AUSTRALIAN PRODUCT INFORMATION
DYSPORT
clostridium botulinum type A toxin - haemagglutinin complex
powder for injection vial

1 NAME OF THE MEDICINE

clostridium botulinum type A toxin - haemagglutinin complex

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DYSPORT Powder for Injection contains 125 300 or 500 IPSEN UNITS* per vial of *clostridium botulinum* type A toxin-haemagglutinin complex, 125 microgram human serum albumin and 2.5 mg lactose in a sterile, lyophilised form without a preservative.

*One Ipsen unit (U) is defined as the median lethal intra-peritoneal dose (LD_{50}) in mice of the reconstituted DYSPORT Powder for Injection.

ONE IPSEN UNIT is not equivalent to ONE UNIT of any other botulinum toxin preparation.

From now on in this Product Information the term Ipsen unit will simply be replaced by the term unit.

Clostridium botulinum type A toxin-haemagglutinin complex has a molecular weight of about 900,000D and is a complex of proteins.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

DYSPORT 125U, 300U, or 500U is a white lyophilised powder for injection in a clear glass vial

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of

- symptomatic treatment of focal spasticity affecting the upper limbs in adults
- symptomatic treatment of focal spasticity affecting the lower limbs in adults
- spasmodic torticollis in adults
- symptomatic treatment of lower limb focal spasticity in children aged 2 years of age and older
- blepharospasm in adults
- hemifacial spasm in adults
- moderate to severe glabellar lines and / or lateral canthal lines (crow’s feet) in adults

4.2 DOSE AND METHOD OF ADMINISTRATION

THE UNITS OF DYSPORT ARE SPECIFIC TO THE PREPARATION AND ARE NOT INTERCHANGEABLE WITH OTHER PREPARATIONS OF BOTULINUM TYPE A TOXIN.

Training: DYSPORT should only be administered by appropriately trained physicians. The product distributor can facilitate training in administration of DYSPORT injections.

Focal spasticity affecting the upper limbs in adults

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 500U, 1000U and 1500U were divided among selected muscles (Table 1) at a given treatment session. The maximum recommended dose is 1000U in a single treatment session. Doses greater than 1000U and up to 1500U, when the shoulder muscles were also injected, have been used but have not been adequately studied.

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

Table 1: DYSPORT Dosing by Muscle for Upper Limb Spasticity

Muscles Injected	Recommended Dose DYSPORT (U)
Wrist Flexors	
Flexor carpi radialis (FCR)	100-200 U
Flexor carpi ulnaris (FCU)	100-200 U
Finger Flexors	
Flexor digitorum profundus (FDP)	100-200 U
Flexor digitorum superficialis (FDS)	100-200 U
Flexor Pollicis Longus	100-200 U
Adductor Pollicis	25-50 U
Elbow flexors and pronators	
Brachialis	200-400 U
Brachioradialis	100-200 U
Biceps Brachii (BB)	200-400 U
Pronator Teres	100-200 U
Shoulder muscles	
Triceps Brachii (long head)	150-300 U
Pectoralis Major	150-300 U
Subscapularis	150-300 U
Latissimus Dorsi	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.

Children: The safety and effectiveness of DYSPORT in the treatment of arm spasticity in children have not been demonstrated.

Focal spasticity affecting the lower limbs in adults

Doses of up to 1500U 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 1500U. No more than 1 mL should generally be administered at any single injection site.

Table 2: DYSPORT Dosing by Muscle for Lower Limb Spasticity

Muscle Injected	Recommended Dose DYSPORT (U)	Number of injection sites per muscle
Distal		
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
Proximal		
Rectus femoris	100 – 400 U	1 - 3
Hamstrings	100 – 400 U	1 - 3
Adductor magnus	100 – 300 U	1 - 3

Adductor Longus	50 – 150 U	1 – 2
Adductor Brevis	50 – 150 U	1 - 2
Gracilis	100 – 200 U	1 - 3
Gluteus maximus	100 – 400 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 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.

Focal spasticity affecting the upper and lower limbs in adults
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 1500U.

Spasmodic torticollis
The doses recommended for the treatment of torticollis are applicable to adults of all ages providing 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 and in women, where a reduced muscle mass may exist.

The recommended initial dose for the treatment of spasmodic torticollis is 250-500 units per patient given as a divided dose and administered into the two or three most active neck muscles.

For rotational torticollis distribute the optimal dose by administering 70% of the dose into the splenius capitis muscle, ipsilateral to the direction of the chin/head rotation and 30% of the dose into the sternomastoid muscle, contralateral to the rotation.

For laterocollis, distribute the optimal dose by administering 70% of the dose into the ipsilateral splenius capitis muscle and 30% of the dose 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 60% of the optimal dose into the splenius capitis, 20% into the sternomastoid and 20% into the third muscle.

For retrocollis distribute the optimal dose by administering 50% of the dose into each of the splenius capitis muscles. Bilateral splenii injections may increase the risk of neck muscle weakness.

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

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

The relief of symptoms of torticollis may be expected within a week after the injection. Injections should be repeated approximately every 16 weeks or as required to maintain a response, but not more frequently than every 12 weeks.

Treatment of lower limb focal spasticity in children aged 2 years and older

Dosing in initial and subsequent 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 30U/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 Table 3 for recommended dosing.

Table 3: DYSPORT Dosing by Muscle for Lower Limb Spasticity in Children > 2 years

Muscle Injected	**Recommended Dose Range per muscle per leg (U/kg Body Weight)**	**Number of injection sites per muscle**
Distal		
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
Proximal		
Hamstrings	5 to 6 U/kg	Up to 2

Hip adductors	3 to 10 U/kg	Up to 2
Total dose	Up to 15 U/kg/leg if injected in only distal muscles, only proximal muscles or multilevel (distal plus proximal muscles)	

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.

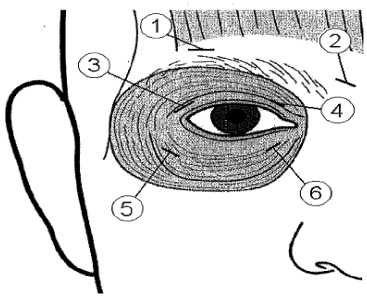
Repeat DYSPORT treatment should be administered when the effect of a previous injection has diminished, but no sooner than 12 weeks after the previous injection. A majority of patients in clinical studies were retreated between 16-22 weeks; however, some patients had a longer duration of response, i.e. 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.

Blepharospasm and hemifacial spasm

In a dose ranging clinical trial of the use of DYSPORT for the treatment of benign essential blepharospasm a dose of 40 units per eye was significantly effective. A dose of 80 units per eye resulted in a longer duration of effect. Thus, if a dose of 40 units per eye is chosen for the initial treatment, the patient may benefit from a dose of 80 units per eye for subsequent treatments if a longer duration of action is required. However, the incidence of local adverse events, specifically ptosis, was dose related.

For an initial dose of 40 units per eye, injection of 10 units should be made medially and of 10 units 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. Dependant on the muscles involved in the blepharospasm symptoms in the patient treated, additional injections in sites 1 and 2 may be necessary.

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, if the response from the initial treatment is considered insufficient, the dose per eye may need to be increased to 60 units: 10 units medially and 20 units laterally, 80 units: 20 units medially and 20 units laterally or up to 120 units: 20 units medially and 40 units laterally above and below each eye in the manner previously described.

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.

In the treatment of blepharospasm and hemifacial spasm, the maximum dose must not exceed the total dose of 120 units per eye.

Glabellar Lines

Remove any make-up and disinfect the skin with a local antiseptic. Anatomical landmarks can be more readily identified if observed and palpated at maximum frown. Before injection, place the thumb or index finger firmly below the orbital rim in order to prevent extravasation below the orbital rim.

Intramuscular injection should be performed at right angles to the skin using a sterile 29-30 gauge needle. The needle should be pointed upward and medially during the injection.

The recommended dose is 50 units (0.25 mL) of DYSPORT to be divided equally among 5 injection sites. 10 units are to be administered intramuscularly into each of the 5 sites shown on the diagram below as follows:

Corrugator muscles: A total of 4 injections (2 into each of the left and right *corrugator* muscles) at 5 mm intervals. The more medial of the two *corrugator* points on each side is localised on a vertical line, parallel to but 8 mm lateral to the medial vertical line and at a point on this vertical line 8 mm above the superior orbital margin. The more lateral *corrugator* injections should be placed at least 1 cm (i.e.10 mm) above the bony supraorbital ridge (orbital rim) and 5 mm from the more medial injection site.

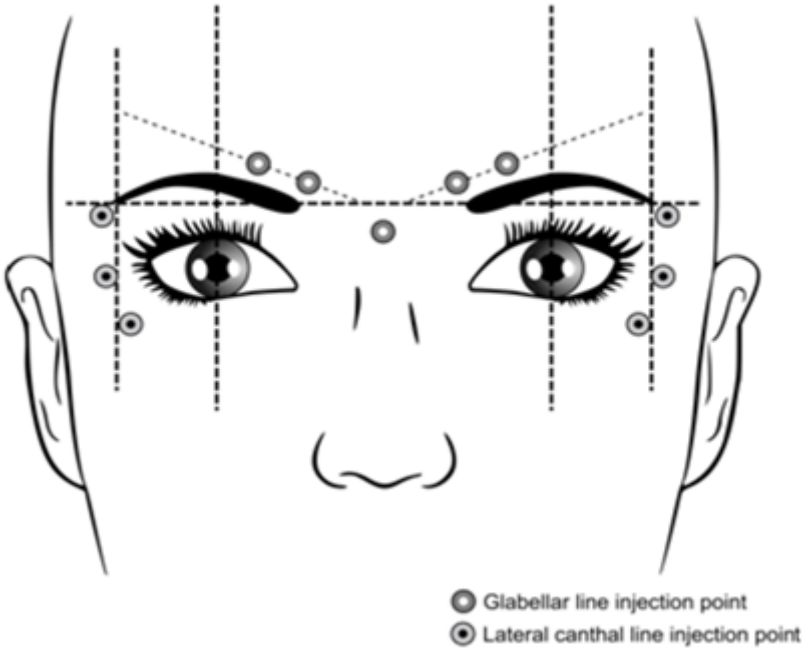
Procerus muscle: One injection into the *procerus* muscle at the intersection of the medial vertical line and the horizontal line at the level of the naso-frontal angles.

In order to reduce the risk of ptosis, injection near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii).

The treatment interval depends on the individual patient response following assessment. In clinical studies, some patients were still responding to treatment for up to 4 months after

injection. Some patients were still responders at 5 months (see 5.1 Clinical trials). There should be a minimum interval of 12 weeks between treatments.

Children: Use of the product is not recommended for the temporary improvement of moderate to severe glabellar lines in patients under 18 years of age.



Lateral Canthal lines

Remove any make-up and disinfect the skin with a local antiseptic. Intramuscular injection should be performed at a 20° - 30° angle to the skin using a sterile 29-30 gauge needle.

The recommended dose per side is 30 units (60 units for both sides, 0.30 mL of reconstituted solution) of DYSPORT, to be divided into 3 injection sites; 10 units (0.05 mL of reconstituted solution) are to be administered intramuscularly into each injection point. Injection should be lateral (20 - 30° angle) to the skin and very superficial. All injection points should be at the external part of the *orbicularis oculi* muscle and sufficiently far from the orbital rim (approximately 1 - 2 cm) as shown above.

The anatomical landmarks can be more readily identified if observed and palpated at maximal smile. Care must be taken to avoid injecting the *zygomaticus major/minor* muscles to avoid lateral mouth drop and asymmetrical smile.

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

The efficacy and safety of repeat injections of DYSPORT has been evaluated in lateral canthal lines for up to 12 months and up to 5 repeat treatment cycles.

Children: Use of the product is not recommended for the temporary improvement of moderate to severe lateral canthal lines in patients under 18 years of age.

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. The product should be reconstituted as described below and injected as described above for each specific indication.

DYSPORT is administered by:

- intramuscular injection for the treatment of focal spasticity affecting the upper and/or lower limb in adults, focal spasticity of the lower limb in children, spasmodic torticollis, glabellar lines and lateral canthal lines.
- subcutaneous injection for the treatment of blepharospasm and hemifacial spasm

Reconstitution

DYSPORT is re-constituted with sodium chloride injection BP (0.9%) to yield a solution containing 100, 200 or 500 units per mL of DYSPORT as described in Table 4 below.

Table 4: Reconstitution of DYSPORT 125U, 300U, 500U per vial (according to indication specific dosage instructions described above)

DYSPORT Presentation	**Solvent added to vial (Sodium chloride 0.9% injection)**	**Resulting dose concentration (DYSPORT Units / 0.1mL)**
500 units/vial	1.0 mL	50
	2.5 mL	20
	5.0 mL	10
300 units/vial	0.6 mL	50
	1.5 mL	20
	3.0 mL	10
125 units/vial	0.63 mL	20

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

Instructions for use / handling

DYSPORT contains no antimicrobial agent. The product should be administered within one hour of reconstitution to reduce microbiological hazard. If required it may be held between 2°C and 8°C for 24 hours after reconstitution. The product is for treatment of one patient only on one occasion. Discard any remaining contents.

Immediately after treatment of the patient, any residual DYSPORT which may be present in either vial or syringe should be inactivated with dilute hypochlorite solution (1% available chlorine). Thereafter, all items should be disposed of in accordance with standard hospital practice. Spillage of DYSPORT should be wiped up with an absorbent cloth soaked in dilute hypochlorite solution.

4.3 CONTRAINDICATIONS

DYSPORT is contra-indicated in individuals with known hypersensitivity to any component of DYSPORT. (see Section 6.1 LIST OF EXCIPIENTS).

DYSPORT is contra-indicated in patients diagnosed with myasthenia gravis or with Eaton-Lambert (myasthenic) syndrome.

DYSPORT is contra-indicated in the presence of any signs of infection at the proposed injection site.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The recommended dosages and frequencies of administration for DYSPORT must not be exceeded. Extensive or inappropriate doses outside the recommended dosage range may lead to an increased risk of adverse effects.

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported. 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 dose possible and by not exceeding the maximum recommended dose.

DYSPORT should be administered with caution to patients with pre-existing problems in swallowing or breathing as these problems can worsen following the distribution of the effects 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.

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.

Very rare cases of death, occasionally in the context of dysphagia, pneumopathy and/or in patients with significant asthenia have been reported after treatment with botulinum toxin type A or B. Patients with disorders resulting in defective neuro-muscular transmission, difficulty in swallowing or breathing are more at risk of experiencing these effects. In these patients, treatment must be administered under the control of a specialist and only if the benefit of treatment outweighs the risk. Patients and their care-givers must be warned of the necessity of immediate medical treatment in case of problems with swallowing, speech or respiratory disorders.

DYSPORT should only be used with extreme caution and under close supervision in patients with sub-clinical or clinical evidence of any defect in neuromuscular transmission (e.g. drug-induced neuromuscular weakness (see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS) or undiagnosed myasthenic syndromes). Such patients may have an increased sensitivity to agents such as DYSPORT, which may result in excessive muscle weakness. DYSPORT is not recommended for use in any patients suffering from any of the motor neurone disorders e.g. amyotrophic lateral sclerosis.

Antibody formation to botulinum toxin has been noted rarely in patients receiving DYSPORT. The principal risk factors for the formation of neutralizing antibodies after DYSPORT treatment are high doses (> 600 units per treatment), short intervals (< 3 months) between injections and booster injections (within the first month of treatment). Clinically, neutralising antibodies might be suspected by substantial deterioration in response to therapy and /or the need for consistent use of increased doses. In three clinical studies investigating the use of DYSPORT to treat upper limb spasticity in adults in whom neutralizing antibodies were evaluated, the presence of such rare antibodies did not appear to have any significant impact on the efficacy of the drug and was not associated with any unexpected safety concerns.

For the treatment of spasticity in children, DYSPORT should only be used in children 2 years of age or over.

As with any intramuscular injection, DYSPORT should be used only where strictly necessary and with due caution in patients with prolonged bleeding times. The same caution applies where there are signs of inflammation at the proposed injection site. In this case, infection must be ruled out (see 4.3 CONTRAINDICATIONS).

It is essential to study the patient's facial anatomy prior to administering DYSPORT for correction of moderate to severe glabellar lines. Facial asymmetry, ptosis, excessive dermatochalasis, scarring and any alterations to this anatomy as a result of previous surgical interventions should be taken into consideration.

This product contains a small amount of human albumin. The risk of transmission of viral infection or prion-related infection such as Creutzfeldt-Jakob disease (CJD) cannot be excluded with absolute certainty following the use of human blood or blood products.

Serious and/or immediate hypersensitivity reactions have been rarely reported. As with all biological products, adrenaline and other precautions as necessary should be available for immediate administration should an anaphylactic reaction occur.

As with any injection, procedure-related injury could occur. An injection could result in localized infection, pain, inflammation, paraesthesia, hypesthesia, tenderness, swelling, erythema and/or bleeding/bruising. Needle-related pain and/or anxiety may result in vasovagal responses, e.g. syncope, hypotension etc. Care should be taken when injecting near vulnerable anatomic structures.

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 Instructions for Use/ Handling

(see 4.2 DOSE AND METHOD OF ADMINISTRATION). Specific precautions must be taken during the preparation and administration of the product and the inactivation and disposal of any unused reconstituted solution.

DUE TO THE LACK OF AN INTERNATIONAL UNIT, DYSPORT IS NOT THERAPEUTICALLY EQUIVALENT TO ANY OTHER BOTULINUM TYPE A TOXIN PREPARATION CURRENTLY AVAILABLE ON THE AUSTRALIAN MARKET. THE POTENCIES OF DYSPORT AND ANY OTHER BOTULINUM TYPE A TOXIN PREPARATION ARE BASED ON DIFFERENT ASSAY METHODS. IN VIEW OF THIS LACK OF HARMONISATION OF UNIT SYSTEMS FOR THE BOTULINUM TYPE A TOXINS ON THE MARKET, EXTREME CAUTION IS REQUIRED IF IT SHOULD PROVE NECESSARY TO SUBSTITUTE THE BOTULINUM TYPE A TOXIN OF ONE PHARMACEUTICAL COMPANY BY ANOTHER. THE EFFECT OF ADMINISTERING DIFFERENT BOTULINUM NEUROTOXIN SEROTYPES AT THE SAME TIME OR WITHIN SEVERAL MONTHS OF EACH OTHER IS UNKNOWN. EXCESSIVE NEUROMUSCULAR WEAKNESS MAY BE EXACERBATED BY ADMINISTRATION OF ANOTHER BOTULINUM TOXIN PRIOR TO THE RESOLUTION OF THE EFFECTS OF A PREVIOUSLY ADMINISTERED BOTULINUM TOXIN.

Use in the elderly
Clinical experience has not identified differences in response between the elderly and younger adult patients. In general, elderly patients should be observed to evaluate their tolerability of DYSPORT, due to the greater frequency of concomitant disease and other drug therapy. A reduced dose may be appropriate in elderly patients where reduced muscle mass may exist.

Paediatric use
DYSPORT is approved for the symptomatic treatment of lower limb focal spasticity in children aged 2 years of age and older. For this indication, DYSPORT should only be used in children over 2 years of age.

The safety and effectiveness of DYSPORT for the approved adult indications have not been demonstrated in children.

There were no adverse effects on postnatal growth (including skeletal evaluation), reproductive, neurological and neurobehavioral development when juvenile, rats received 11 administrations over 10 weeks (up to a total cumulative dose of approximately 70U/kg) from the age of weaning on Postnatal Day 21 up to 13weeks of age (comparable to children of 2 years old, to young adulthood).

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on DYSPORT

Any drugs which interfere with neuromuscular transmission, such as muscle relaxants; or drugs which interfere with the intraneuronal concentrations of Ca^{2+}, have the potential to interact with botulinum type A toxin. Aminoglycoside antibiotics cause flaccid paralysis by a similar mechanism to that of botulinum neurotoxin. Therefore, in patients undergoing treatment with DYSPORT, the additive action of aminoglycoside antibiotics may raise the total neuromuscular blockade to the minimum required for an overt effect. Other drugs that may react pharmacologically with botulinum type A toxin include penicillamine, procainamide, spectinomycin, polymixins, tetracyclines and lincomycin. Such drugs should be used with caution in patients treated with botulinum toxin.

Effect of DYSPORT on other medicinal products

No data available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fertility in rats was decreased at intramuscular doses of Clostridium botulinum type A toxin-haemagglutinin complex of 33 units per kg per week in males and 80 units per kg per week in females, due to reduced mating secondary to muscle paralysis.

Use in pregnancy (Category B3)

There are limited data from the use of DYSPORT in pregnant women. There was no evidence of teratogenicity in rats and rabbits given Clostridium botulinum type A toxin-haemagglutinin complex during the period of organogenesis at respective doses up to 50 and 12 units per kg by daily or weekly intramuscular injection. Maternal toxicity and implantation losses were observed at high doses in both species. Intramuscular administration of Clostridium botulinum type A toxin-haemagglutinin complex to rats during gestation and lactation was associated with slightly reduced pup birth weight and weight gain at severe maternotoxic doses (50 units per kg). Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition or postnatal development other than at doses causing maternal toxicity.

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

Use in lactation.

It is not known whether Clostridium botulinum type A toxin-haemagglutinin complex is excreted in human or animal milk. The use of DYSPORT 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

The following section is presented in terms of, firstly, those adverse effects which have been reported in association with the use of DYSPORT in all approved indications and secondly, any additional adverse effects associated with each specific indication for which DYSPORT may be used. Only those adverse effects which are considered possibly or probably related to treatment with DYSPORT are included in this section and the frequency of reporting is indicated as follows:

Very common >1/10: Common >1/100, <1/10: Uncommon >1/1000, <1/100: Rare >1/10 000, < 1/1000: Very rare <1/10 000.

General

In clinical trials in patients suffering from blepharospasm, hemifacial spasm, torticollis or spasticity associated with cerebral palsy or stroke, approximately 30% of patients treated with DYSPORT experienced an adverse event.

Nervous system disorders

Rare: Neuralgic amyotrophy / muscular atrophy

Skin and subcutaneous tissue disorders

Uncommon: Pruritis

Rare: Rash

General disorders and administration site conditions

Common: Asthenia, fatigue (exhaustion, lethargy, tiredness, and/or asthenia), Influenza like illness, injection site pain / bruising / swelling / reddening

Focal spasticity affecting the upper limbs in adults

The following adverse events were observed in adult patients treated with DYSPORT for focal spasticity affecting the upper limbs:

General disorders and administration site conditions

Common: Injection site reactions (e.g. pain, erythema, swelling etc.) asthenia, fatigue, influenza like illness

Gastrointestinal disorders

Uncommon: Dysphagia*

*The frequency for dysphagia was derived from pooled data from open-label studies. Dysphagia was not observed in the double-blind studies in the upper limb spasticity indication

Musculoskeletal and connective tissue disorders

Common: Muscular weakness, musculoskeletal pain

Uncommon: Pain in extremity

Focal spasticity affecting the lower limbs in adults.
The following adverse events were observed in adult patients treated with DYSPORT for focal spasticity affecting the lower limbs.

General disorders and administration site conditions

Common: Asthenia, fatigue, influenza-like illness, injection site reactions (pain, bruising, rash, pruritis)

Injury, poisoning and procedural complications

Common: Fall

Musculoskeletal and connective tissue disorders

Common: Muscular weakness, myalgia

Gastrointestinal disorders

Common: Dysphagia

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

Spasmodic torticollis
In 21 clinical trials involving approximately 4100 patients the following adverse effects were reported:

Nervous system disorders

Common: Headache, dizziness, facial paresis

Eye disorders

Common: Vision blurred, visual acuity reduced

Uncommon: Diplopia

Respiratory, thoracic and mediastinal disorders

Common: Dysphonia, dyspnoea

Rare: Aspiration, pharyngitis

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.

In addition, during clinical trials, there have been reports of increased salivation in two patients, the causality of which was not assessed by the reporting investigator.

Treatment of lower limb focal spasticity in children aged 2 years and older

The following adverse events were observed in paediatric patients treated with DYSPORT for lower limb spasticity due to cerebral palsy.

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

Blepharospasm and hemifacial spasm

In 13 clinical trials involving approximately 1400 patients treated with DYSPORT the following adverse effects were reported:

Nervous system disorders

Common: Facial paresis

Uncommon: VIIth nerve paralysis

Eye disorders

Very common: Ptosis

Common: Diplopia, dry eyes, lacrimation increased

Rare: Ophthalmoplegia, photophobia, lagophthalmos

Skin and subcutaneous tissue disorders

Common: Eyelid oedema

Rare: Entropion

In addition, there was 1 report of dysphagia, 19 reports of facial stiffness / numbness, 4 reports of conjunctivitis, 2 reports of facial swelling and 3 reports of local burning sensation from a clinical trial where the reporting investigator did not provide an assessment of causality of the reaction with treatment with DYSPORT.

Glabellar lines

In clinical studies, over 1500 patients with moderate to severe glabellar lines have been treated at the recommended dose of 50 Units in double-blind placebo-controlled (Y-97-52120-718 and Y-97-52120-719) and long-term open-label (Y-97-52120-720) studies.

In double-blind placebo-controlled single dose studies, 22.5% of patients treated at the recommended DYSPORT dose (50U) and 16.6% of patients treated with placebo, experienced an adverse effect that was related to treatment. In the long-term open-label dose Phase III study in which patients received multiple injection cycles, 26% of patients experienced at least one treatment related adverse effect after the first injection. The incidence of treatment related adverse effects decreased over repeat cycles.

The most frequently occurring related adverse effects are headache and injection site reactions. Most of the adverse effects reported were of mild to moderate severity.

Patients receiving the recommended dose of 50 units experienced the following adverse effects.

Nervous system disorders

Very common: Headache

Common: Facial paresis

Eye disorders

Common: Asthenopia, ptosis, eyelid oedema, lacrimation increased, dry eye, muscle twitching

Uncommon: Visual impairment, vision blurred, diplopia, eye movement disorder

Skin and subcutaneous tissue disorders

Uncommon: Pruritis, skin rash

Rare: Urticaria

Immune System Disorders

Uncommon: Hypersensitivity

Musculoskeletal and connective tissue disorders

Common: Muscular weakness of adjacent muscle to the area of injection. This may commonly lead to eyelid ptosis, asthenopia or uncommonly to paresis of facial muscles or visual disturbances.

General disorders and administration site conditions

Very common: Injection site reactions (including pain, bruising, pruritis, paraesthesia, erythema, rash). Note these events were also frequently seen in placebo group.

Injection site haemorrhage was also noted in an open label study.

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

Lateral Canthal Lines

Based on placebo-controlled clinical trials, patients could experience an adverse effect after the first injection of DYSPORT at a rate of 6.2 % for the treatment of lateral canthal lines (2.9 % for placebo). Most of these adverse effects were of mild to moderate severity and reversible. The most frequent adverse effects were injection site reactions, headache and eyelid oedema for lateral canthal lines.

Nervous system disorders

Common: Headache

Eye disorders

Common: Eyelid oedema

Uncommon: Dry eye

General disorders and administration site conditions

Common: Injection site reactions (e.g. haematoma, pruritus and swelling)

Injury, poisoning and procedural complications

Common: Periorbital haematoma

In general, treatment/injection technique related reactions occurred within the first week following injection and were transient. The incidence of treatment/injection technique related reactions decreased over repeat cycles.

The safety profile of DYSPORT for concomitant treatment of glabellar lines and lateral canthal lines was evaluated in the open label part of a phase III study; the nature and frequency of adverse events were comparable to what was observed when patients were treated for the individual indications.

Post-Marketing reports

The profile of adverse effects reported to the company during post-marketing use reflects the pharmacology of the product and those seen during clinical trials. During post-marketing surveillance studies, ptosis was rarely observed in patients treated for spasmodic torticollis. In addition in the same studies, nausea was reported as uncommon.

During a post-marketing surveillance study a number of reports of neck / shoulder pain (22), unspecified pain (10), heavy head / neck / shoulder (5), local pain (2), rigid neck (1), muscle soreness (1), ear pain (1), back pain (1), neck tension (1), arm pain (1), heavy arm (1), neuralgia (1) and muscle pain (1) were received which were assessed by the reporters as being related to treatment.

Hypersensitivity: There have been sporadic reports of hypersensitivity.

Adverse effects resulting from distribution of the effects of the toxin: 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).

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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 agents.

ATC Code: M03AX01

Mechanism of action
Pharmacodynamic effects

Clostridium botulinum type A toxin-haemagglutinin complex blocks peripheral cholinergic transmission at the neuromuscular junction by a presynaptic action at a site proximal to the release of acetylcholine. The toxin acts within the nerve ending to antagonise those events that are triggered by Ca2+ which culminate in transmitter release. It does not affect postganglionic cholinergic transmission or postganglionic sympathetic transmission.

The action of toxin involves an initial binding step whereby the toxin attaches rapidly and avidly to the presynaptic nerve membrane. Secondly, there is an internalisation step in which toxin crosses the presynaptic membrane, without causing onset of paralysis. Finally the toxin inhibits the release of acetylcholine by disrupting the Ca2+ mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis.

Recovery of impulse transmission occurs gradually as new nerve terminals sprout and contact is made with the postsynaptic motor endplate, a process which takes 6 - 8 weeks in the experimental animal.

Clinical trials

Focal spasticity affecting the upper limb in adults
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 (Modified Ashworth Scale (MAS) score ≥2 in the primary targeted muscle group (PTMG: finger, or wrist, or elbow flexors) for toxin naive subjects or MAS score ≥3 in the PTMG for toxin non-naive subjects where at least 4 months elapsed since their last botulinum toxin injection, of any serotype) who were at least 6 months post-stroke or post-traumatic brain injury.

The Modified Ashworth Scale (MAS) is the most commonly used measure of efficacy in the reduction of upper limb spasticity and is a direct measure of the degree of spasticity. The MAS assessment of spasticity involves separate assessment of the muscle tone of the elbow, wrist and fingers. The investigator or an appropriate delegate (e.g. physiotherapist) assesses the resistance encountered to passive movement at each joint on a six-point scale as follows:

0 = No increase in muscle tone.

1 = Slight increase in muscle tone, manifested by a catch and release, or by minimal resistance at the end of the range of motion when the affected part is moved in flexion or extension.

1+= Slight increase in muscle tone, manifested by a catch, or by minimal resistance throughout the remainder (<1/2) of the range of movement (ROM).

2 = More marked increase in muscle tone through most of ROM, but affected part easily moved.

3 = Considerable increase in muscle tone, passive movement difficult.

4 = Affected part rigid in flexion or extension.

The total volume (i.e. 5.0 mL) of either DYSPORT 500 U (N=80), DYSPORT 1000 U (N=79), or placebo (N=79) was injected intramuscularly into the affected upper limb muscles. The volume of either DYSPORT or placebo injected in the PTMG is presented in Table 5. After injection of the PTMG the remainder of the dose (2.0 or 3.0 mL) was injected into at least two additional upper limb muscles. Muscles suggested to the investigator are listed in Table 5. No more than 1.0 mL was allowed to be administered per injection site. However more than one injection site per muscle was permitted.

An EMG/nerve stimulator was used to assist in proper muscle localization for injection. Patients were followed for 24 weeks.

Table 5: Dose Range per Muscle

Muscles Injected	**Volume (mL)**	**DYSPORT 500 U**	**DYSPORT 1000 U**
Wrist Flexors			
Flexor carpi radialis*	1 mL	100 U	200 U
Flexor carpi ulnaris*	1 mL	100 U	200 U
Finger Flexors			
Flexor digitorum profundus*	1 mL	100 U	200 U
Flexor digitorum superficialis*	1 mL	100 U	200 U
Flexor Pollicis Longus	1 mL	100 U	200 U
Adductor Pollicis	0.25 mL	25 U	50 U
Elbow Flexors and Pronators			
Brachioradialis*	1 mL	100 U	200 U

Brachialis*	2 mL	200 U	400 U
Biceps Brachii	2 mL	200 U	400 U
Pronator Teres	1 mL	100 U	200 U
Shoulder Muscles			
Triceps Brachii (long head)	1.5 mL	150 U	300 U
Pectoralis Major	1.5 mL	150 U	300 U
Subscapularis	1.5 mL	150 U	300 U
Latissimus Dorsi	1.5 mL	150 U	300 U

* PTMG

The primary efficacy variable was the PTMG tone at week 4, as measured by the derived MAS and the first secondary endpoint was the Physician Global Assessment (PGA). The PGA was based on answer to the following question: "How would you rate the response to treatment in the subject's upper limb since the last injection?". Responses were made on a 9-point rating scale (-4: markedly worse, -3: much worse -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved, +4: markedly improved). Results at week 4 and week 12 are presented in Table 6 and Table 7, respectively.

Table 6: Primary Endpoint PTMG MAS, First secondary endpoint PGA and MAS by Muscle Group at Week 4

	Placebo (N=79)	DYSPORT (500 units) (N=80)	DYSPORT (1000 units) (N=79)
Baseline PTMG Muscle Tone on the MAS (Mean (SD))	3.9 (0.4)	3.9 (0.5)	3.9 (0.4)
LS Mean Change from Baseline in PTMG Muscle Tone on the MAS	-0.3	-1.2**	-1.4**
LS Mean PGA of Response to Treatment	0.7	1.4*	1.8**
Baseline Wrist Flexor Muscle Tone on the MAS (Mean (SD))	3.7 (0.5) (n=54)	3.5 (0.8) (n=57)	3.5 (0.7) (n=58)
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)

Baseline Finger Flexor Muscle Tone on the MAS (Mean (SD))	3.8 (0.5) (n=70)	3.8 (0.7) (n=66)	3.7 (0.6) (n=73)
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)
Baseline Elbow Flexor Muscle Tone on the MAS (Mean (SD))	3.5 (0.7) (n=56)	3.7 (0.6) (n=62)	3.6 (0.7) (n=48)
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)
Baseline Shoulder Extensors Muscle Tone on the MAS (Mean (SD))	3.5 (0.7) (n=12)	3.0 (0.8) (n=7)	2.7 (0.5) (n=6)
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)
*p≤0.0004; ** p<0.0001; LS= Least Square (1): No statistical tests performed due to low frequency by treatment and placebo groups.			

Table 7: Primary Endpoint PTMG MAS, First secondary endpoint PGA and MAS by Muscle Group at Week 12

	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	-0.1 n=75	-0.7**** n=76	-0.8**** n=76
LS Mean PGA of Response to Treatment	0.4 n=75	0.5 (ns) n=76	1.0** n=75
LS Mean Change from Baseline in Wrist Flexor Muscle Tone on the MAS	-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	-0.1 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=53	-0.7** n=58	-0.8*** n=46
Mean Change from Baseline in Shoulder Extensors Muscle Tone on the MAS (1)	0.0 n=12	-0.9 n=7	0.0 n=6
*p<0.05; **p<0.01; ***p<0.001; ****p≤0.0001; LS= Least Square; ns = not significant (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. DYSPORT 1000U produced a statistically significant increase in the number of DAS responders (subjects achieving a one grade or greater improvement) relative to placebo for the Principal Target of Treatment at Week 4 and 12, Table 8.

Table 8: Disability Assessment Scale* Score Responders for the Principal Target of Treatment - ITT Population

Treatment Group	Week 4 % Responders	Week 12 % Responders
DYSPORT 500U	50.0 (ns) n=80	41.3 (ns) n=76
DYSPORT 1000U	62.0** n=78	55.7*** n=76
Placebo	39.2 n=79	32.9 n=75

**p<0.01; ***p<0.001; ns = not significant

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

Both 500U and 1000U 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 1000U dose when compared to placebo.

DYSPORT 1000U statistically improved the active range of motion (AROM) by clinically meaningful margins in the elbow (+18.3degrees, Baseline 138.7 degrees), wrist (+35.2 degrees, Baseline 63.2 degrees) and finger muscles (+11.8 degrees, Baseline 47.5 degrees) at Week 4 while there was no improvement in placebo group. DYSPORT 500U showed similar benefit on finger muscles AROM.

Improvements in ease of applying a splint by the subject were statistically significantly greater in the DYSPORT 1000U and 500U treatment groups than in the placebo group at Weeks 4 and 12.

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. Subjects with co-existing lower limb spasticity were able to receive injections of DYSPORT 500U into the affected lower limb in addition to 1000U in the upper limb, with a maximum total dose of 1500U. 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.

Focal spasticity affecting the lower limbs in adults

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 1000U (N=127), DYSPORT 1500U (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 1500U. When assessing MAS at the ankle with the knee flexed (involving all plantar flexors except the gastrocnemius), statistically significant improvement was observed for both 1000U and 1500U.

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 1000U and 1500U doses. DYSPORT treatment was also associated with statistically significant clinical improvement at both doses as measured by the Physician Global Assessment (PGA) Score.

Numerical improvement in ankle dorsiflexion for the higher Dysport dose was seen with the change peaking at 4 weeks post administration. Additional endpoints such as reduction in pain, using walking aids and quality of life measures did not show statistically significant improvement.

On completion of this study, 345 patients entered an open-label extension study in which re-treatment with DYSPORT 1000U or 1500U was determined by clinical need. Subjects with co-existing upper limb spasticity were able to receive injections of DYSPORT 500U into the affected upper limb in addition to 1000U in the lower limb, with a maximum total dose of

1500U. 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.

Improvements in 10-m walking speed (comfortable and maximal, with or without shoes) were observed, which increased with successive treatment cycles. No significant improvements in lower limb pain using the SPIN scale, use of walking aids or quality of life measures were observed.

Several small studies in adult lower limb spasticity did not show a significant benefit.

Spasmodic torticollis in adults

In a dose-finding study (n=74) conducted in 5 neurology clinics in Germany, doses of 250 units (n=19), 500 units (n=17) and 1000 units (n=18) of Dysport were compared with placebo (n=20) in a randomised, parallel group study in male and female patients aged 18 years or over with rotational torticollis. Improvements in symptoms were statistically significantly better than placebo for the 500 unit and 1000 unit dose groups at 4 weeks using Tsui score. A dose relationship was also demonstrated by patient and investigator assessments of improvement since injection. Compared with placebo, statistically significant differences were observed at 8 weeks for the 500 unit and the 1000 unit treatment groups but at 4 weeks only the comparisons of the 250 unit and the 1000 unit groups were statistically significant. Associated with an increase in dose is an increased risk, particularly of dysphagia and therefore the optimal initial dose appears to be 250-500 units. A dose range of 250-1000 units is appropriate for simple rotational torticollis.

In a double blind study (n=73) conducted in 7 centres in Sweden and Finland in male or female patients over the legal age of consent where DYSPORT (n=38) was compared with the other botulinum toxin preparation available in Australia, a ratio of approximately 3 units of DYSPORT was found to achieve similar effects to one unit of Botox for the treatment of spasmodic torticollis within the therapeutic dose range (250 to 1000 units).

Treatment of lower limb focal spasticity in children aged 2 years and 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. (Table 9) Secondary efficacy variables were the mean Physicians Global Assessment (PGA) score and Mean Goal Attainment Scaling (GAS) score at Week 4 (Table 9). Patients were followed up for at least 12 weeks post-treatment and up to a maximum of 28 weeks.

Table 9: 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)**
Baseline MAS score	3.2	3.1	3.1
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≤ 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 U/kg/leg and 15 U/kg/leg DYSPORT treatment groups at Week 4 and Week 12, and the angle of catch (Xv3) was significant for the 10 U/kg/leg DYSPORT group at Week 12 and at both Week 4 and Week 12 for the 15 U/kg/leg DYSPORT group.

Both DYSPORT treatment groups, 10 U/kg/leg and 15 U/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 CP for the Paediatric Quality of Life Inventory. There was a statistically significant improvement from baseline in fatigue at Week 12 in the DYSPORT 10 U/kg/leg and 15 U/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 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.

Another double-blind, placebo-controlled multicentre study (A-94-52120-094) was conducted for the treatment of hip adductor spasticity in 61 children with cerebral palsy 2 to 10 years of age. DYSPORT 30 U/kg (15 U/kg/leg) or placebo was injected into the adductor and medial hamstring muscles of both legs.

Significant improvement compared to placebo was observed at Week 4 in the primary variables of change in passive range of motion at the hip (mean change from baseline of 4.8 degrees versus 0.5 degrees; $p=0.04$) and inter-medial condyli distance at fast stretch (mean change from baseline of 6.4 degrees versus 1.9 degrees, $p<0.001$). Significant improvements in muscle tone, measured by the MAS, were observed for adductor muscles and medial hamstrings post-treatment.

There is limited placebo-controlled clinical study data for the treatment of paediatric lower limb spasticity in proximal muscles.

Blepharospasm and hemifacial spasm in adults

A Phase II, multi-centre, randomized, double-blind, parallel group, placebo-controlled study (Study Y-47-52125-706) has been conducted to assess the efficacy and safety of a single administration, in 6 injection sites by subcutaneous injection, of three doses of DYSPORT (40U / eye, 80U / eye, 120U / eye) for the treatment of benign essential blepharospasm. Results of this study support a recommended starting dose of 40 units per eye, increasing to 80 units per eye where a sustained effect is required.

In open label, uncontrolled studies from the published literature, the treatment of hemifacial spasm was generally the same as for the treatment of unilateral blepharospasm.

The studies showed that visual function improved in the majority of cases, returning to normal or near to normal. Injection of DYSPORT abolished or reduced muscle spasm in patients with blepharospasm or hemifacial spasm, for whom a benefit was reported in 70-100% of the cases according to the investigator. Discomfort was also reduced, and the patients' facial appearance improved.

Criteria for assessment of results varied from one study to another. However, the assessment techniques were mainly qualitative and subjective, relying on a nominal scale which takes into account criteria such as visual function, frequency of spasm or severity of spasm. Neither the severity of the illness, the length of time it existed before commencement of DYSPORT injections, nor the gender or age of the patient influenced response to treatment.

Despite the variety of doses and administration techniques reported in the published studies, the overall response profile was favourable across the studies. Following the initial treatment,

substantial improvements were reported for both blepharospasm (success rate range: 77-100%) and hemifacial spasm (success rate range: 75-100%).

The onset of improvement post the initial injection varied from 1 day to 3 weeks for blepharospasm and from 2 to 7 days for hemifacial spasm. The duration of effect lasted between 5 and 24 weeks for blepharospasm and between 6 and 24 weeks for hemifacial spasm. The issue of time to peak effect post initial injection was assessed somewhat loosely in only about four of the submitted publications and the latter appeared to range from 3 days to 6 weeks and from 1 week to 6 weeks respectively for blepharospasm and hemifacial spasm. There was a tendency for repeat injection to produce a comparable level of efficacy to the initial injection for both conditions.

There are no satisfactory efficacy and safety data on the use of DYSPORT for the treatment of blepharospasm and hemifacial spasm in children and adolescents younger than 18 years of age.

Glabellar Lines

During the clinical development of DYSPORT for the treatment of glabellar lines, more than 2600 patients were included in the different clinical trials.

In glabellar lines clinical studies, 1907 patients with moderate to severe glabellar lines have been treated at the recommended dose of 50 Units. Of these, 305 were treated with 50U in two Phase III double-blind placebo-controlled studies (Y-97-52120-718 and Y-97-52120-719) and 1200 treated with 50U in a long-term open-label repeated dose Phase III study (Y-97-52120-720).

The median time to onset of response was 2 to 3 days following treatment.

The maximum effect on the number of responders was observed at day thirty following injection, when the assessment of the investigators showed that 90% (273/305) of patients had responded to treatment (exhibited no or mild glabellar lines at maximum frown), compared to 3% (4/153) of placebo-treated patients. The patient's own assessment at maximum frown after thirty days gave a response rate of 82% (251/305) for those treated with DYSPORT and 6% (9/153) for those treated with placebo.

In both placebo-controlled phase III studies, DYSPORT injections significantly reduced the severity of glabellar lines for up to 4 months. In one of these two studies, the effect was still statistically significant ($p<0.001$) at 5 months with 17% (32/190) of patients treated with DYSPORT still responding to treatment compared to 1% (1/92) of placebo treated patients. In the other study the corresponding effect after 4 months ($p=0.002$) was 24% (24/99) vs. 4% (2/49) with no statistically significant difference beyond 4 months.

The long-term repeat dose open label study showed that the median time to onset of response of 3 days was maintained across repeated dose cycles. The responder rate at maximum frown as determined by the investigator at day 30 was maintained over repeated cycles (ranging between 80% and 91% over the 5 cycles). In patients who were rated 'moderate' or 'severe' as baseline, the responder rate at rest over repeated dose cycles was also consistent with the

single dose studies, with ~70% of DYSPORT-treated patients considered by investigators to be responders thirty days after treatment.

Lateral Canthal Lines

In clinical studies, 306 patients with moderate to severe lateral canthal lines (LCL) at maximum smile have been treated at the recommended DYSPORT dose of 30 units per side in double blind studies and had follow-up data. Of these, 252 were treated in a Phase III double-blind placebo controlled study and 54 patients were treated in a double-blind Phase II dose- ranging study.

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

A subset of 241 patients had moderate to severe canthal lines at rest prior to treatment. In this subset, the proportion of subjects exhibiting a one-grade improvement at Week 4, according to the investigator assessment at rest, was statistically significantly higher in DYSPORT-treated patients than in placebo-treated subjects.

The primary efficacy endpoint was at 4 weeks following injection: the assessment of the investigators showed that 47.2% (119/252) of patients had responded to treatment (no or mild LCL at maximum smile), compared to 7.2% (6/83) placebo-treated patients. In a post-hoc analysis, at the same time point, 4 weeks following injection, 75% (189/252) of DYSPORT treated patients had at least 1 grade improvement at maximum smile compared with only 19% (16/83) of placebo-treated subjects.

A total of 315 subjects entered the open label extension phase of the Phase III study in which they could be treated concomitantly for both lateral canthal lines and glabellar lines.

Patients treated with DYSPORT in the double-blind and open label phases of the Phase III study received a median of 3 treatments for LCL. The median interval between injections for LCL, which was largely determined by the protocol design, ranged from 85 to 108 days. The results showed that efficacy is maintained with repeated treatments over the period of one year.

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

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

No patients developed the presence of neutralising antibodies after receiving repeated treatments with DYSPORT over one year.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetics have not been formally studied in humans or animals. Following intramuscular injection to man, there is usually a delay of 2-3 days with a peak effect between 10 and 21 days after injection. The duration of response varies but on average is 8-12 weeks.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No studies to assess the mutagenic potential of DYSPORT have been conducted.

Carcinogenicity
Long term animal studies to evaluate the carcinogenic potential of DYSPORT have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

125 microgram human serum albumin and 2.5 mg lactose in a sterile, lyophilised form without a preservative.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials must be maintained at temperatures between 2°C and 8°C.

DYSPORT must be stored in a refrigerator at the hospital or clinic where the injections are to be carried out and should not be given to the patient to store. DYSPORT should not be frozen.

6.5 NATURE AND CONTENTS OF CONTAINER

DYSPORT is provided in type 1 glass vials with bromobutyl rubber stoppers, containing 125, 300 or 500 units of botulinum toxin type A powder for injection.

Boxes of 1 vial are available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Clostridium botulinum type A toxin-haemagglutinin complex has a molecular weight of about 900,000D and is a complex of proteins.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Ipsen Pty Ltd
Level 2, Building 4
Brandon Office Park
540 Springvale Road
Glen Waverley Victoria 3150

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

DYSPORT 125U: 28 October 2015

DYSPORT 300U: 10 February 2011

DYSPORT 500U: 16 June 2000

10 DATE OF REVISION

8 June 2018

Summary table of changes

Section changed	Summary of new information
4.1, 4.2, 4.8 and 5.1	Addition of new indication and associated clinical trial summaries