SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DYSPORT 500 U, powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Clostridium botulinum toxin type A haemagglutinin complex 500 units (U)

For the 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 affecting the upper limbs in adults
- Symptomatic treatment of focal lower limb spasticity in adults with pes equinus
- Spasmodic torticollis in adults
- Pes equinus due to spastic cerebral paralysis in ambulant paediatric patients over 2 years of age
- Symptomatic treatment of focal spasticity of upper limbs in paediatric cerebral palsy patients, 2 years of age or older
- 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.
- Blepharospasm in adults
- Hemifacial spasm in adults
- Symptomatic treatment of persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment

4.2 Posology and method of administration

Dysport should only be administered by appropriately trained physicians.

The units given for Dysport are specific and are not interchangeable with other preparations of botulinum toxin.

In case of multi-focal injections, example given, in both upper and lower extremities, the maximum recommended total body dose must be taken into consideration.

Reconstitution instructions are specific for the 500 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 see Section 6.6).

Resulting Dose Unit per ml	Diluent* per 500 Unit Vial
500 Units	1 ml
200 Units	2.5 ml
100 Units	5 ml

*Preservative-free Sodium Chloride 9mg/ml (0.9%) solution for Injection

For pes equinus due to spastic cerebral paralysis in ambulant paediatric patients and focal spasticity of upper limbs in paediatric cerebral palsy patients, which are 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 limb

Posology
The maximum dose administered must not exceed 1000 units when the arm muscles are injected and 1500 units when also the shoulder muscles are injected.

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 Toxin Type A-Hemagglutinin Complex. 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 1000 units and up to 1500 units can be administered, as per the physician´s judgement based on efficacy and safety response of each patient to previous treatment cycles when the shoulder muscles are injected in addition to other muscles of the upper limb. 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 1500 units of Dysport were not investigated for the treatment of upper limb spasticity in adults.

Muscles Injected	**Recommended Dose DYSPORT (U)**
Flexor carpi radialis (FCR)	100-200 U
Flexor carpi ulnaris (FCU)	100-200 U
Flexor digitorum profundus (FDP)	100-200 U
Flexor digitorum superficialis (FDS)	100-200 U

Flexor Pollicis Longus Adductor Pollicis	100-200 U 25-50 U
Brachialis Brachioradialis Biceps Brachii (BB) Pronator Teres	200-400 U 100-200 U 200-400 U 100-200 U
Triceps Brachii (long head) Pectoralis Major Subscapularis Latissimus Dorsi	150-300 U 150-300 U 150-300 U 150-300 U

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 12-16 weeks; however some patients had a longer duration of response, i.e. 20 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 one week after administration of Dysport.

Lower limb

Posology

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**
Soleus muscle	300 – 550 U	2 - 4
Gastrocnemius		
Medial Head	100 – 450 U	1 - 3
Lateral Head	100 – 450 U	1 - 3
Tibialis posterior	100 – 250 U	1 - 3
Flexor digitorum longus	50 – 200 U	1 - 2
Flexor digitorum brevis	50 – 200 U	1 - 2
Flexor hallucis longus	50 – 200 U	1 - 2
Flexor hallucis brevis	50 – 100 U	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 accurate 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 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 needs, without exceeding a total dose of 1500 units.

Elderly patients (≥ 65 years): Clinical experience has not identified differences in response between the elderly and younger adult patients.

Method of Administration
When treating focal spasticity affecting the upper and/or lower limbs in adults, Dysport is reconstituted with Sodium chloride injection (0.9%) 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.

Spasmodic torticollis in adults

Posology
The doses recommended for the treatment of torticollis are applicable to adults of all ages, provided they are of normal weight with no sign of low neck muscle mass. A reduced dose may be required in patients who are clearly underweight or in the elderly where reduced muscle mass may be found.

The initial recommended dose for the treatment of spasmodic torticollis is 500 units, which should be administered as a divided dose and injected in 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 an increase in side effects, particularly dysphagia. The maximum dose administered must not exceed 1000 units. The symptoms of torticollis may be expected to diminish within a week of 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.

In rotation torticollis, it is recommended that the 500 units are divided as follows: 350 units administered in to the splenius capitis muscle ipsilateral to the direction of the chin or head's rotation and 150 units into the sternocleidomastoid muscle contralateral to the rotation.

In laterocollis, it is recommended that the 500 units are divided as follows: 350 units into the ipsilateral splenius capitis muscle and 150 units into the ipsilateral sternocleidomastoid muscle.
If elevation of the shoulder is involved, the ipsilateral trapezius or levator scapulae muscles may also require treatment if hypertrophy of the muscles is noticeable or is observed when examined by electromyogram (EMG). When three muscles need to be injected it is recommended that the 500 units are divided up as follows:
300 units into the splenius capitis, 100 units into the sternocleidomastoid and 100 units in to the third muscle.

In retrocollis distribute the 500 units by administrating 250 units into each splenius capitis muscle. Bilateral injections into splenius muscles may increase the risk for weakness in the neck muscles.

All other forms of torticollis call for specialist knowledge and EMG for identification and treatment of the most active muscles. EMG should be used diagnostically in all complex instances of torticollis, in reassessment of non-complicated cases where treatment has not produced a satisfactory result and for guidance in injections into deep muscles and in overweight patients with neck muscles which are difficult to palpate.

Children:

Safety and effectiveness of the product in the treatment of spasmodic torticollis in children have not been demonstrated.

Method of administration
When treating spasmodic torticollis Dysport is reconstituted with 1.0 ml of sodium chloride injection (0.9%) to yield a solution containing 500 units per ml of Dysport. Dysport is administered by intramuscular injection as above when treating spasmodic torticollis.

Focal spasticity of upper and lower limbs in paediatric cerebral palsy patients, 2 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 indication, i.e. treatment of focal spasticity of the upper limbs or lower limbs in paediatric cerebral palsy patients, 2 years of age or older. The dose of Dysport to be injected for concomitant treatment should not exceed a total dose per treatment session of 30 units/kg or 1000 units, 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 indication, i.e. treatment of focal spasticity of upper limbs or lower limbs in paediatric cerebral palsy patients, 2 years of age or older.

Pes equinus due to spastic cerebral paralysis in ambulant paediatric patients over 2 years of age

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 30 units/kg or 700 units whichever is lower. In case of concomitant treatment of upper extremities, the total Dysport dose per treatment session must not exceed 30 units/kg or 1000 units 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 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.

The symptoms may be expected to fade within two weeks of the injection.

Method of administration
When treating lower 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 limbs in paediatric cerebral palsy patients, 2 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.

The maximum dose of Dysport administered per treatment session when injecting unilaterally must not exceed 16 units/kg or 640 units whichever is lower. When injecting bilaterally, the maximum Dysport dose per treatment session must not exceed 21 units/kg or 840 units, whichever is lower. In case of concomitant treatment of lower extremities, the total Dysport dose per treatment session must not exceed 30 units/kg or 1000 units 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
Total dose	**Up to 16 U/kg in a single upper limb (and not exceeding 21 U/kg if both upper limbs injected)**	

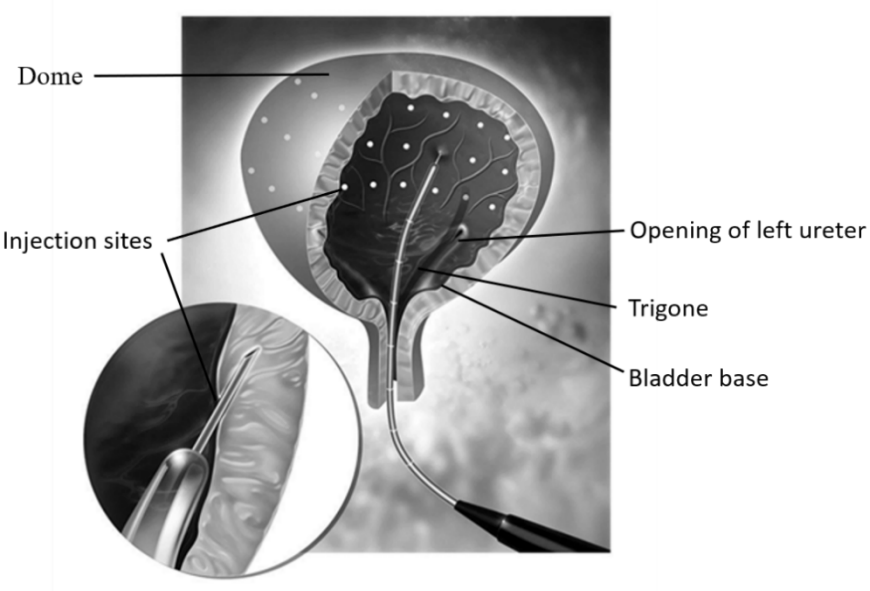
Although actual location of the injection sites can be determined by palpation the use of injection guiding technique, e.g. electromyography, electrical stimulation or ultrasound is recommended to target the injection sites.

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 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.

Urinary incontinence due to neurogenic detrusor overactivity:

Posology
The recommended dose is 600 units. 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 units 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.

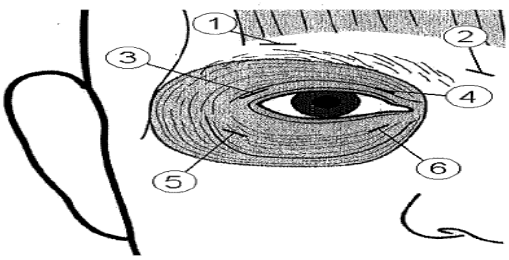
When treating urinary incontinence due to neurogenic detrusor overactivity, Dysport is reconstituted with sodium chloride 9 mg/ml (0.9%) solution for injection to yield a 15 mL solution containing either 600 units or 800 units. For instructions on reconstitution of the medicinal product before administration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

Blepharospasm and hemifacial spasm in adults

Posology
In the treatment of bilateral blepharospasm the recommended initial dose is 40 units per eye. At the next treatment session dosage should be adjusted to clinical response and the side effects observed. An increase of the dose to 80 units per eye may result in a longer duration of effect but may also lead to an increase in side effects, especially ptosis.
In the treatment of blepharospasm and hemifacial spasm, the maximum dose must not exceed the total dose of 120 units per eye.

Injection of 10 units (0.05 ml) should be made medially and of 10 units (0.05 ml) should be made laterally into the junction between the preseptal and orbital parts of both the upper (3 and 4) and lower orbicularis oculi muscles (5 and 6) of each eye.

In order to reduce the risk of ptosis, injections near the levator palpebrae superioris should be avoided.



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

Injections should be repeated approximately every twelve weeks or as required to prevent recurrence of symptoms but not more frequently than every twelve weeks. On such subsequent administrations, dosage should be adjusted to clinical response and the side effects observed. 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 frontalis muscle above 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 2.5 ml of sodium chloride injection to yield a solution containing 200 units per 1 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.

Symptomatic treatment of persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment

Posology

The maximum dose administered must not exceed 200 units per axilla.

The recommended initial dosage is 100 units per axilla. If the desired effect is not attained, up to 200 units per axilla can be administered for subsequent injections.

The area to be injected should be determined beforehand using the iodine-starch test. Both axillae should be cleaned and disinfected. Intradermal injections at ten sites, each site receiving 10 units, 100 units per axilla, are then administered. The maximum effect should be seen by week two after injection. In the majority of cases, the recommended dose will provide adequate suppression of sweat secretion for approximately 1 year. The time point for further applications should be determined on an individual basis, when the clinical effect of a previous injection diminishes and the treating physician deems it necessary. Injections should not be repeated more frequently than every 16 weeks. There is some evidence for a cumulative effect of repeated doses so the time of each treatment for a given patient should be assessed individually.

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

Method of administration
The exposed central portion of the rubber stopper should be cleaned with alcohol immediately prior to piercing the septum. A sterile 23 or 25 gauge needle should be used.

When treating axillary hyperhidrosis, Dysport is reconstituted with 2.5 ml of sodium chloride injection (0.9%) to yield a solution containing 200 units per ml of Dysport. Dysport is administered by intradermal injection at ten sites per axilla when treating axillary hyperhidrosis.

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

Dysport should only be administered by appropriately trained physicians.

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported (see section 4.8). Patients treated with therapeutic doses may present excessive muscle weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose and by not exceeding 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 existing problems in swallowing or breathing as these problems can worsen following the distribution of the effect of toxin into the relevant muscles. Aspiration has occurred in rare cases and is a risk when treating patients who have a chronic respiratory disorder.

Dysport should only be used with caution and under close medical supervision in patients with clinical or sub-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.

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.
In the elderly subjects ≥65 years, the incidence of fall was 10.4% in Dysport treated subjects versus 7.3% in the placebo group.

Dry eyes have been reported with use of Dysport in periocular regions (see section 4.8). Attention to this side effect 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)

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

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

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

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).

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

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 section 6.6 (instructions for use, handling and disposal). Specific precautions must be taken for the preparation and administration of the product; the inactivation and disposal of any unused reconstituted solution (see section 6.6).

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

Antibody formation to botulinum toxin has been reported rarely in patients receiving Dysport. Clinically, neutralising antibodies might be suspected by substantial deterioration in response to therapy and/or a need for consistent use of increased doses. The risk of antibody formation increases when high doses of Dysport are used and when the intervals between injections are short. For all indications, the interval between injections should be at least 3 months, and booster injections should not be given.

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 rarely reported in paediatric patients. In general the dose used in these cases was in excess of that recommended (see section 4.8), but cases with distant spread of toxin after distribution of recommended dose have also been reported.

There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. 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 as treatment with botulinum toxin may increase the risk for aspiration.

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 directly or indirectly with the neuromuscular function and such drugs should be used with caution in patients treated with botulinum toxin.

4.6 Fertility, pregnancy and lactation

There are limited data from the use of *Clostridium botulinum* toxin type A – haemagglutinin complex in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development other than at high doses causing maternal toxicity (see Preclinical Safety section).

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.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Very common (≥1/10); common (≥1/100 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).

In patients who were treated with Dysport in clinical trial programme approximately 25% experienced an adverse event.

General

The following adverse reaction were seen in patients treated across variety of indications including blepharospasm, hemifacial spasm, torticollis, spasticity associated with cerebral palsy, spasticity in upper and lower limbs in adults and axillary hyperhidrosis, urinary incontinence due to neurogenic detrusor overactivity:

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

System Organ Class	**Adverse Drug Reaction**	**Frequency**
Nervous system disorders	Neuralgic amyotrophy	Rare
Skin and subcutaneous tissue disorders	Pruritus	Uncommon
	Rash	Rare
Musculoskeletal and connective tissue disorders	Local muscle weakness	Common
General disorders and administration site conditions	Asthenia, fatigue, influenza like illness, injection site pain/bruising	Common

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

Symptomatic treatment of focal spasticity in adults

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

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

*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.

Lower limb
The following adverse events were observed in adult patients treated with Dysport for focal spasticity affecting the lower limbs.

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

The safety profile of Dysport at a total dose of up to 1500 units was similar when treating both the upper and lower limbs concomitantly as when injected in the upper or lower limbs only. No new safety concerns were identified compared with the known safety profile of Dysport.

Spasmodic torticollis in adults
The following adverse events were observed in patients treated with Dysport for spasmodic torticollis.

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

System Organ Class	Adverse Drug Reaction	Frequency
	Nausea	Uncommon
Musculoskeletal and connective tissue disorders	Muscle weakness	Very common
	Neck pain, musculoskeletal pain, myalgia, pain in extremity, musculoskeletal stiffness	Common
	Muscle atrophy, jaw disorder	Uncommon

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.

In severely affected patients, an accumulation of saliva has been demonstrated at laryngoscopy.

Pes equinus due to spastic cerebral paralysis in ambulant paediatric patients over 2 years of age
The following adverse events were observed in patients treated with Dysport for paediatric lower limb spasticity due to cerebral palsy.

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

* Some of the dysphagia cases reported resulted from the distribution of the effects of the toxin to sites remote from the site of administration.

Focal spasticity of upper limbs in paediatric cerebral palsy patients, 2 years of age or older
The following adverse events were observed in patients treated with Dysport for paediatric upper limb spasticity due to cerebral palsy.

System Organ Class	Adverse Drug Reaction	Frequency
Gastrointestinal disorders	Dysphagia*	Not known
Musculoskeletal and connective tissue disorders	Localised muscle weakness, pain in extremity	Common
	Generalised muscle weakness Myalgia	Uncommon
General disorders and administration site conditions	Influenza-like illness, asthenia, fatigue, injection site bruising	Common
	Injection site eczema, injection site pain, injection site rash, injection site swelling	Uncommon
Skin and subcutaneous tissue disorders	Rash	Common

* Dysphagia was not observed in the paediatric upper limb spasticity study; the data are based on post-marketing reports where subjects were injected to lower limbs or concomitantly to upper limbs and lower limbs.

Focal spasticity of upper and lower limbs in paediatric cerebral palsy patients, 2 years of age or older

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

Urinary incontinence due to neurogenic detrusor overactivity

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

[a] can be procedure 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*

Blepharospasm and hemifacial spasm in adults

The following adverse events were observed in patients treated with Dysport for Blepharospasm and hemifacial spasm.

System Organ Class	Adverse Drug Reaction	Frequency
Nervous system disorders	Facial paresis	Common
	VIIth nerve paralysis	Uncommon
Eye disorders	Ptosis	Very common
	Diplopia, dry eye, lacrimation increased	Common
	Opthalmoplegia	Rare

System Organ Class	Adverse Drug Reaction	Frequency
Skin and subcutaneous tissue disorders	Eyelid oedema	Common
	Entropion	Rare

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

Symptomatic treatment of persistent severe primary hyperhidrosis of the axillae, which interferes with the activities of daily living and is resistant to topical treatment
The following adverse events were observed in patients treated with Dysport for hyperhidrosis.

System Organ Class	Adverse Drug Reaction	Frequency
Nervous system disorders	Dizziness, headache, paraesthesia, involuntary muscle contractions of the eyelid	Uncommon
Vascular disorders	Flushing	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
	Epistaxis	Uncommon
Skin and subcutaneous tissue disorders	Compensatory sweating	Common
	Allergic reactions such as skin rashes may also occur	Rare
Musculoskeletal and connective tissue disorders	Pain in the shoulder, upper arm and neck, myalgia of the shoulder and calf	Common

Post-marketing experience
The profile of adverse reactions reported to the Company during post-marketing use reflects the pharmacology of the product.

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

Adverse effects resulting from distribution of the effects of the toxin to sites remote from the site of injection have been reported in the post-marketing setting for both adult and paediatric populations.

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 the national reporting system listed in
[To be completed nationally]

4.9 Overdose

Excessive doses may produce distant and profound neuromuscular paralysis. Overdose could lead to an increased risk of the neurotoxin entering the bloodstream and may cause complications associated

with the effects of oral botulinum poisoning (e.g. dysphagia and dysphonia). Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. There is no specific antidote; antitoxin should not be expected to be beneficial and general supportive care is advised.

In the event of overdose the patient should be medically monitored for 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 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 drugs. ATC code: M03AX01
Pharmacotherapeutic group: Antihidrotics. ATC code: D11AA

Clostridium botulinum, toxin haemagglutinin complex A blocks peripheral cholinergic transmission at the neuromuscular junction by a pre-synaptic action when acetylcholine is released. The toxin acts in the nerve endings by counteracting the processes controlled by calcium ions and which lead to the liberation of the transmitters. Post-ganglionic cholinergic or sympathetic transmission are not affected. The effect of the toxin involves an initial binding step in which the toxin attaches rapidly to the pre-synaptic nerve membrane. This is followed by an internalisation step in which the toxin crosses the pre-synaptic membrane without causing paralysis. Finally the toxin inhibits the release of acetylcholine by interrupting the calcium ion mediated mechanism for acetylcholine release, thereby reducing the nerve end-plate potential and causing paralysis. The recovery of the impulse transmission occurs gradually as new nerve terminals sprout and make contact with the post-synaptic motor endplate. This process takes 6-8 weeks in animal models.

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 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 or post-traumatic brain injury. The cause of spasticity in the study was stroke in 90.3% of subjects and traumatic brain injury in 9.7% of subjects.
The primary efficacy variable was the primary targeted muscle group (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 (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						

To investigate the effect of treatment on functional impairment, assessments on the Disability Assessment Scale (DAS) were performed. The second secondary endpoint was the mean change from baseline in the Principal Target of Treatment (PPT) of the DAS. Some improvements in the mean change from baseline in the PTT of the DAS were observed at Week 4 in the Dysport groups compared to placebo, but did not reach statistical significance. The DAS score responders (subjects achieving a one grade or greater improvement) for the PPT (ITT Population) was a tertiary endpoint, results of this analysis are shown below:

Treatment Group	Week 4 % Responders	Week 12 % Responders
Dysport 500 U	50.0 n=80 p = 0.1279	41.3 n=76 p = 0.1053
Dysport 1000 U	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.

Both 500 units and 1000 units resulted in statistically significant improvements in spasticity angle and spasticity grade, as assessed by the Tardieu Scale, at week 4 in all muscle groups (finger, wrist or elbow flexors) when compared to placebo. Reductions in spasticity grade were also significant at week 12 for all muscle groups at the 1000 units dose when compared to placebo.
Dysport 1000 units statistically improved the active range of motion (AROM) by clinically meaningful margins in the elbow (+18.3 degrees), wrist (+35.2 degrees) and finger muscles (+11.8 degrees) at Week 4 while there was no improvement in placebo group. Dysport 500 units showed similar benefit on finger muscles AROM.
Improvements in ease of applying a splint by the subject were statistically significantly greater in the Dysport 1000 units and 500 units treatment groups than in the placebo group at Weeks 4 and 12.

There were no statistically significant differences in changes from baseline to End of Study/Early Withdrawal Visit between the Dysport 500 units, 1000 units and placebo groups in the Short Form (36) Health Survey®(SF-36) and European Quality of Life 5 Dimensions (EQ-5D) QoL questionnaires.

In a subsequent open-label extension study, re-treatment was determined by clinical need after a minimum of 12 weeks. Doses greater than 1000 units and up to 1500 units were permitted when the shoulder muscles were injected. 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. After repeated administration, the efficacy of Dysport is maintained for up to 1 year.

Lower limb

The efficacy and safety of Dysport for the treatment of lower limb spasticity was evaluated in a pivotal randomized, 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.

The total volume of 7.5 ml of either Dysport 1000 units (N=125), Dysport 1500 units (N= 128) or Placebo (N =128) was divided between the gastrocnemius and soleus muscles and at least one other lower limb muscle according to clinical presentation.

When assessing 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.

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. Dysport treatment was also associated with statistically significant clinical improvement at both doses as measured by the Physician Global Assessment (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.

Pes equinus due to spastic cerebral paralysis in ambulant paediatric patients over 2 years of age

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.

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

Parameter	Placebo	DYSPORT

	(N=77)	10 U/kg/leg (N=79)	15 U/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			
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 unis/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.

Focal spasticity of upper limbs in paediatric cerebral palsy patients, 2 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 units/kg and 16 units/kg in the selected study upper limb were compared with a low dose control group of 2 units/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.
After the initial treatment, up to 3 further treatments of Dysport could be administered at planned doses of either 8 units/kg or 16 units/kg, although the investigator could elect to increase or decrease the dose (but not exceeding 16 units/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.

An Electrical stimulation (ES) and/or ultrasound was used to assist muscle localization for injection.

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)**
LS Mean Change from Baseline in PTMG MAS score			
Week 6	-1.6	-2.0 *	-2.3***
Week 16	-0.9	-1.2*	-1.5**
LS Mean Change from Baseline in Wrist Flexors MAS score			
Week 6	-1.4	-1.6	-1.7*
Week 16	-0.9	-0.9	-1.1
LS Mean Change from Baseline in Elbow Flexors MAS score			
Week 6	-1.1	-1.7**	-1.9***
Week 16	-0.6	-0.9*	-1.1***
LS Mean Change from Baseline in Finger Flexors MAS score			
Week 6	-0.6	-1.5**	-1.4*
Week 16	-0.8	-1.1	-1.4*
LS Mean PGA score			
Week 6	1.8	2.0	2.0
Week 16	1.8	1.7	1.9
LS Mean Total GAS score [a]			
Week 6	52.1	52.6	52.6
Week 16	55.1	54.2	55.7

LS=least square
PTMG: elbow flexors or wrist flexors

For MAS and PGA score, LS mean based on back transformed value and p-value based on ranked ANCOVA/ANOVA analysis.

* $p \leq 0.05$; ** $p \leq 0.001$; *** $p \leq 0.0001$; 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 units/kg at Week 6 for both the 8 and 16 units/kg treatment groups and also at Week 16 for the Dysport 16 units/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 units/kg group compared with Dysport 2 units/kg. In the PTMG wrist flexors, statistically significant improvements from Baseline in Xv3 and Y were observed in the Dysport 16 units/kg group compared with the Dysport 2 units/kg group at Week 6 but not for the 8 units/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 units/kg group and, in movement and balance ($p=0.0253$) in the 16 units/kg group compared with the Dysport 2 units/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 units/kg group and 61.4% in the Dysport 16 units/kg group), though more than 24% of subjects in both treatment groups had not yet required retreatment 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

Investigations using I^{125} labelled toxin have demonstrated that receptor bonding is specific. Dose-response studies in apes have shown that at low doses there is a delay of 2-3 days with a maximum effect 5-6 days after the injection.
Period of effect – measured as changes in ocular line as well as muscular paralysis ranged from 2 weeks to 8 months. This pattern is also seen in humans and is ascribed to the binding of the toxin, transport across the nerve membranes and the change in neuromuscular transfer.

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* toxin type A – 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/foetal toxicity. Severe maternal toxicity associated with implantation losses were observed at higher doses in both species. *Clostridium botulinum* toxin type A – haemagglutinin complex demonstrated no teratogenic activity in either rats or rabbits and no effect 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 33 units/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* toxin type A – haemagglutinin complex.

There was no ocular irritation following administration of *Clostridium botulinum* toxin type A – 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

Albumin, lactose monohydrate.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6.

6.3 Shelf life

2 years.
After reconstitution, stability has been demonstrated for 24 hours at 2°C – 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°C to 8°C.

6.4 Special precautions for storage

Store at 2°C - 8°C. Do not freeze.

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

6.5 Nature and contents of container

3ml vials - colourless glass (type I) sealed with a rubber stopper and aluminium cap.
Packs of 1 x 1 and 2 x 1 injection bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Dysport injection substance which is a white freeze-dried powder should be dissolved before use in 1 ml, 2.5 ml or 5 ml sodium chloride 9 mg/ml (0.9%) solution for injection to produce a solution of 500, 200 or 100 units per ml.
The exposed centre of the rubber stopper should be cleaned with alcohol before the needle is inserted into the septum.

Dilution instructions for all indications except urinary incontinence due to neurogenic detrusor overactivity:

When using 1 ml or 2.5 ml of diluent the reconstitution can be performed in the Dysport powder vial.
When using 5 ml of diluent for a 500 unit vial of Dysport, complete the following steps:

1. Reconstitute a 500 unit vial of Dysport with 2.5 ml NaCl solution 9 mg/ml (0.9%), gently mix, and set the vial aside.
2. Withdraw 2.5 ml of NaCl solution 9 mg/ml (0.9%) into a 5 ml syringe.
3. Take the 5 ml syringe with 2.5 ml NaCl solution 9 mg/ml (0.9%), and draw up the Dysport solution from the reconstituted vial without inverting and mix gently. The resulting concentration will be 100 units/ml.
4. Use immediately after reconstitution in the syringe.

A size 23 or 25 needle should be used. Dysport must be administered intramuscularly, intradermally or subcutaneously.

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 500 unit vials

- **For a dose of 600 U:** Reconstitute two 500 unit vials each with 2.5 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 unit of reconstituted Dysport.
- **For a dose of 800 U:** Reconstitute two 500 unit vials each with 2.5 mL of preservative-free sodium chloride 9 mg/ml solution for injection. Into the first 10 mL syringe draw 2 mL from the first vial and into the second 10 mL syringe draw 2 mL from the second 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 unit of reconstituted Dysport.

Dilution instructions using combination of 500 U and 300 U vials (only applicable for dose of 800 U)

- **For a dose of 800 U:** Reconstitute the 500 unit vial with 2.5 mL of preservative-free sodium chloride 9 mg/ml solution for injection and the 300 U vial with 1.5 mL of preservative-free sodium chloride 9 mg/ml solution for injection. Into the first 10 mL syringe draw 2 mL from the 500 unit vial. Into the second 10 mL syringe draw the remaining 0.5 mL from the 500 U vial and all of the 1.5 mL from the 300 unit 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 unit of reconstituted Dysport.

All used injection bottles, syringes and items with spillage must be autoclaved or any remaining botulinum toxin A inactivated using diluted hypochlorite solution (0.5%).

7. MARKETING AUTHORISATION HOLDER

Institut Produits Synthèse (IPSEN) AB
Kista Science Tower
Färögatan 33
164 51 Kista

8. MARKETING AUTHORISATION NUMBER(S)

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