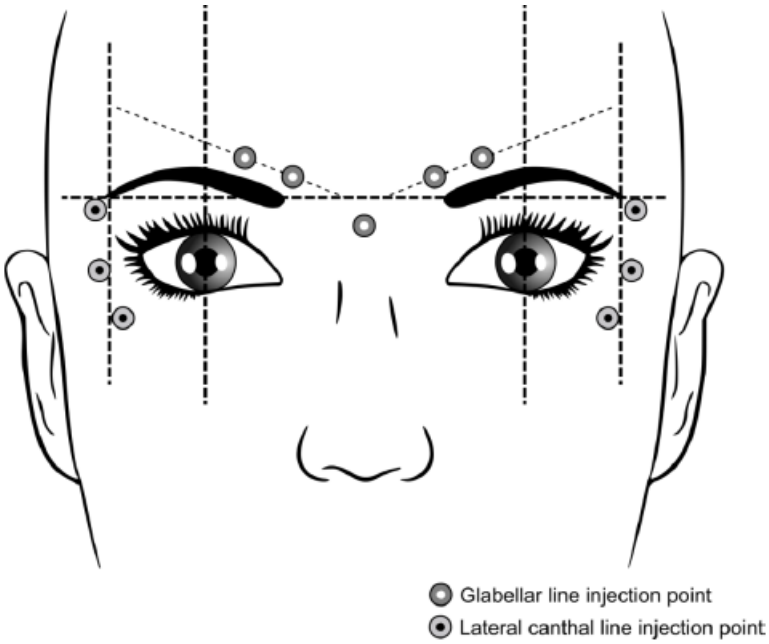
When treating blepharospasm and hemifacial spasm, Dysport is reconstituted with sodium chloride injection BP (0.9% w/v) to yield a solution containing 200 units per mL of Dysport (see section 6.6).

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 as described above.

Moderate to severe glabellar lines and/or lateral canthal lines

Posology
The treatment interval depends on the individual patient's response after assessment. Treatment interval with Dysport should not be more frequent than every three months.

Remove any make-up and disinfect the skin with a local antiseptic.
Intramuscular injections should be performed using a sterile 29 – 30 gauge needle. The recommended injection points for glabellar lines and lateral canthal lines are described below:



Glabellar lines

The recommended dose is 50 units (0.25 mL of reconstituted solution) of Dysport to be divided into 5 injection sites, 10 units (0.05 mL of reconstituted solution) are to be administered intramuscularly, at right angles to the skin, into each of the 5 sites: 2 injections into each corrugator muscle and one into the procerus muscle near the nasofrontal angle as shown in the diagram above.

The anatomical landmarks can be more readily identified if observed and palpated at maximum 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 upwards and medially during the injection. In order to reduce the risk of ptosis, avoid injections near the levator palpebrae superioris muscle, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections into the corrugators muscle must be made into the central part of that muscle, at least 1 cm above orbital rim.

In clinical studies, an optimal effect, in glabellar lines, was demonstrated for up to 4 months after injection. Some patients were still responders at 5 months (see section 5.1).

Lateral canthal lines

The recommended dose per side is 30 units (60 units for both sides, 0.30 mL of reconstituted solution) of Dysport, to be divided into 3 injection sites; 10 units (0.05 mL of reconstituted solution) are to be

administered intramuscularly into each injection point.
Injection should be lateral (20 – 30° angle) to the skin and very superficial. All injection points should be at the external part of the orbicularis oculi muscle and sufficiently far from the orbital rim (approximately 1 – 2 cm) as shown above.
The anatomical landmarks can be more readily identified if observed and palpated at maximal smile. Care must be taken to avoid injecting the zygomaticus major/minor muscles to avoid lateral mouth drop and asymmetrical smile.

General information
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, inappropriate injection technique, and formation of toxin-neutralizing antibodies
- Re-evaluation of the relevance of treatment with Dysport

The efficacy and safety, of repeat injections of Dysport, has been evaluated in glabellar lines up to 24 months and up to 8 repeat treatment cycles and for lateral canthal lines up to 12 months and up to 5 repeat treatment cycles.

Children: The safety and effectiveness of Dysport in treating moderate to severe glabellar lines and lateral canthal lines in individuals under 18 years of age have not been demonstrated.

Method of administration
For moderate to severe glabellar lines or lateral canthal lines, Dysport is reconstituted with sodium chloride injection BP (0.9% w/v) to yield a solution containing 200 units per mL of Dysport (see section 6.6). Dysport is administered by intramuscular injection as described above.

Axillary hyperhidrosis

Posology
The recommended initial dose is 100 units per axilla (armpit). If the desired effect is not achieved, up to 200 units per axilla may be administered in subsequent injections. The maximum dose administered should not exceed 200 unit per axilla.

The injection site may be determined beforehand by using the iodine starch test. Both armpits should be cleaned thoroughly and disinfected. Intradermal injections at ten sites, each site receiving 10 units, i.e., to deliver 100 units per axilla, are then administered. The maximum effect should be seen by week two after injection. In many 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 according to clinical need. Injections should not be repeated more frequently than every 12 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 treating axillary hyperhidrosis in children has not been demonstrated.

Method of administration
When treating axillary hyperhidrosis, Dysport is reconstituted with 2.5 mL of sodium chloride solution (0.9% w/v) to yield a solution containing 200 units per mL of Dysport. In treating axillary hyperhidrosis, Dysport is administered by intradermal injections as described above.

4.3 Contraindications

Known hypersensitivity to the active substance or to any excipients listed in section 6.1.

4.4 Special warnings and special precautions

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 possible dose and by not exceeding the maximum recommended dose.

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 with therapeutic doses. Patients with underlying neurological disorders are at increased risk of this side effect.

Caution should be exercised when treating adult patients especially the elderly, with focal spasticity affecting the lower limbs, who may be at increased risk of fall. In placebo-controlled clinical studies, where patients were treated for lower limb spasticity, 6.3% and 3.7% of patients experienced a fall in the Dysport and placebo groups, respectively.

Dry eye has been reported with the use of Dysport in the treatment of glabellar lines, lateral canthal lines, blepharospasm and hemifacial spasm (see section 4.8). Reduced tear production, reduced blinking, and corneal disorders, may occur with the use of botulinum toxins, including Dysport.

Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported following treatment with botulinum toxin A or B. Patients with disorders resulting in defective neuromuscular 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.

Dysport should be administered with caution to patients with pre-existing swallowing or breathing problems as these 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 who have a chronic respiratory disorder.

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

Patients and their caregivers must be warned of the necessity to seek immediate medical treatment in case of swallowing, speech or respiratory problems.

Dysport should not be used to treat spasticity in patients who have developed a fixed contracture.

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

Caution should be taken when Dysport is used where the targeted muscle shows excessive weakness or atrophy.

Dysport should only be used to treat a single patient, during a single session. Specific precautions must be taken during 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).

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

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

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

Paediatric use

For the treatment of spasticity associated with cerebral palsy in children, Dysport should only be used in children of 2 years of age or over. Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general, the dose used in these cases was in excess of that recommended (see section 4.8).

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin, including following off-label use (e.g. neck area). Extreme caution should be exercised when treating paediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. Treatment in patients with poor underlying health status should be administered only if the potential benefit to the individual patient is considered to outweigh the risks.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of botulinum toxin may be potentiated by drugs interfering either directly or indirectly with neuromuscular function (e.g. aminoglycosides, curare-like non-depolarising blockers, muscle relaxants) and such drugs should be used with caution in patients treated with botulinum toxin due to the potential for undesirable effects.

4.6 Fertility, 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 high 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.

Breast-feeding

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.

Fertility

Studies in male and female rats have shown effects on fertility (see section 5.3).

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

General

Side effects related to spread of toxin distant from the site of administration have been reported such as dry mouth, exaggerated muscle weakness, dysphagia, aspiration/aspiration pneumonia, with fatal outcome in some very rare cases. (see section 4.4). Hypersensitivity reactions have also been reported post-marketing.

The frequency of adverse reactions reported in placebo-controlled trials after a single administration is defined as follows:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

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/TBI and axillary hyperhidrosis:

System Organ Class	Frequency	Adverse Drug Reaction
Nervous system disorders	Rare	Neuralgic amyotrophy
Skin and subcutaneous tissue disorders	Uncommon	Pruritus
	Rare	Rash
General disorders and administration site conditions	Common	Asthenia, fatigue, influenza-like illness, injection site reactions (e.g. pain, bruising, pruritus, oedema)

Frequency of specific adverse reactions by indication

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

Focal spasticity affecting the upper limbs in adults

System Organ Class	Frequency	Adverse Drug Reaction
Gastrointestinal disorders	Uncommon	Dysphagia*
Musculoskeletal and connective tissue disorders	Common	Muscular weakness Musculoskeletal pain, pain in the extremity

*The frequency for dysphagia was derived from pooled data from open-label studies. Dysphagia was not observed in the double-blind studies in the Adult Upper Limb (AUL) indication

Focal spasticity affecting the lower limbs in adults

System Organ Class	Frequency	Adverse Drug Reaction
Gastrointestinal disorders	Common	Dysphagia
Musculoskeletal and connective tissue disorders	Common	Muscular weakness, myalgia
General disorders and administration site conditions	Common	Asthenia, fatigue, influenza-like illness, injection site reactions (pain, bruising, rash, pruritus)
Injury, poisoning and procedural complications	Common	Fall

Dynamic equinus foot deformity due to focal spasticity in ambulant paediatric cerebral palsy patients, two years of age or older

System Organ Class	Frequency	Adverse Drug Reaction
Musculoskeletal and connective tissue disorders	Common	Myalgia, muscular weakness
Renal and urinary disorders	Common	Urinary incontinence
General disorders and administration site conditions	Common	Influenza-like illness, injection site reaction (e.g. pain, erythema, bruising etc.), gait disturbance, fatigue
	Uncommon	Asthenia
Injury, poisoning and procedural complications	Common	Fall

Focal spasticity of upper limbs in paediatric cerebral palsy patients, two years of age or older

System Organ Class	Frequency	Adverse Drug Reaction
Musculoskeletal and connective tissue disorders	Common	Muscular weakness, pain in extremity
	Uncommon	Myalgia
General disorders and administration site conditions	Common	Influenza-like illness, asthenia, fatigue, injection site bruising
	Uncommon	Injection site eczema, injection site pain, injection site rash, injection site swelling
Skin and subcutaneous tissue disorders	Common	Rash

Focal spasticity of upper and lower limbs in paediatric cerebral palsy patients, two years of age or older

When treating upper and lower limbs concomitantly with Dysport at a total dose of up to 30 U/kg or 1000 U whichever is lower, there are no safety findings in addition to those expected from treating either upper limb or lower limb muscles alone.

Spasmodic torticollis

System Organ Class	Frequency	Adverse Drug Reaction
Nervous system disorders	Common	Headache, dizziness, facial paresis
Eye disorders	Common	Vision blurred, visual acuity reduced
	Uncommon	Diplopia, ptosis
Respiratory, thoracic and mediastinal disorders	Common	Dysphonia, dyspnoea
	Rare	Aspiration
Gastrointestinal disorders	Very common	Dysphagia, dry mouth
	Uncommon	Nausea
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

System Organ Class	Frequency	Adverse Drug Reaction
Nervous system disorders	Common	Facial paresis
	Uncommon	VIIth nerve paralysis
Eye disorders	Very common	Ptosis
	Common	Diplopia, dry eye, lacrimation increased
	Rare	Ophthalmoplegia
Skin and subcutaneous tissue disorders	Common	Eyelid oedema
	Rare	Entropion

Side effects may occur due to deep or misplaced injections of Dysport paralysing other nearby muscle groups.

Moderate to severe glabellar lines

System Organ Class	Frequency	Adverse Drug Reaction
Nervous system disorders	Very common	Headache
	Common	Temporary facial paresis (due to temporary paresis of facial muscle proximal to injection sites predominantly describes brow paresis)
	Uncommon	Dizziness

Eye disorders	Common	Asthenopia, eyelid ptosis, eyelid oedema, lacrimation increased, dry eye, muscle twitching (twitching of muscles around the eyes)
	Uncommon	Vision impairment, 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 haemotoma)
Immune system disorders	Uncommon	Hypersensitivity

Moderate to severe lateral canthal lines

System Organ Class	Frequency	Adverse Drug Reaction
Nervous system disorders	Common	Headache, temporary facial paresis (temporary paresis of facial muscles proximal to injection sites)
Eye disorders	Common	Eyelid oedema, eyelid ptosis
	Uncommon	Dry eye
General disorders and administration site conditions	Common	Injection site reactions (e.g. haematoma, pruritus and oedema)

Axillary hyperhidrosis

System Organ Class	Frequency	Adverse Drug Reaction
Nervous system disorders	Common	Dizziness, headache, paraesthesias, involuntary muscle contractions of the eyelid
Vascular disorders	Uncommon	Flushing
Respiratory, thoracic and mediastinal disorders	Common	Dyspnea
	Uncommon	Epistaxis
Skin and subcutaneous tissue disorders	Common	Compensatory sweating
Musculoskeletal and connective tissue disorders	Common	Pain in the shoulder, upper arm and neck, myalgia of the shoulder and calf

Post-marketing experience

System Organ Class	Frequency	Adverse Drug Reaction
Immune system disorders	Not known	Hypersensitivity
Nervous system disorders	Not known	Hypoaesthesia
Musculoskeletal and connective tissue disorders	Not known	Muscle atrophy

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. General supportive care is advised. In the event of overdose the patient should be medically monitored for any signs and/or symptoms 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 occurs the patient should be medically supervised for several weeks for signs and/or 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 postganglioni 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.

Focal spasticity in adults

Upper limb

The efficacy and safety of Dysport for the treatment of upper limb spasticity was evaluated in a randomized, multi-centre, double-blind, placebo-controlled study that included 238 patients (159 Dysport and 79 placebo) with upper limb spasticity who were at least 6 months post-stroke (90%) or post-traumatic brain injury (10%). The primary targeted muscle group (PTMG) was the extrinsic finger flexors (56%), followed by the elbow (28%) and wrist flexors (16%).

The primary efficacy variable was the PTMG muscle tone at week 4, as measured by the Modified Ashworth Scale (MAS), a 5 point scale ranging from 0 (no increase in muscle tone) to 4 (affected in part[s] rigid in flexion or extension) and the first secondary endpoint was the Physician Global Assessment (PGA) of response to treatment (a 9 point scale ranging from -4 [markedly worse], through 0 [no change], to +4 [markedly improved]). The main results achieved at Week 4 and Week 12 are shown below:

	Week 4	Week 12

	Placebo (N=79)	Dysport (500 units) (N=80)	Dysport (1000 units) (N=79)	Placebo (N=79)	Dysport (500 units) (N=80)	Dysport (1000 units) (N=79)
LS Mean Change from Baseline in PTMG Muscle Tone on the MAS	-0.3	-1.2**	-1.4**	-0.1 n=75	-0.7** n=76	-0.8** n=76
LS Mean PGA of Response to Treatment	0.7	1.4*	1.8**	0.4 n=75	0.5 n=76	1.0* n=76
LS Mean Change from Baseline in Wrist Flexor Muscle Tone on the MAS	-0.3 n=54	-1.4** n=57	-1.6** n=58	-0.3 n=52	-0.7 n=54	-0.9* n=56
LS Mean Change from Baseline in Finger Flexor Muscle Tone on the MAS	-0.3 n=70	-0.9* n=66	-1.2** n=73	-0.1 n=67	-0.4* n=62	-0.6* n=70
LS Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS	-0.3 n=56	-1.0* n=61	-1.2** n=48	-0.3 n=53	-0.7* n=58	-0.8* n=46
Mean Change from Baseline in Shoulder Extensors Muscle Tone on the MAS (1)	-0.4 n=12	-0.6 n=7	-0.7 n=6	0.0 n=12	-0.9 n=7	0.0 n=6
*p<0.05; **p<0.0001; LS = Least Square (1) No statistical tests performed due to low frequency by treatment and placebo groups as there are limited data in patients treated in the shoulder muscles.						

The Principal Target of Treatment (PTT) of the Disability Assessment Scale [DAS] was used to investigate the effect of treatment on functional impairment (passive function). Although some improvement in the mean change from baseline at Week 4 in the Dysport groups did not reach statistical significance compared to placebo, the proportion of DAS score responders (subjects achieving at least a one grade improvement) for the PTT was significantly higher at the 1000U dose as shown below.

Treatment Group	Week 4 % Responders	Week 12 % Responders
Dysport 500U	50.0 n=80 p=0.13	41.3 n=76 p=0.11
Dysport 1000U	62.0 n=78 p=0.0018	55.7 n=76 p=0.0004
Placebo	39.2 n=79	32.9 n=75

Domains included in DAS are hygiene, limb position, dressing and pain.

In addition, statistically significant improvements in spasticity (grade and angle) assessed by the Tardieu scale, in the active range of motion of the fingers, wrist or elbow, and in ease of applying a splint by the subject were observed, especially at the 1000U dose. However, there was no effect of treatment shown on the active function, as assessed by the Modified Frenchay Score, and on quality of life EQ5D or SF-36 questionnaires.

Lower limb affecting the ankle joint

The efficacy and safety of Dysport for the treatment of lower limb spasticity was evaluated in a pivotal randomised, multi-centre, double-blind, placebo-controlled study that included 385 post-stroke and brain injury patients (255 Dysport and 130 placebo-treated subjects) with lower limb spasticity primarily affecting the ankle joint. Two doses of Dysport were evaluated for efficacy; Dysport 1000U (N = 125), Dysport 1500U (N = 128) against Placebo (N =128). The primary target muscle group was the gastrocnemius - soleus complex (GSC). The primary end point was Modified Ashworth Scale (MAS) score assessed at the ankle joint (with the knee extended) at week 4.

Dysport was divided between the GSC and at least one other distal or proximal lower limb muscle according to clinical presentation.

When assessing the primary endpoint, MAS at the ankle with the knee extended (involving all plantar flexors), statistically significant improvement was observed for 1500U. When assessing MAS at the ankle with the knee flexed (involving all plantar flexors except the gastrocnemius), statistically significant improvement was observed for both 1000U and 1500U.

	Week 4			Week 12		
	Placebo (N=128)	Dysport (1000U) (N=125)	Dysport (1500U) (N=128)	Placebo (N=128)	Dysport (1000U) (N=125)	Dysport (1500U) (N=128)
LS Mean Change from Baseline on the MAS (knee extended)	-0.5	-0.6	-0.8*	-0.4	-0.4	-0.6*
LS Mean Change from baseline on MAS (knee flexed)	-0.4	-0.7*	-0.8**	-0.3	-0.5*	-0.6*
*p<0.05; **p<0.001; LS = Least Square						

Spasticity assessment using the Tardieu Scale (TS) showed that there were statistically significant improvements in spasticity grade at Weeks 4 to 20 in the Dysport 1500U group and at Weeks 4 to 12 in the Dysport 1000U group. In addition, it showed statistically significant differences in Angle of Catch at Week 1 and 16, favouring the higher dose of Dysport.

Based on post hoc analysis due to non-normality of PGA data, Dysport treatment was also associated with statistically significant clinical improvement at both doses as measured by the Physician Global Assessment (PGA) Score.

Numerical improvement in ankle dorsiflexion for the higher Dysport dose was seen with the change peaking at 4 weeks post administration.

Additional endpoints such as reduction in pain, using walking aids and quality of life measures did not show statistically significant improvement.

On completion of this study, 345 patients entered an open-label extension study in which re-treatment with Dysport 1000U or 1500U was determined by clinical need.

This long term follow up study confirmed a prolonged treatment effect on spasticity related outcome measures following repeated injections.

Improvements in efficacy parameters (MAS, PGA and TS) seen after 4 weeks of double blind treatment with Dysport in the lower limb were maintained over repeated treatment.

Improvements in 10-m walking speed (comfortable and maximal, with or without shoes) were observed, which increased with successive treatment cycles.

No significant improvements in lower limb pain using the SPIN scale, use of walking aids or quality of life measures were observed.

Blepharospasm

Three Dysport doses were investigated over 1 treatment cycle in a clinical study.

Efficacy was measured by the medians of differences in the Percentage of Normal Activity (PNA) values (derived from the Blepharospasm Disability Scale) between each treatment group and placebo. A dose-dependent improvement in blepharospasm was evident with Dysport dose, with all treatment groups being superior to placebo.

Difference between the median of the changes in PNA values from baseline in the active group and the median of the changes in PNA values from baseline in the placebo group	Dysport 40U (N=30)	Dysport 80U (N=31)	Dysport 120U (N=31)
Week 4:	31.2%	41.3%	48.5%
Week 8:	36.0%	48.3%	55.0%
Week 12:	36.0%	36.3%	50.0%
Week 16:	10.5% [a]	24.2%	31.3%

[a] p value >0.001

For the 40 units, 80 units and 120 units Dysport treatment groups, the medians of the changes from baseline in PNA values were statistically significantly higher compared to those in placebo group at weeks 4, 8, and 12.

A statistically significant difference compared to placebo group was also observed for the 80 units and 120 units Dysport treatment groups at week 16, indicating a greater duration of response at the 80 units and 120 units doses.

The incidence of related Treatment Emergent Adverse Events (TEAEs), specifically ptosis, was higher in the Dysport treatment groups than in the placebo treatment group and was dose-dependent with greater incidence seen at higher Dysport doses. See table below:

	Statistic	Placebo (N=26)	Dysport 40U (N=31)	Dysport 80U (N=31)	Dysport 120U (N=31)
Patients with related TEAEs	n (%)	3 (12)	19 (61)	23 (74)	26 (84)
Patients with related eye	n (%)	3 (12)	16 (52)	23 (74)	26 (84)

TEAEs					

Focal spasticity in paediatric cerebral palsy patients, two years of age or older

Dynamic equinus foot deformity due to focal spasticity in ambulant paediatric cerebral palsy patients, two years of age or older

A double-blind, placebo-controlled multicentre study (Study Y-55-52120-141) was conducted in children with dynamic equinus foot deformity due to spasticity in children with cerebral palsy. A total of 235 botulinum toxin naïve or non-naïve patients with a Modified Ashworth Score (MAS) of grade 2 or greater were enrolled to receive Dysport 10 units/kg/leg, Dysport 15 units/kg/leg or placebo. Forty one percent of patients were treated bilaterally resulting in a total Dysport dose of either 20 units/kg or 30 units/kg. The primary efficacy variable was the mean change from baseline in MAS in ankle plantar flexors at Week 4. Secondary efficacy variables were the mean Physicians Global Assessment (PGA) score and Mean Goal Attainment Scaling (GAS) score at Week 4. Patients were followed up for at least 12 weeks post-treatment and up to a maximum of 28 weeks. On completion of this study, patients were offered entry into an open-label extension study (Study Y-55-52120-147).

MAS Change from Baseline at Week 4 and Week 12, PGA and GAS at Week 4 and Week 12 (ITT Population)

Parameter	Placebo (N=77)	Dysport	
		10U/kg/leg (N=79)	15U/kg/leg (N=79)
LS mean change from baseline in ankle plantar MAS score			
Week 4	-0.5	-0.9**	-1.0***
Week 12	-0.5	-0.8**	-1.0***
LS mean score for PGA response to treatment [b]			
Week 4	0.7	1.5***	1.5***
Week 12	0.4	0.8*	1.0**
LS mean GAS score [a]			
Week 4	46.2	51.5***	50.9**
Week 12	45.9	52.5***	50.5*
* $p \leq 0.05$; ** $p \leq 0.003$; *** $p \leq 0.0006$ compared to placebo; LS = least square [a] GAS score measures progress towards goals that were selected at baseline from a list of twelve categories. The five most commonly selected goals were improved walking pattern (70.2%), improved balance (32.3%), decreased frequency of falling (31.1%), decreased frequency of tripping (19.6%) and improved endurance (17.0%)			

Improvement in the spasticity of the ankle plantar flexors was observed, as assessed by the Tardieu scale. The spasticity grade (Y) was statistically significantly improved compared to placebo for both the 10 units/kg/leg and 15 units/kg/leg Dysport treatment groups at Week 4 and Week 12, and the angle of catch (Xv3) was significant for the 10 units/kg/leg Dysport group at Week 12 and at both Week 4 and Week 12 for the 15 units/kg/leg Dysport group.

Both Dysport treatment groups, 10 units/kg/leg and 15 units/kg/leg, demonstrated a significant improvement from baseline in the Observational Gait Scale (OGS) overall score at Week 4 when compared

to placebo and a statistically significantly higher proportion of patients were treatment responders for initial foot contact on the OGS at Week 4 and Week 12.

Parents completed the condition-specific Module for cerebral palsy for the Paediatric Quality of Life Inventory. There was a statistically significant improvement from baseline in fatigue at Week 12 in the Dysport 10 units/kg/leg and 15 units/kg/leg Dysport treatment groups compared to placebo. No other statistically significant improvements were observed in the other subscales.

On completion of this study, 216 patients entered an open-label extension study (Y-55-52120-147) where they could receive re-treatment based on clinical need. Both distal (gastrocnemius, soleus and tibialis posterior) and proximal (hamstrings and hip adductors) muscles were permitted to be injected, including multilevel injections. Efficacy was observed over repeated treatment sessions for up to 1 year as assessed by MAS, PGA and GAS.

Focal spasticity of upper limbs in paediatric cerebral palsy patients, two years of age or older

The efficacy and safety of Dysport for the treatment of upper limb spasticity in children was evaluated in a randomised, multi-centre, double-blind, controlled, study in which doses of 8 U/kg and 16 U/kg in the selected study upper limb were compared with a low dose control group of 2 U/kg. A total of 210 botulinum toxin naïve or non-naïve patients with upper limb spasticity due to cerebral palsy (Modified Ashworth Scale (MAS) score ≥2 in the primary targeted muscle group (PTMG)) were randomised and treated in the study.

The total dose of Dysport was injected intramuscularly into the affected upper limb muscles which included the PTMG of either elbow flexors or wrist flexors as well as other upper limb muscles according to the disease presentation. No more than 0.5 ml was allowed to be administered per injection site. However more than one injection site per muscle was permitted. An Electrical stimulation (ES) and/or ultrasound was used to assist muscle localization for injection.

After the initial treatment, up to 3 further treatments of Dysport could be administered at planned doses of either 8 U/kg or 16 U/kg, although the investigator could elect to increase or decrease the dose (but not exceeding 16 U/kg). The minimum retreatment interval was 16 weeks. For treatment cycles 2, 3 and 4, injection into the lower limbs and the non-study upper limb was also allowed at the same time as the study upper limb was injected. Subjects were followed-up for a minimum of 1 year to a maximum of 1 year 9 months after entry into the study.

The primary efficacy variable was the mean change from baseline in MAS in PTMG at Week 6. Secondary efficacy variables were the mean Physicians Global Assessment (PGA) score and mean Goal Attainment Scale (GAS) score at Week 6.

MAS Change from Baseline at Week 6 and Week 16, PGA and GAS at Week 6 and Week 16 – Treatment Cycle 1 (mITT)

	Dysport 2 U/kg (N=69)	Dysport 8 U/kg (N=69)	Dysport 16 U/kg (N=70)
Week 6 LS Mean Change from Baseline in PTMG MAS score Difference in LS Means (95% CI)	-1.5	-1.9**	-2.2***

compared to 2 U/kg		-0.4 (-0.8, -0.1)	-0.7 (-1.0, -0.4)
Week 16 LS Mean Change from Baseline in PTMG MAS score Difference in LS Means (95% CI) compared to 2 U/kg	-1.0	-1.3 -0.3 (-0.7, 0.0)	-1.6** -0.6 (-1.0, -0.3)
Week 6 LS Mean Change from Baseline in Wrist Flexors MAS score Difference in LS Means (95% CI) compared to 2 U/kg	-1.3	-1.5 -0.2 (-0.6, 0.2)	-1.7 -0.3 (-0.7, 0.0)
Week 16 LS Mean Change from Baseline in Wrist Flexors MAS score Difference in LS Means (95% CI) compared to 2 U/kg	-0.9	-1.0 -0.0 (-0.4, 0.4)	-1.2 -0.2 (-0.6, 0.1)
Week 6 LS Mean Change from Baseline in Elbow Flexors MAS score Difference in LS Means (95% CI) compared to 2 U/kg	-1.1	-1.7** -0.7 (-1.0, -0,3)	-1.9*** -0.8 (-1.2, -0,5)
Week 16 LS Mean Change from Baseline in Elbow Flexors MAS score Difference in LS Means (95% CI) compared to 2 U/kg	-0.6	-1.1* -0.5 (-0.9, -0.1)	-1.3*** -0.7 (-1.1, -0.4)
Week 6 LS Mean Change from Baseline in Finger Flexors MAS score Difference in LS Means (95% CI) compared to 2 U/kg	-0.6	-1.5* -0.9 (-1.4, -0.4)	-1.4* -0.7 (-1.3, -0.2)
Week 16 LS Mean Change from Baseline in Finger Flexors MAS score Difference in LS Means (95% CI) compared to 2 U/kg	-0.7	-1.1 -0.4 (-1.0, 0.2)	-1.4* -0.7 (-1.4, -0.1)

Week 6 LS Mean PGA score Difference in LS Means (95% CI) compared to 2 U/kg	1.8	2.0 0.3 (-0.0, 0.6)	2.0 0.2 (-0.1, 0.5)
Week 16 LS Mean PGA score Difference in LS Means (95% CI) compared to 2 U/kg	1.7	1.6 -0.1 (-0.4, 0.3)	1.8 0.1 (-0.2, 0.5)
Week 6 LS Mean Total GAS score [a] Difference in LS Means (95% CI) compared to 2 U/kg	52.1	52.6 0.5 (-2.7, 3.7)	52.6 0.5 (-2.6, 3.7)
Week 16 LS Mean Total GAS score [a] Difference in LS Means (95% CI) compared to 2 U/kg	55.1	54.2 -0.9 (-4.4, 2.7)	55.7 0.6 (-2.9, 4.1)
LS=least square PTMG: elbow flexors or wrist flexors * p≤ 0.05; **p≤ 0.001; *** p≤ 0.0001; compared to 2 U/kg dose group [a] The four most commonly selected primary goals were Reaching, Grasp and release, Use of limb as a helping hand to stabilise and Involving affected arm more in daily activities.			

Improvement in the spasticity of the PTMG was observed, as assessed by the Tardieu scale. In the PTMG elbow flexors, the angle of catch (Xv3) was statistically significantly improved compared with Dysport 2 U/kg at Week 6 for both the 8 and 16 U/kg treatment groups and also at Week 16 for the Dysport 16 U/kg group. In addition, a statistically significant decrease from Baseline in spasticity grade (Y) at Week 6 and 16 was observed for the Dysport 16 U/kg group compared with Dysport 2 U/kg. In the PTMG wrist flexors, statistically significant improvements from Baseline in Xv3 and Y were observed in the Botulinum Toxin Type A 16 U/kg group compared with the Dysport 2 U/kg group at Week 6 but not for the 8 U/kg group.

Parents completed the condition-specific Module for Cerebral Palsy for the Paediatric Quality of Life Inventory. At Week 16, there was a statistically significant improvement from Baseline in fatigue (p=0.0251) in the Dysport 8 U/kg group and, in movement and balance (p=0.0253) in the 16 U/kg group compared with the Dysport 2 U/kg group. No other statistically significant improvements were observed in the other subscales.

The majority of subjects treated with Dysport were retreated by Week 28 (62.3% in the Dysport 8 U/kg group and 61.4% in the Dysport 16 U/kg group), though more than 24% of subjects in both treatment groups had not yet required retreatment by Week 34.

Following repeated treatment, efficacy was generally maintained across treatment cycles for both Dysport 8 U/kg and 16 U/kg groups.

Moderate to severe glabellar lines and lateral canthal lines

During the clinical development of Dysport, for the treatment of moderate to severe glabellar lines and lateral canthal lines, more than 4500 patients were included in the different clinical trials and approximately 3800 patients were exposed to Dysport.

Glabellar lines

In clinical studies, 2032 patients with moderate to severe glabellar lines have been treated at the recommended dose of 50U of Dysport. Of these, 305 were treated with 50U in two pivotal Phase III double-blind placebo-controlled studies and 1200 treated with 50U in a long-term open-label repeated dose Phase III study. The remaining patients were treated in supportive and dose-ranging studies.

The median time to onset of response was 2 to 3 days following treatment, with the maximum effect observed at day thirty. In both pivotal placebo-controlled phase III studies, Dysport injections significantly reduced the severity of glabellar lines for up to 4 months. The effect was still significant after 5 months in one of the two pivotal studies.

Thirty days after injection, the assessment of the investigators showed that 90% (273/305) of patients had responded to treatment (exhibited no or mild glabellar lines at maximum frown), compared to 3% (4/153) placebo-treated patients. Five months after injection, 17% (32/190) of patients treated with Dysport were still responding to treatment compared to 1% (1/92) of placebo treated patients in the concerned study. The patients' own assessment at maximum frown after thirty days gave a response rate of 82% (251/305) for those treated with Dysport and 6% (9/153) for those treated with placebo. The proportion of patients exhibiting a two-grade improvement according to the investigator assessment at maximum frown, was 77% (79/103) in the one pivotal Phase III study where this was assessed.

A subset of 177 patients had moderate or severe glabellar lines at rest prior to treatment. Assessment by investigators of this population, thirty days after treatment, showed that 71% (125/177) of Dysport-treated patients were considered responders versus 10% (8/78) of placebo treated patients.

The long-term repeat dose open-label study showed that the median time to onset of response of 3 days was maintained across repeated dose cycles. The responder rate at maximum frown as determined by the investigator at day 30 was maintained over repeated cycles (ranging between 80% and 91% over the 5 cycles). The responder rate at rest over repeated dose cycles was also consistent with the single dose studies, with 56% to 74% of Dysport-treated patients considered by investigators to be responders thirty days after treatment.

Lateral canthal lines

In clinical studies, 308 patients with moderate to severe lateral canthal lines at maximum smile have been treated at the recommended dose of 30 units per side in double-blind studies. Of these, 252 were treated in a Phase III double-blind placebo controlled study and 56 patients were treated in a double-blind Phase II dose-ranging study.

In the phase III study, Dysport injections significantly reduced the severity of lateral canthal lines compared with placebo ($p \leq 0.001$) at 4, 8 and 12 weeks (assessed at maximum smile by the investigators). For the subjects' assessment of satisfaction with the appearance of their lateral canthal lines, there was a statistically significant difference between Dysport and placebo ($p \leq 0.010$) in favour of Dysport at 4, 8, 12 and 16 weeks.

The primary efficacy endpoint was at 4 weeks following injection: the assessment of the investigators showed that 47.2% (119/252) of patients had responded to treatment (exhibited no or mild lateral canthal lines at maximum smile), compared to 7.2% (6/83) placebo-treated patients.

In a post-hoc analysis, at the same time point, 4 weeks following injection, 75% (189/252) of Dysport treated patients had at least 1 grade improvement at maximum smile compared with only 19% (16/83) of placebo-treated subjects.

A total of 315 subjects entered the open label extension phase of the Phase III study in which they could be treated concomitantly for both lateral canthal lines and glabellar lines. Patients treated with Dysport in the double-blind and open label phases of the Phase III received a median of 3 treatments for lateral canthal lines. The median interval between injections for lateral canthal lines, which was largely determined by the protocol design, ranged from 85 to 108 days. The results showed that efficacy is maintained with repeated treatments over the period of one year.

The patient satisfaction levels at weeks 4, 16 and 52 show after the first treatment with Dysport that 165/252 subjects (65.5%) were either very satisfied or satisfied with the appearance of their LCLs.

At week 16, 4 weeks after either a second Dysport treatment for those randomised to Dysport in Part A or the first treatment for those randomised to placebo the proportion who were very satisfied or satisfied was 233/262 (89.0%). At week 52 when subjects could have had up to five cycles of Dysport treatment with the last one being at week 48 the proportion of very satisfied/satisfied subjects was 255/288 (84.7%).

No patient tested positive for toxin-neutralising antibodies after receiving repeated treatments with Dysport over one year.

Axillary hyperhidrosis

The efficacy and safety of Dysport for the treatment of Axillary Hyperhidrosis was evaluated in a multi-centre, randomised, double-blind clinical study that included 152 adult patients with Axillary Hyperhidrosis who had symptoms for greater than one year and had failed standard therapy. Patients were injected with 200U in one axilla and placebo into the other. Two weeks later patients were injected with 100U Dysport in the axilla previously injected with placebo.

At the primary end point i.e. two weeks after treatment with Dysport, efficacy was measured as PCF (Proportional Change Function of sweat production on gravimetric analysis mg/min) relative to baseline. The results are shown below:

PCF in Sweat Production 2 Weeks Post Injection	Dysport 200U (N=152)	Dysport 100U (N=151)	Placebo (N=152)
Mean reduction (SD)	-0.814 (0.239)*#	-0.769 (0.257)	-0.051 (0.546)
% reduction	81.4	76.9	5.1
Median reduction [range]	-0.900 [-1.000; 0.545]	-0.845 [-1.000; 0.835]	-0.110 [-0.917; 3.079]

PCF = proportional change function; SD = standard deviation; U = units; vs = versus
*Paired t-test Dysport 200U vs placebo: $p<0.0001$
#Paired t-test Dysport 200U vs Dysport 100U: $p=0.0416$

In the same study, absolute sweat production was a secondary endpoint: 200U Dysport treatment resulted in an average absolute sweat production decrease from 165 ± 112 mg/min to 24 ± 27 mg/min 2 weeks after injection, and 86.2% of patients achieved an absolute sweat rate of less than 50 mg/min. The 100U treatment

resulted in an average absolute sweat production decrease from 143 ± 111 mg/min to 31 ± 48 mg/min 2 weeks after injection, and 83.4 % of patients achieved an absolute sweat rate of less than 50 mg/min. The placebo treatment resulted in an average absolute sweat production decrease from 173 ± 131 mg/min to 143 ± 111 mg/min 2 weeks after injection, and 3.9% of patients achieved an absolute sweat rate of less than 50 mg/min.

Efficacy was observed for up to 48 weeks. Subsequent injections under a follow up open label study showed a similar decrease in sweating though there was some evidence that duration of effect may persist for longer in subsequent treatment cycles.

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 Pre-clinical safety data

In a chronic toxicity study performed in rats, up to 12 units/animal, there was no indication of systemic toxicity. 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 (see section 4.6).

In a pivotal single dose study, juveniles showed a slight delay in sexual maturation (not observed in the repeat dose study), an effect associated with decreased body weight, but subsequent mating performance and fertility were unaffected. In a pivotal repeated dose juvenile study, rats treated weekly from the age of weaning on Postnatal Day 21 up to 13 weeks of age comparable to children of 2 years old, to young adulthood (11 administrations over 10 weeks, up to total dose of approximately 33 units/kg) do not show adverse effects on postnatal growth (including skeletal evaluation), reproductive, neurological and neurobehavioral development.

The effects in reproduction, juvenile and chronic toxicity non-clinical studies were limited to changes in 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
Lactose

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial
2 years

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C – 8°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial 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.

6.4 Special precautions for storage

Unopened vial
Store in a refrigerator (2°C – 8°C).
Do not freeze.

Reconstituted solution
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

3 mL vial (type 1 glass) with a stopper (bromobutyl rubber), with an overseal (aluminium), containing 300 or 500 units of Dysport powder for solution for injection. Pack sizes of 1 or 2 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

When preparing and handling Dysport solutions, the use of gloves is recommended. If Dysport dry powder or reconstituted solution should come into contact with the skin or mucous membranes, they should be washed thoroughly with water.

Instructions for reconstitution

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.

Each vial is for single use only.

Reconstitution instructions are specific for each of the 300 U vial and the 500 U vial. These volumes yield concentrations specific for the use for each indication.

Resulting Dose Unit per ml	Diluent* per 500 U Vial	Diluent* per 300 U Vial
500 Units 200 Units 100 Units	1 mL 2.5 mL 5 mL	0.6 mL 1.5 mL 3 mL

*Preservative-free 0.9% sodium chloride injection

For pediatric cerebral palsy spasticity, which is dosed using unit per body weight, further dilution may be required to achieve the final volume for injection.

Appearance of product after reconstitution
A clear, colorless solution, free from particulate matter.

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).

Spillage of Dysport should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

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

8. DATE OF REVISION OF THE LEAFLET

November 2023
UK SmPC dated March 2023

IPSEN