Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dysport 300 units Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Clostridium botulinum type A toxin-haemagglutinin complex 300 units.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
Uncoloured Type I glass vial containing a sterile white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dysport is indicated for focal spasticity including the:

- Symptomatic treatment of focal spasticity affecting the upper limbs in adults.
- Symptomatic treatment of focal spasticity in adults affecting the ankle joint due to stroke or traumatic brain injury (TBI).
- Treatment of dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients, two years of age or older.
- Symptomatic treatment of focal spasticity affecting the upper limbs in paediatric cerebral palsy patients, two years of age or older.

Dysport is indicated for the management of urinary incontinence in adults with neurogenic detrusor overactivity due to spinal cord injury (traumatic or non-traumatic) or multiple sclerosis, who are regularly performing clean intermittent catheterisation.

Dysport is also indicated for the following treatments:

- Spasmodic torticollis.
- Blepharospasm.
- Hemifacial spasm.
- Persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment.

4.2 Posology and method of administration

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.
Reconstitution instructions are specific for the 300 unit vial. These volumes yield concentrations specific for the use for each indication, except for the indication of urinary incontinence due to neurogenic detrusor overactivity for which there are specific instructions (please see section 6.6).

Appearance of product after reconstitution:
Reconstituted Dysport should be clear, colourless, and free of particulate matter, otherwise it must not be injected.

These volumes yield concentrations specific for the use for each indication.

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

*Preservative-free sodium chloride 9 mg/ml (0.9%) solution for injection

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

Symptomatic treatment of focal spasticity in adults

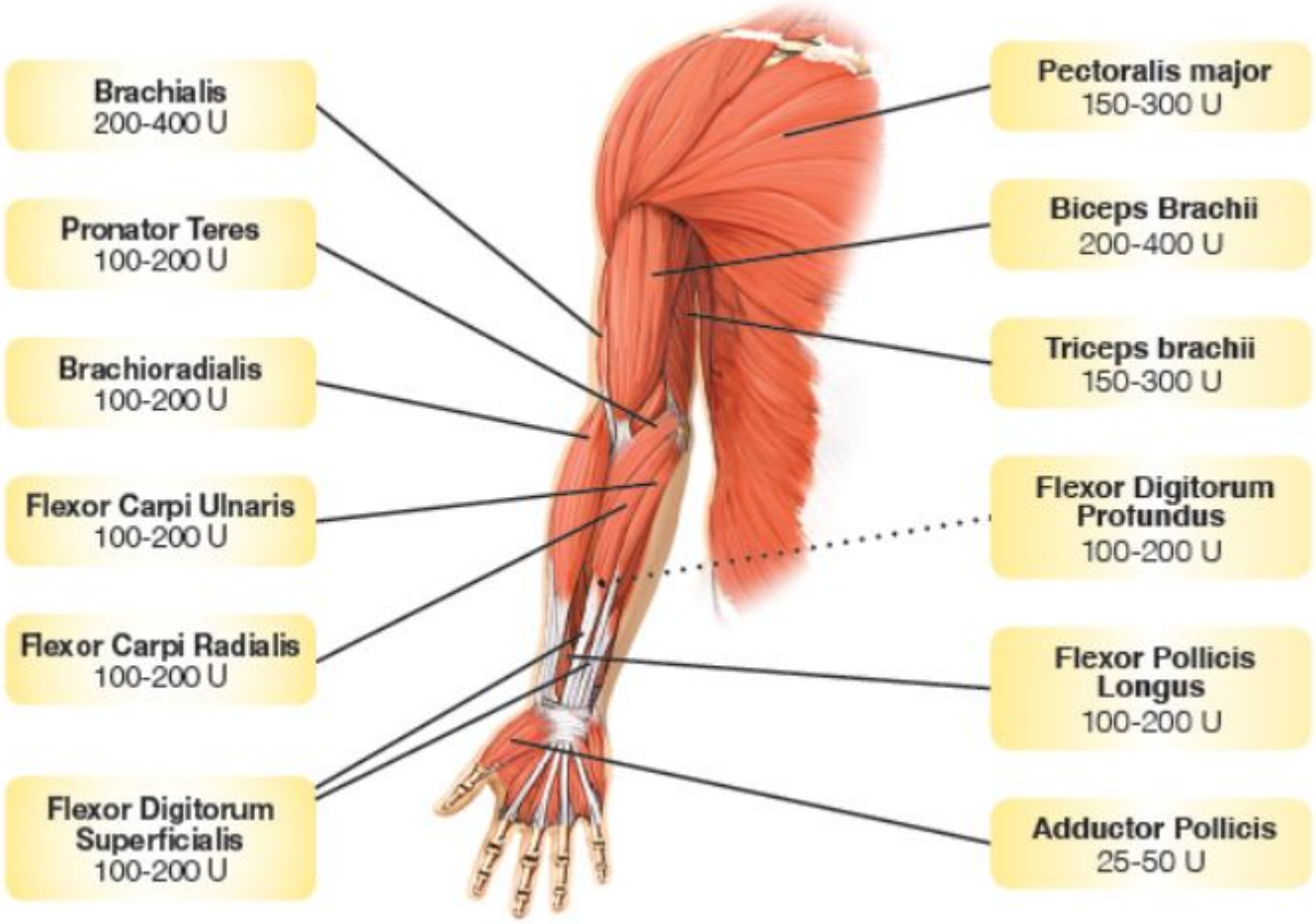
Upper limbs:

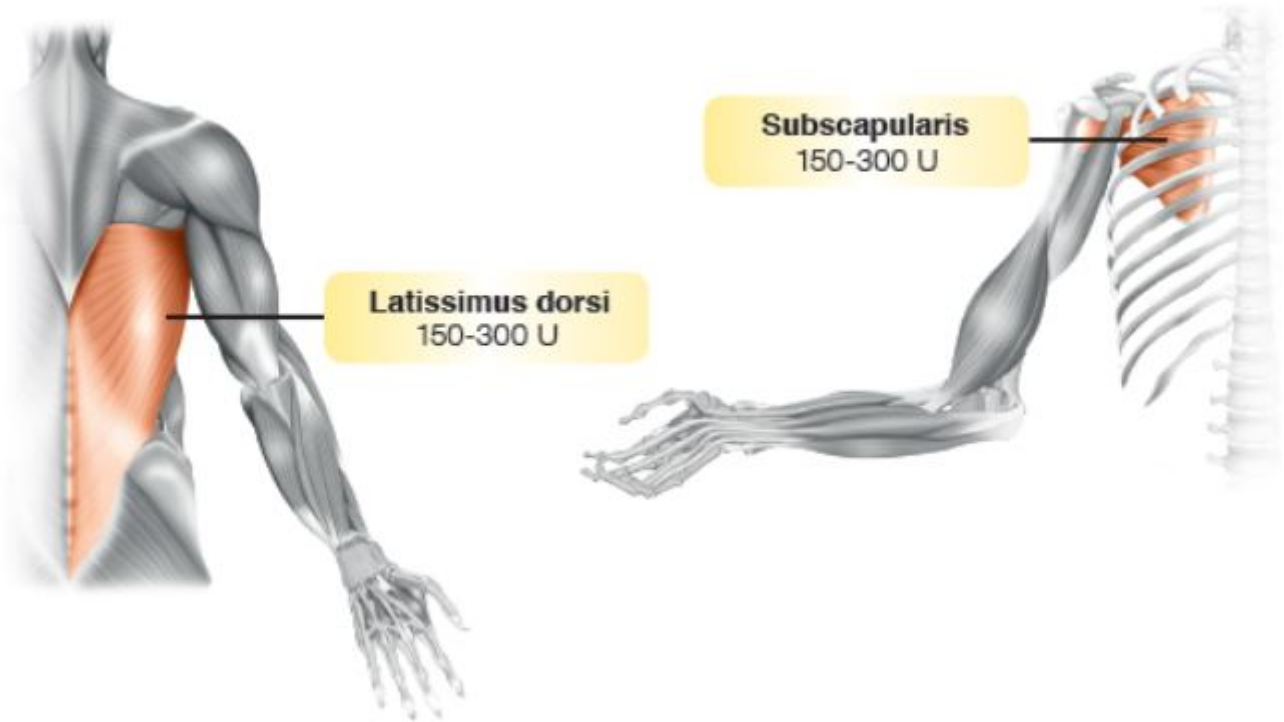
Posology

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, 1000 units and 1500 units were divided among selected muscles at a given treatment session as shown below. Doses greater than 1000U and up to 1500U can be administered when the shoulder muscles are also injected. The total dose recommended in the selected shoulder muscles is up to 500 units.

No more than 1 ml should generally be administered at any single injection site. Doses exceeding 1500U of Dysport were not investigated for the treatment of upper limb spasticity in adults.

Muscles Injected	Recommended Dose Dysport (U)	Recommended Number of Injection(s) per Muscle
Flexor carpi radialis (FCR)	100-200U	1 to 2
Flexor carpi ulnaris (FCU)	100-200U	1 to 2
Flexor digitorum profundus (FDP)	100-200U	1 to 2
Flexor digitorum superficialis (FDS)	100-200U	1 to 2
Flexor pollicis longus	100-200U	1
Adductor pollicis	25-50U	1
Brachialis	200-400U	1 to 2
Brachioradialis	100-200U	1 to 2
Biceps brachii (BB)	200-400U	1 to 2
Pronator teres	100-200U	1
Triceps brachii (long head)	150-300U	2
Pectoralis major	150-300U	2
Subscapularis	150-300U	1 to 2
Latissimus dorsi	150-300U	1 to 2





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 is recommended to target the injection sites.

Repeat Dysport treatment should be administered when the effect of a previous injection has diminished, approximately every 16 weeks (however some patients had a longer duration of response, i.e. 20 weeks) or as required to maintain the clinical response. The frequency of one injection every 12 weeks must not be exceeded (see section 5.1).

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 one week after administration of Dysport.

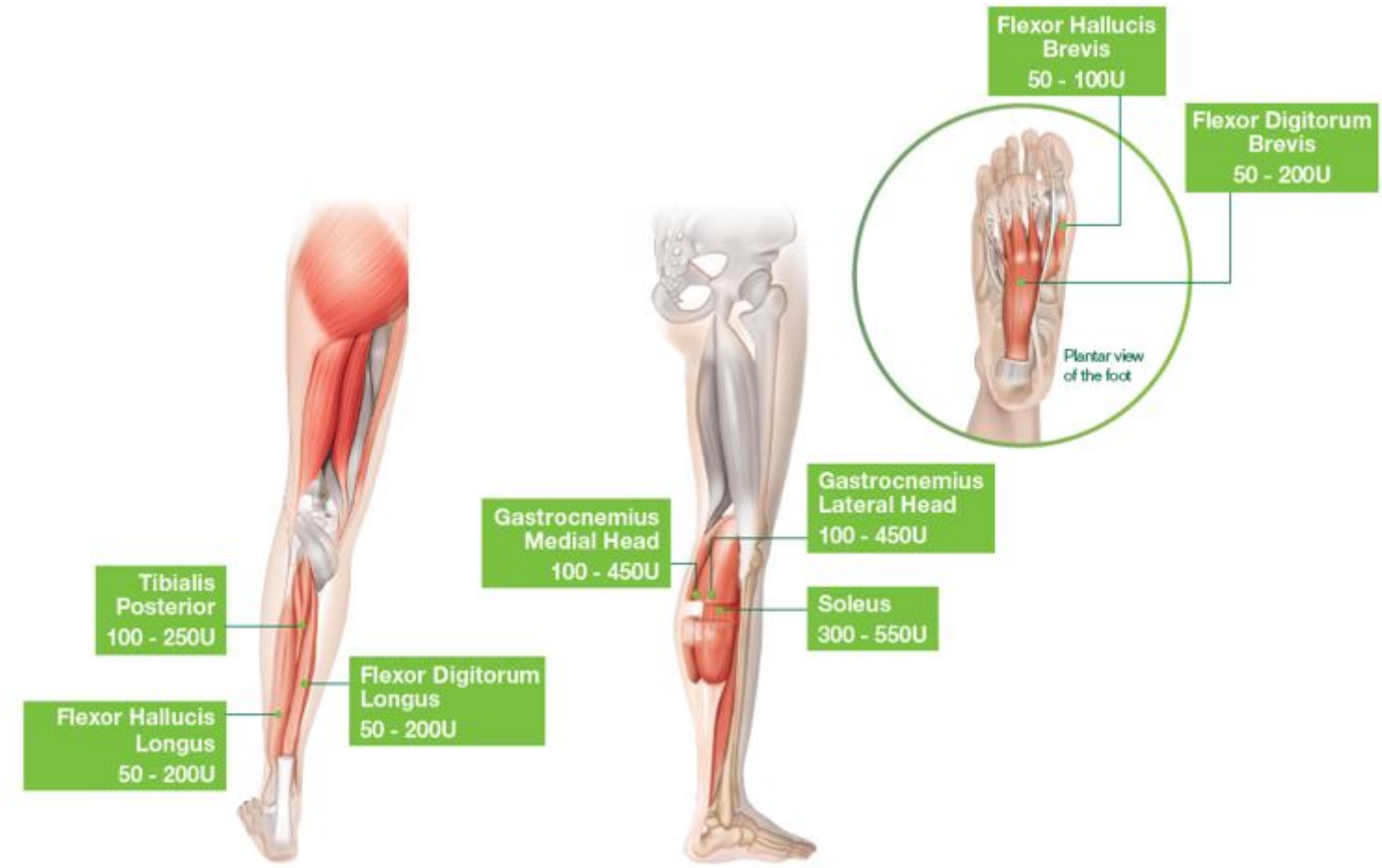
Ankle joint due to stroke or TBI:

Posology

In clinical trials, doses of 1000 units and 1500 units were divided among selected muscles. Doses of up to 1500 units may be administered intramuscularly in a single treatment session. 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 1500 units.

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
Distal		
Soleus muscle	300 - 550U	2 - 4
Gastrocnemius		
Medial head	100 - 450U	1 - 3
Lateral head	100 - 450U	1 - 3
Tibialis posterior	100 - 250U	1 - 3
Flexor digitorum longus	50 - 200U	1 - 2
Flexor digitorum brevis	50 - 200U	1 - 2
Flexor hallucis 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 and no sooner than 12 weeks after the previous injection.

Upper limbs and ankle joint due to stroke or TBI:
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, without exceeding a total dose of 1500 units.

Elderly patients (≥ 65 years): 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 they might be receiving. Undesirable effects may be reduced by using the lowest effective dose possible and by not exceeding the maximum recommended dose.

Method of administration
When treating focal spasticity affecting the upper and lower limbs in adults, 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. Dysport is administered by intramuscular injection into the muscles described above.

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

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.

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/leg	

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 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 re-treated 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.

Focal spasticity of upper limbs in paediatric cerebral palsy patients:

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.

The maximum dose of Dysport administered per treatment session when injecting unilaterally 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 brevis/ opponens pollicis	0.5 to 1 U/kg	1
Adductor pollicis	0.5 to 1 U/kg	1
Totaldose	**Up to 16 U/kg in a single upper limb (and not exceeding 21 U/kg if both upper limbs injected)**	

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 re-treated 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.

Focal spasticity of dynamic foot deformity and upper limbs in paediatric cerebral palsy patients:

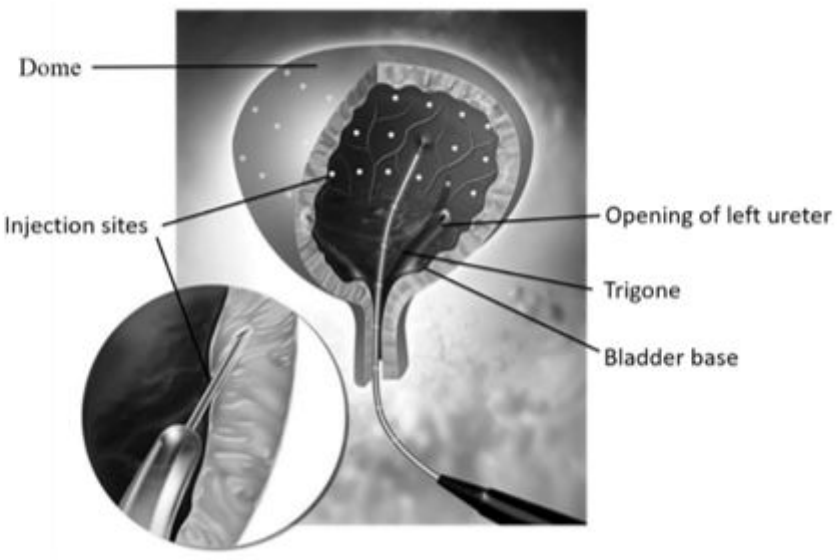
Posology
When treating combined upper and lower spasticity in children aged 2 years or older refer to the posology section for the individual indication, i.e. treatment of focal spasticity of the upper limbs or of dynamic foot deformity in paediatric cerebral palsy patients. The dose of Dysport to be injected for concomitant treatment should not exceed a total dose per treatment session of 30 U/kg or 1000 U, whichever is lower.
Re-treatment of the upper and lower limbs combined should be considered when the effect of the previous injection has diminished, but 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 focal spasticity of dynamic foot deformity or of upper limb associated with cerebral palsy in children or a combination of both, 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.

Urinary incontinence due to neurogenic detrusor overactivity:

Posology
The recommended dose is 600 U. In case of insufficient response, or in patients with severe disease presentation (e.g. according to severity of signs and symptoms, and/or urodynamic parameters), a dose of 800 U may be used.
Dysport should be administered to patients who are regularly performing clean intermittent catheterisation.
The total dose administered should be divided across 30 intradetrusor injections evenly distributed throughout the detrusor muscle, avoiding the trigone. Dysport is injected via a flexible or rigid cystoscope and each injection should be to a depth of

approximately 2 mm with the delivery of 0.5 mL to each site. For the final injection, approximately 0.5 mL of sodium chloride 9 mg/ml (0.9%) solution for injection should be injected to ensure that the full dose is delivered.



Prophylactic antibiotics should be commenced in line with the local guidelines and protocols or as used in the clinical studies (see section 5.1).

Medicinal products with anticoagulant effects should be stopped at least 3 days prior to Dysport administration and only restarted on the day after administration. If medically indicated, low molecular weight heparins may be administered 24 hours prior to Dysport administration.

Prior to injection, local anaesthesia to the urethra or lubricating gel can be administered to facilitate comfortable cystoscope insertion. If required, either an intravesical instillation of diluted anaesthetic (with or without sedation) or general anaesthesia may also be used.

If a local anaesthetic instillation is performed, the local anaesthetic solution must be drained, then the bladder instilled (rinsed) with sodium chloride 9 mg/ml (0.9%) solution for injection and drained again before continuing with the intradetrusor injection procedure.

Prior to injection, the bladder should be instilled with enough sodium chloride 9 mg/ml (0.9%) solution for injection to achieve adequate visualisation for the injections.

After administration of all 30 intradetrusor injections, the sodium chloride 9 mg/ml (0.9%) solution for injection used for bladder wall visualisation should be drained. The patient should be observed for at least 30 minutes post-injection.
Onset of effect is usually observed within 2 weeks of treatment. 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. The median time to retreatment in patients treated with Dysport in the clinical studies (see Section 5.1) was between 39 to 47 weeks, although a longer duration of response may occur as more than 40% of patients had not been retreated by 48 weeks.

Children: Safety and efficacy of Dysport for the treatment of urinary incontinence due to NDO in children (under 18 years) has not been established.

Method of administration
Dysport is administered by intradetrusor injection as detailed above.

When treating urinary incontinence due to neurogenic detrusor overactivity, Dysport is reconstituted with sodium chloride 9 mg/ml (0.9%) solution for injection to yield a 15 mL solution containing either 600 units or 800 units. For instructions on reconstitution of the medicinal product before administration see section 6.6.

Spasmodic torticollis

Posology

The doses recommended for torticollis are applicable to adults of all ages provided they are of normal weight and have 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 recommended initial dose for the treatment of spasmodic torticollis is 500 units given as a divided dose and administered into the two or three most active neck muscles.

On subsequent administration, doses may be adjusted according to both the clinical response and the side effects observed. Doses within the range of 250 - 1000 units are recommended, although the higher doses may be accompanied by 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.

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 into the *splenius capitis*, 100 units into the *sternomastoid* and 100 units into 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.

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

Method of administration

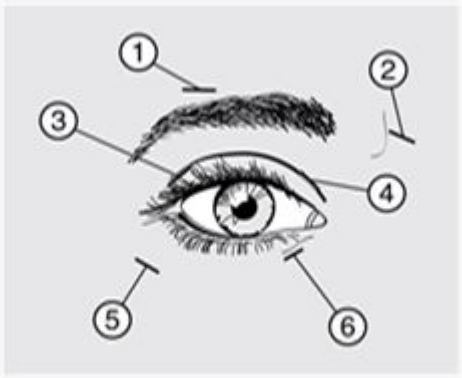
When treating spasmodic torticollis, Dysport is reconstituted with sodium chloride injection B.P. (0.9 % w/v) to yield a solution containing 500 units per ml of Dysport. Dysport is administered by intramuscular injection as detailed above.

Blepharospasm and hemifacial spasm

Posology

In a dose ranging clinical trial of the use of Dysport for the treatment of benign essential blepharospasm (BEB) a dose of 40 units per eye was significantly effective. A dose of 80 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 following the initial treatment is considered insufficient, the dose per eye may need to be increased as follows:

- 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.

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

Children: The safety and effectiveness of Dysport in the treatment of blepharospasm and hemifacial spasm in children has not been demonstrated.

Method of administration
When treating blepharospasm and hemifacial spasm, Dysport is reconstituted with sodium chloride injection B.P. (0.9 % w/v) 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
The recommended initial dosage is 100 units per axilla. If the desired effect is not attained with this dose, up to 200 units per axilla can be administered for subsequent injections. The maximum dose administered must not exceed 200 units per axilla.

The area to be injected should be determined beforehand using the iodine-starch test. Both axillae should be cleaned thoroughly and disinfected. Intradermal injections at ten sites, each site receiving 10 units (i.e. 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 one year. The time point for further applications should be determined on an individual basis, when the patient's sweat secretion has returned to normal, but not more often than every 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
When treating axillary hyperhidrosis, Dysport is reconstituted with sodium chloride injection B.P. (0.9 % w/v) to yield a solution containing 200 units per ml. Dysport is administered by intradermal injection as described above.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Urinary tract infection at the time of treatment for the management of urinary incontinence due to neurogenic detrusor overactivity.

4.4 Special warnings and precautions for use

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported (see section 4.8: Undesirable effects). 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 recommended dose.

Very rare cases of death, occasionally in a context of dysphagia, pneumopathy (including but not limited to dyspnoea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported after 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 distributionof 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.

Dysport should only be used with caution and under close medical supervision in patients with clinical or subclinical evidence of marked defective neuromuscular transmission (e.g. myasthenia gravis). Such patients may have an increased sensitivity to agents such as Dysport, which may result in excessive muscle weakness.

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 eyes have been reported with use of Dysport in periocular regions (see section 4.8). Attention to this side effects is important since dry eyes may predispose to corneal disorders. Protective drops, ointment, closure of the eye by patching or other means may be required to prevent corneal disorders.

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

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

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

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

Autonomic dysreflexia associated with the treatment procedure for neurogenic detrusor overactivity can occur. Prompt medical attention may be required.

Caution should be taken when Dysport is used where the targeted muscle shows atrophy. Cases of muscle atrophy have been reported after use of botulinum toxin (see section 4.8).

Dysport should only be used to treat a single patient, during a single session. Any unused product remaining should be disposed of in accordance with Special Precautions for Disposal and Other Handling (see section 6.6). Specific precautions must be taken during the preparation and administration of the product, and the inactivation and disposal of any unused reconstituted solution.

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

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

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 medical 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 and such drugs should be used with caution in patients treated with botulinum toxin.

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. Animal studies do not indicate any direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development other than at high doses causing maternal toxicity (see section 5.3: Preclinical safety data).

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

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

Fertility
There are no clinical data from the use of Dysport on fertility. There is no evidence of direct effect of Dysport on fertility in animal studies.

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

In general, the observed adverse reactions vary across indications. Across all indications, the most common adverse reactions following treatment are generalised weakness (asthenia), fatigue, flu-like syndrome and injection site pain/bruising. These reactions usually disappear within a few weeks of treatment. Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been rarely reported (excessive muscle weakness, dysphagia, aspiration pneumonia that may be fatal). The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose possible and by not exceeding the maximum recommended dose.

The frequency of adverse drug reactions to Dysport are classified 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 tables below list adverse drug reactions collected from clinical trial data.

General

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 and injection site pain/bruising

In addition, the following adverse drug reactions relating to specific conditions were reported:

Symptomatic treatment of focal spasticity in adults

Upper limbs:
The following adverse drug reactions were observed in patients treated with Dysport for symptomatic treatment of focal spasticity affecting the upper limbs in adults.

System Organ Class	Frequency	Adverse Drug Reaction
General disorders and administration site conditions	Common	Injection site reactions (e.g. pain, erythema, swelling etc.), asthenia, fatigue, influenza-like illness
Musculoskeletal and connective tissue disorders	Common	Muscular weakness, musculoskeletal pain, pain in extremity
Gastrointestinal disorders	Uncommon	Dysphagia*
Injury, poisoning and procedural complications	Common	Accidental lesions/fall**

*The frequency for Dysphagia was derived from pooled data from open-label studies. Dysphagia was not observed in the double-blind studies in the AUL indication.
**Incidence of fall: 2.0% in Dysport treated subjects, 2.2% in placebo treated subjects

Ankle joint due to stroke or TBI:

The following adverse drug reactions were observed in patients treated with Dysport for symptomatic treatment of 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

When treating both upper and lower limbs concomitantly with Dysport at a total dose of up to 1500U, there are no safety findings in addition to those expected from treating either upper limb or lower limb muscles alone.

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

Dynamic equinus foot deformity in ambulant paediatric cerebral palsy patients:

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

Upper limbs in paediatric cerebral palsy patients:

System Organ Class	Frequency	Adverse Drug Reaction
Musculoskeletal and connective tissue disorders	Common	Muscular weakness, myalgia
General disorders and administration site conditions	Common	Influenza-like illness, fatigue, injection site reactions (eczema, bruising, pain, swelling, rash)
	Uncommon	Asthenia
Skin and subcutaneous tissue disorders	Common	Rash

Concomitant treatment of dynamic equinus foot deformity and of upper limbs in ambulant paediatric cerebral palsy patients:

No data of placebo-controlled clinical trials are available, according to the existing data the number of treatment-related side effects is not higher in doses of up to 30 U/kg or 1000 U whichever is lower in comparison to treating either upper limb or lower limb muscles alone.

Urinary incontinence due to neurogenic detrusor overactivity

System Organ Class	Frequency	Adverse Drug Reaction
Infections and infestations	Common	Urinary tract infection[a,b], Bacteriuria[a]
Nervous system disorders	Common	Headache
	Uncommon	Hypoaesthesia
Gastrointestinal disorders	Common	Constipation
Musculoskeletal and connective tissue disorders	Uncommon	Muscle weakness
Renal and urinary disorders	Common	Haematuria [a]
	Uncommon	Urinary retention[c]
	Uncommon	Urethral haemorrhage, Bladder haemorrhage
Reproductive system and breast disorders	Common	Erectile dysfunction
General disorders and administration site conditions	Common	Pyrexia
	Uncommon	Bladder pain [a]
Injury, poisoning and procedural complications	Uncommon	Autonomic dysreflexia [a]

[a]*can beprocedure related*

[b]*In the pivotal double-blind placebo-controlled studies, in the first 2 weeks following treatment, urinary tract infections were reported in 4.0% of Dysport treated patients and 6.2% of placebo treated patients. Urinary tract infections can lead to pyelonephritis.*

[c]can occur if patients have an inadequate catheterisation schedule

Spasmodic torticollis

The following adverse drug reactions were observed in patients treated with Dysport for 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.

Blepharospasm and hemifacial spasm

The following adverse drug reactions were observed in patients treated with Dysport for 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 temporarily paralysing other nearby muscle groups.

Axillary hyperhidrosis

The following adverse drug reactions were observed in patients treated with Dysport for hyperhidrosis.

System Organ Class	Frequency	Adverse Drug Reaction
Nervous tissue disorders	Uncommon	Dizziness, headache, paraesthesia, involuntary muscle contractions of the eyelid
Vascular disorders	Uncommon	Flushing
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea
	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

Paediatric population
Dysport should only be used for the treatment of spasticity associated with cerebral palsy in children 2 years of age or over. The safety and effectiveness of the product in other indications has not been demonstrated.

Elderly patients (≥ 65 years)
In general, elderly patients should be observed to evaluate their tolerability of Dysport, due to the greater frequency of concomitant diseases and other drug therapy they might be receiving. Undesirable effects may be reduced by using the lowest effective dose possible and by not exceeding the maximum recommended dose.

Post-marketing experience
The profile of adverse reactions reported to the company during post-marketing use reflects the pharmacology of the product and those seen during clinical trials.

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

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, which 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 ofrespiratory muscles. General supportive care is advised. In the event of overdose, the patient should be medically monitored for up to several weeks for symptoms of systemic weakness or muscle paralysis. Symptomatic treatment should be instigated if necessary.

Symptoms of overdose may not present immediately following injection. Should accidental injection or oral ingestion occur, the patient should be medically supervised for several weeks for any 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: M03A X01

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

The action of toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally, the toxin inhibits the release of acetylcholine by disrupting the 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.

Following intradetrusor injection for the treatment of neurogenic detrusor overactivity, the toxin affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. In addition, the toxin may inhibit afferent neurotransmitters and sensory pathways.

Symptomatic treatment of focal spasticity in adults

Upper limbs:

The efficacy and safety of Dysport for the treatment of upper limb spasticity was evaluated in a randomised, 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) and the first secondary endpoint was the Physician Global Assessment (PGA) of response to treatment. The main results achieved at Week 4 and Week 12 are shown below:

	Week 4			**Week 12**		
	Placebo (N=79)	**Dysport (500U) (N=80)**	**Dysport (1000U) (N=79)**	**Placebo (N=79)**	**Dysport (500U) (N=80)**	**Dysport (1000U) (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 improvements 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 1000 units 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 (severity grade and spasticity angle) assessed by the Tardieu scale, in the active range of motion of the fingers, wrist and elbow, and in ease of applying a splint by the subject were observed, especially at the 1000 units 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.

In a subsequent open-label extension study, re-treatment was determined by clinical need after a minimum of 12 weeks. Doses greater than 1000U and up to 1500U were permitted when the shoulder muscles were injected. After repeated administration, the efficacy of Dysport is maintained for up to 1 year as assessed by MAS (as evidenced by the responder rates ranging from 75% to 80% in the open label study compared to 75% in the placebo-controlled study) and PGA when injected in the upper limb muscles. Dysport effect was also maintained or improved on passive function (Disability Assessment Scale), spasticity (Tardieu scale), AROM and ease of applying splints. The results achieved at Week 4 for the MAS in the shoulder muscles and PTT of the DAS in patients treated with 1500U of Dysport in the upper limb are shown below:

	1st Cycle at Dysport 1500U	**2nd Cycle at Dysport 1500U**	**3rd Cycle at Dysport 1500U**
MAS in Shoulder muscles - Change from Baseline to Week 4			
	n=39	**n=36**	**n=18**

Mean (SD)	2.6 (0.9)	2.7 (0.9)	2.8 (0.9)
Mean Change (SD)	-0.7 (0.8)	-0.6 (0.8)	-0.6 (0.8)
PTT of the DAS - Responder at Week 4			
	n=45	**n=37**	**n=18**
Responders n (%)	34 (75.6%)	28 (75.7%)	13 (72.2%)

n=number of subjects with data;
Responders: At least one grade reduction

In a subsequent open-label extension study, subjects with co-existing lower limb spasticity were able to receive injections of Dysport 500 units into the affected lower limb in addition to 1000 units in the upper limb, with a maximum total dose of 1500 units.

Ankle joint due to stroke or TBI:

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. The primary end point was Modified Ashworth Scale (MAS) score assessed at the ankle joint.

Two doses of Dysport were evaluated for efficacy; 1000 units (N = 125), Dysport 1500 units (N = 128) against Placebo (N =128) and were divided between the *gastrocnemius* and *soleus* muscles and at least one other lower limb muscle according to clinical presentation.

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

	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 the MAS (knee flexed)	-0.4	-0.7*	-0.8**	-0.3	-0.5*	-0.6*
*p<0.05; **p<0.001; LS = Least Square						

Improvements in the spasticity at the ankle joint were also demonstrated using the Tardieu Scale (TS) with statistically significant improvements in the spasticity severity grade observed at both the 1000 units and 1500 units doses. Based on post-hoc analysis due to non-normality of Physician Global Assessment (PGA) data, Dysport treatment was also associated with statistically significant clinical improvement at both doses as measured by the PGA Score.

On completion of this study, 345 patients entered an open-label extension study in which re-treatment with Dysport 1000 units or 1500 units was determined by clinical need. Subjects with co-existing upper limb spasticity were able to receive injections of Dysport 500 units into the affected upper limb in addition to 1000 units in the lower limb, with a maximum total dose of 1500 units. Improvements in efficacy parameters (MAS, PGA and TS) seen after 4 weeks of double blind treatment with Dysport in the lower limb continued to improve over repeated treatment. Improvement in walking speed was not observed after a single treatment in the double blind study but was observed after repeated treatment.

Dynamic equinus foot deformity due to spasticity in 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	
		10 U/kg/leg (N=79)	15 U/kg/leg (N=79)
LS Mean Change from Baseline in ankle plantar MAS score Week 4 Week 12	 -0.5 -0.5	 -0.9 ** -0.8 *	 -1.0 *** -1.0 ***
LS Mean Score for PGA response to treatment Week 4 Week 12	 0.7 0.4	 1.5 *** 0.8 *	 1.5 *** 1.0 **
LS Mean GAS Score [a] Week 4 Week 12	 46.2 45.9	 51.5 *** 52.5 ***	 50.9 ** 50.5 *
*p ≤ 0.05; **p ≤ 0.003; ***p ≤ 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 212 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 in the study.

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 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.

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 in the Primary targeted muscle Group (PTMG), PGA and GAS at Week 6 and Week 16 - Treatment Cycle 1 (Randomised Population)

	Dysport 2 U/kg (N=71)	Dysport 8 U/kg (N=70)	Dysport 16 U/kg (N=71)
PTMG MAS Score			
Week 6			
LS Mean Change (95% CI)	-1.4 (-1.7, -1.2)	-1.9 (-2.1, -1.6)	-2.2 (-2.4, -2.0)
Difference to 2 U/kg (95% CI)		-0.4 (-0.8, -0.1)	-0.8 (-1.1, -0.5)
p-value		0.0093	<0.0001
Week 16			
LS Mean Change (95% CI)	-0.9 (-1.2, -0.7)	-1.3 (-1.5, -1.0)	-1.5 (-1.7, -1.2)
Difference vs 2 U/kg (95% CI)		-0.3 (-0.7, 0.0)	-0.8 (-1.1, -0.5)
p-value		0.0573	0.0008
MAS responders, Week 6			
≥ 1-grade improvement			
Number of subjects (%)	56 (78.9)	61 (87.1)	66 (93.0)
Odds ratio vs 2 U/kg (95% CI)		1.7 (0.7, 4.2)	4.6 (1.4, 15.4)
p-value		0.2801	0.0132
≥ 2-grade improvement, n (%)			
Number of subjects (%)	32 (45.1)	47 (67.1)	55 (77.5)
Odds ratio vs 2 U/kg (95% CI)		2.4 (1.2, 4.8)	4.3 (2.0, 9.0)
p-value		0.0129	0.0001
≥ 3-grade improvement, n (%)			
Number of subjects (%)	14 (19.7)	25 (35.7)	35 (49.3)
Odds ratio vs 2 U/kg (95% CI)		2.3 (1.1, 5.1)	4.2 (1.9, 9.0)
p-value		0.0326	0.0003
PGA Score			
Week 6			
LS Mean (95% CI)	1.6 (1.4, 1.9)	2.0 (1.7, 2.2)	2.0 (1.7, 2.2)
Difference to 2 U/kg (95% CI)		0.3 (0.0, 0.7)	0.3 (0.0, 0.7)
p-value		0.0445	0.0447
Week 16			
LS Mean (95% CI)	1.6 (1.3, 1.8)	1.5 (1.3, 1.8)	1.7 (1.5, 2.0)
Difference vs 2 U/kg (95% CI)		-0.1 (-0.4, 0.3)	0.2 (-0.2, 0.5)
p-value		0.7797	0.3880
Total GAS Score [a]			
Week 6			
LS Mean (95% CI)	51.2 (48.8, 53.6)	51.4 (48.9, 53.8)	52.3 (49.8, 54.7)
Difference to 2 U/kg (95% CI)		0.2 (-3.2, 3.5)	1.1 (-2.2, 4.4)
p-value		0.9255	0.5150
Week 16			
LS Mean (95% CI)	53.3 (50.6, 56.1)	52.8 (50.1, 55.6)	54.6 (51.8, 57.4)
Difference vs 2 U/kg (95% CI)		-0.5 (-4.3, 3.3)	1.3 (-2.5, 5.0)
p-value		0.7862	0.5039

LS=least square
PTMG: primary target muscle group (elbow flexors or wrist flexors)
[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 elbow flexors and wrist flexors was observed, as assessed by the Tardieu scale.
For the elbow flexors the angle of catch (Xv3) was significantly improved for Dysport 8 U/kg and 16 U/kg at Week 6 and Week 16 compared to Dysport 2U/kg. The spasticity grade (Y) was statistically significant for Dysport 16 U/kg at Week 6 and Week 16 but not for Dysport 8U/kg.
For the wrist flexors Dysport 16 U/kg was significantly improved in the angle of catch (Xv3) and the spasticity grade (Y) at Week 6 but not at Week 16. Dysport 8U/kg did not show a statistically significant effect compared to Dysport 2 U/kg.

The results of primary and secondary efficacy variables were additionally supported by positive results in the Paediatric Quality of Life Inventory in the Module Cerebral palsy.

In the first treatment cycle the majority of subjects treated with Dysport were re-treated 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 re-treatment by Week 34.

Urinary incontinence due to Neurogenic Detrusor Overactivity:

Two randomised, double-blind, placebo-controlled, multi-centre pivotal clinical studies were conducted in patients with urinary incontinence due to neurogenic detrusor overactivity. All patients were already using catheterisation to regularly empty their bladder and were inadequately managed with oral therapies; patients were botulinum toxin naive or non-naive for prior intradetrusor treatment. Across both studies, a total of 485 spinal cord injury patients (N=341) or multiple sclerosis patients (N=144) were randomised to receive either Dysport 600 U (N=162), Dysport 800 U (N=161), or placebo (N=162). Treatment was administered cystoscopically as 30 evenly distributed intradetrusor injections, avoiding the trigone. Prophylactic antibiotics were commenced at least 3 days prior to Dysport administration and continued for at least 3 days following Dysport administration. After the initial treatment, patients could receive further treatments of Dysport 600 U or Dysport 800 U on fulfilment of retreatment criteria.

The primary efficacy endpoint was the change from baseline to Week 6 in weekly urinary incontinence episodes. Secondary endpoints included the proportion of patients at Week 6 with no urinary incontinence episodes (100% reduction), change from baseline to Week 6 in volume per void, a range of urodynamic (filling cystometry) parameters, patient-reported incontinence quality of life questionnaire (I-QOL; includes avoidance limiting behaviour, psychosocial impact and social embarrassment) and global impression of treatment response.

Results from the pooled pivotal studies are presented in the table below:

Primary and Secondary Endpoints in Pooled Pivotal Studies (Randomised Population)

	Placebo (N=162)	Dysport 600 U (N=162)	Dysport 800 U (N=161)
Weekly Urinary Incontinence episodes			
Week 2			
LS mean change (SE)	-11.3 (1.4)	-19.9 (1.4)	-21.9 (1.4)
Difference to placebo (95% CI)		-8.6 (-12.2, -4.9)	-10.6 (-14.3, -7.0)
p-value		<0.0001	<0.0001
Week 6			
LS mean change (SE)	-12.7 (1.4)	-22.7 (1.3)	-23.6 (1.3)
Difference to placebo (95% CI)		-10.0 (-13.5, -6.5)	-10.9 (-14.4, -7.4)
p-value		<0.0001	<0.0001
Week 12			
LS mean change (SE)	-9.2 (1.5)	-20.4 (1.5)	-22.8 (1.5)
Difference to placebo (95% CI)		-11.3 (-15.2, -7.3)	-13.6 (-17.6, -9.7)
p-value		<0.0001	<0.0001
No urinary incontinence episodes, Week 6[a]			
Proportion of subjects	2.9%	36.1%	28.8%
Odds ratio vs placebo (95% CI)		18.9 (6.9, 51.9)	15.5 (5.6, 42.9)
p-value		<0.0001	<0.0001
Maximum cystometric capacity(mL), Week 6 [b]			
LS mean change (SE)	-4.0 (13.9)	164.6 (13.6)	175.8 (13.7)
Difference to placebo (95% CI)		168.5 (132.4, 204.7)	179.8 (143.5, 216.1)
p-value		<0.0001	<0.0001
No involuntary detrusor contractions, Week 6 [b]			
Proportion of subjects	6.6%	44.0%	55.0%
Odds ratio vs placebo (95% CI)		11.9 (5.3, 26.6)	18.6 (8.3, 41.7)
p-value		<0.0001	<0.0001
Volume at first involuntary detrusor contraction (mL), Week 6 [b]			
LS mean change (SE)	12.3 (14.7)	166.4 (14.4)	191.2 (14.6)
Difference to placebo (95% CI)		154.1 (116.0, 192.1)	178.9 (140.4, 217.5)
p-value		<0.0001	<0.0001
Maximum detrusor pressure during storage (cmH_2O), Week 6 [b]			
LS mean change (SE)	-4.9 (2.3)	-33.1 (2.2)	-35.4 (2.2)
Difference to placebo (95% CI)		-28.2 (-34.0, -22.3)	-30.4 (-36.3, -24.5)
p-value		<0.0001	<0.0001
I-QOL total score [c], Week 6			
LS mean change (SE)	7.1 (1.8)	22.1 (1.8)	22.2 (1.7)
Difference to placebo (95% CI)		15.0 (10.4, 19.6)	15.1 (10.5, 19.7)
p-value		<0.0001	<0.0001

I-QOL = incontinence quality of life; LS = least square; SE = Standard Error

[a] The proportion of patients achieving at least a 75% reduction from baseline at Week 6 in incontinence episodes were 62.5% and 57.6% in Dysport 600 U and 800 U groups respectively compared to 15.0% in placebo group. The corresponding proportions achieving at least a 50% reduction were 73.6% and 67.6% versus 34.3%.

[b] Based on urodynamic population (N=447) as study-specific urodynamics not performed on all patients: N=148 (placebo), N=153 (Dysport 600 U), N=146 (Dysport 800 U)

[c] I-QOL total score scale ranges from 0 (maximum problem) to 100 (no problem at all). The reported minimally important difference for I-QOL total score the neurogenic detrusor overactivity population is 11 points. Significant improvements compared to placebo were also observed for each individual domain score (avoidance limiting behaviour, psychosocial impact and social embarrassment)

Significant improvements over placebo in change from baseline were also observed in the two Dysport groups for volume per void and the urodynamic parameter of detrusor compliance. In addition to the incontinence-specific health related quality of life measured by I-QOL, the patient's global impression of treatment response, as measured by the 7-point rating scale (from 'very much better' to 'very much worse') showed a significantly better response following Dysport treatment compared to placebo.

For all efficacy endpoints, patients experienced a consistent response with Dysport re-treatment; there were 426, 217 and 76 subjects who received at least 1, 2 and 3 treatments with Dysport. The mean decrease in weekly urinary incontinence episodes at Week 6 across the Dysport cycles was -21.2 to -22.3 for Dysport 600 U and -21.3 to -23.7 for Dysport 800 U.

The median time to re-treatment was 39 to 47 weeks after receiving the initial Dysport treatment, although more than 40% of subjects were not retreated by 48 weeks.

5.2 Pharmacokinetic properties

Pharmacokinetic studies with botulinum toxin pose problems in animals because of the high potency, the minute doses involved, and the large molecular weight of the compound and the difficulty of labelling 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 in the high potency. Dose and time responses in monkeys showed that at low doses there was a delay of 2 - 3 days with peak effect seen 5 - 6 days after injection. The duration of action, measured by changes of ocular alignment and muscle paralysis varied between 2 weeks and 8 months. This pattern is also seen in man, and is attributed to the process of binding, internalisation and changes at the neuromuscular junction.

5.3 Preclinical safety data

Intramuscular administration (Striated muscles)
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 79 units/kg and 42 units/kg in rats and rabbits respectively, did not result in embryo/fetal toxicity. Severe maternal toxicity associated with implantation losses 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 post-natal study on the F1 generation in rats. Fertility of the males and females was decreased due to reduced mating secondary to muscle paralysis at high doses.

In a juvenile toxicity 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 33units/kg) do not show adverse effects on postnatal growth (including skeletal evaluation), reproductive, neurological and neurobehavioral development.

Effects in reproduction, juvenile and chronic toxicity non-clinical studies were limited to changes on injected muscles related to the mechanism of action of *Clostridium botulinum* type A toxin-haemagglutinin complex.

There was no ocular irritation following administration of *Clostridium botulinum* type A toxin-haemagglutinin complex onto the eye of rabbits.

Intradetrusor administration
In single-dose toxicity studies in rats and monkeys, no *Clostridium botulinum* toxin type A-related findings were found in the bladder at any of the tested doses. At doses above the NOAELs of 67 U/kg in rats and 40 U/kg in monkeys, body weight loss, decreased activity and signs of respiratory distress were reported in both species. These signs are indicative of systemic toxicity that were also observed in non-clinical studies conducted to evaluate the safety of *Clostridium botulinum* toxin type A in striated muscles.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Human albumin solution 200 g/l

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products except those listed in section 6.6.

6.3 Shelf life

Unopened product:
2 years when stored at 2 - 8°C.

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store unopened vials in a refrigerator at 2 - 8°C.
Unopened vials of Dysport can be used following a single exposure to temperatures up to 25°C for up to 72 hours, after which time the unopened vial should be stored in a refrigerator (2°C - 8°C) for the duration of shelf-life.
Do not freeze.

6.5 Nature and contents of container

Nature of container/closure:
Dysport is contained in 3 ml white neutral glass vials (Ph Eur/BP Type 1), injection sulphate treated to reduce the surface alkalinity, with 13 mm neck.

The vial is sealed with a 13 mm butyl freeze drying stopper and 13 mm Type I aluminium overseal.

Contents of container:
Boxes of 1 or 2 vials of Dysport are available. Each vial of Dysport contains 300 units of the toxin complex. 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, it 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.

Dysport is reconstituted with sodium chloride 9 mg/ml (0.9%) solution for injection B.P. For instructions on dilution of the product before administration for all indications except for the indication of urinary incontinence due to neurogenic detrusor overactivity, see section 4.2.

Dilution instructions for urinary incontinence due to neurogenic detrusor overactivity:
The overall result following preparation is to have the required 15 mL of reconstituted Dysport for injection equally divided between two 10 mL syringes, with each syringe containing 7.5 mL of reconstituted Dysport at the same concentration.
After reconstitution in the syringe the medicinal product should be used immediately.

Dilution instructions using 300 U vials

- **For a dose of 600 U:** Reconstitute two 300 U vials each with 1.5 mL of preservative-free sodium chloride 9 mg/ml solution for injection. Into the first 10 mL syringe draw 1.5 mL from the first vial and into the second 10 mL syringe draw 1.5 mL from the second vial. Complete the reconstitution by adding 6 mL of preservative-free sodium chloride 9 mg/ml solution for injection into both syringes and mix gently.

This will result in two 10 mL syringes, each containing 7.5 mL, providing a total of 600 U of reconstituted Dysport.

- **For a dose of 800 U:** Reconstitute three 300 U vials each with 1.5 mL of preservative-free sodium chloride 9 mg/ml solution for injection. Into the first 10 mL syringe draw 1.5 mL from the first vial and 0.5 mL from the second vial. Into the second 10 mL syringe draw 0.5 mL from the second vial and 1.5 mL from the third vial. Complete the reconstitution by adding 5.5 mL of preservative-free sodium chloride 9 mg/ml solution for injection into both syringes and mix gently. This will result in two 10 mL syringes, each containing 7.5 mL, providing a total of 800 U of reconstituted Dysport.

Appearance of product after reconstitution:
Reconstituted Dysport should be clear, colourless, and free of particulate matter, otherwise it must not be injected.

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).

Spillages 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 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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