New Zealand Datasheet

1 PRODUCT NAME
DYSPORT®

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Clostridium botulinum type A toxin-haemagglutinin complex

3 PHARMACEUTICAL FORM
DYSPORT Powder for Injection contains 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 is not equivalent to ONE UNIT of another 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.

DYSPORT is a white lyophilised powder for reconstitution contained in Type 1 glass vials 3 mL of capacity, with 13 mm bromobutyl freeze-drying closures oversealed by 13 mm aluminium overseals with centre hole, crimped over.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

DYSPORT is indicated for the treatment of focal spasticity of:
- Upper limbs in adults
- Lower limbs in adults
- Upper limbs in children aged 2 years and older
- Lower limbs in children aged 2 years and older.

DYSPORT is indicated in adults for the treatment of:
- Spasmodic torticollis
- Blepharospasm
- Hemifacial spasm
- Moderate to severe glabellar lines and / or lateral canthal lines (crow’s feet)

DYSPORT is also indicated for the symptomatic treatment of axillary hyperhidrosis (excessive sweating).

4.2 Dosage and method of administration

The units of DYSPORT are specific to the preparation and are not interchangeable with other preparations of botulinum toxin.

DYSPORT should only be administered by appropriately trained physicians.

The exposed central portion of the rubber stopper should be cleaned with alcohol and allowed to dry immediately prior to piercing the septum. Sterile needles of a suitable gauge should be used for drawing up and administering the product.

Reconstitution with preservative-free 0.9% sodium chloride for injection is recommended, according to indication-specific instructions described below. The vial should be gently swirled to ensure complete dissolution of DYSPORT powder. Do not shake or invert the vial when reconstituting or drawing up DYSPORT solution. Reconstitution volumes are provided in Table 1.

Table 1: DYSPORT Reconstitution Volumes and Resulting Concentrations

DYSPORT Presentation	Solvent added to vial (Sodium chloride 0.9% injection)	Resulting dose concentration (DYSPORT units / 0.1mL)
500 units/vial	1 mL	50
	2.5 mL	20
	5 mL	10
300 units/vial	0.6 mL	50
	1.5 mL	20
	3 mL	10

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.

Glabellar lines

Dosage

The dosage is dependent on the severity of the lines and the specific muscle being treated.

Adults and elderly: Remove the make-up and disinfect the skin with a local antiseptic. Intramuscular injections should be performed at right angles to the skin using a sterile suitable gauge needle.

The recommended dose is 50 units (0.25 mL) of DYSPORT to be divided into 5 injection sites shown on the diagram below (see Figure 1).

10 units (0.05 mL) are to be administered intramuscularly into each of these 5 sites: 2 injections into each corrugator muscle at 5 mm intervals and one into the procerus muscle near the nasofrontal angle. The most internal point of the corrugator is located 8 mm out of the point which is in the procerus and 8 mm from the upper side of the orbit. Patients are asked to frown regularly in order to help these injection points to be located.

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

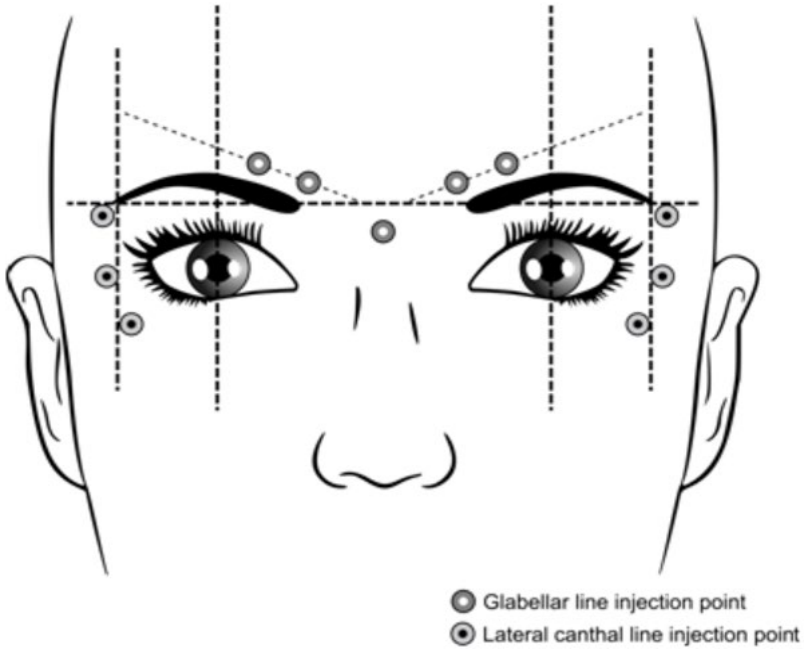
Improvement of severity of glabellar lines generally occurs within 72 hours after treatment and persists for 3 to 6 months. The interval between treatment cycles should not be less than 12 weeks.

Children: Use of DYSPORT is not recommended for the treatment of moderate to severe glabellar lines in patients under the age of 18.

Method of administration

When treating glabellar lines, DYSPORT 500U is reconstituted with 2.5 mL of sodium chloride injection BP (0.9%) and DYSPORT 300U is reconstituted with 1.5 mL of sodium chloride injection BP (0.9%) to yield a solution containing 10 units of DYSPORT per 0.05 mL. DYSPORT is administered by intramuscular or subcutaneous injection.

Figure 1



Lateral Canthal lines

Dosage

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 suitable 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 in Figure 1 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
When treating lateral canthal lines, DYSPORT 500U is reconstituted with 2.5 mL of sodium chloride injection BP (0.9%) and DYSPORT 300U is reconstituted with 1.5 mL of sodium chloride injection BP (0.9%) to yield a solution containing 10 units of DYSPORT per 0.05 mL. DYSPORT is administered by intramuscular or subcutaneous injection.

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 2, at a given treatment session. Doses greater than 1000U and up to 1500U can be administered when the shoulder muscles are also injected.

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

Table 2: DYSPORT Dosing by Muscle for Adult 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

Muscles Injected	Recommended Dose DYSPORT (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.

Method of administration

When treating symptomatic focal spasticity of the upper limb in adults DYSPORT is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing either 100 units/mL, 200 units/mL or 500 units/mL of DYSPORT. DYSPORT is administered by intramuscular injection into the muscles described above (see Table 2).

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. See Table 3 for recommended dosing for individual muscles.

Table 3: DYSPORT Dosing by Muscle for Lower Limb Spasticity

Muscle	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

Muscle	Recommended Dose DYSPORT (U)	Number of injection sites per muscle
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 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.

Method of administration
When treating symptomatic focal spasticity affecting the lower limbs in adults DYSPORT is reconstituted with sodium chloride injection B.P. (0.9% w/v) to yield a solution containing either 100 units per mL, 200 units per mL or 500 units per mL of DYSPORT (see Table 1). DYSPORT is administered by intramuscular injection into the recommended muscles as detailed above (see Table 3).

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 body dose of 1500U.

Method of administration
When treating combined upper and lower spasticity in adults refer to the method of administration section for the individual indication i.e. treatment of focal spasticity of the upper limb or lower limbs in adults.

Focal spasticity of upper limbs in children aged 2 years and older
Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins.

The maximum dose of DYSPORT administered per treatment session when injecting unilaterally must not exceed 16 U/kg or 640 U whichever is lower. When injecting bilaterally, the maximum DYSPORT dose per treatment session must not exceed 21 U/kg or 840 U, whichever is lower. The total dose administered should be divided between the affected spastic muscles of the upper limb(s). No more than 0.5 mL of DYSPORT should be administered in any single injection site. See Table 4 below for recommended dosing.

Table 4: DYSPORT Dosing by Muscle for Upper Limb Spasticity in Children ≥ 2 years

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 21U/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.

Spasticity affecting the lower limbs in children aged 2 years or older.
Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with botulinum toxins.

The maximum total dose of DYSPORT administered per treatment session must not exceed 15 units/kg for unilateral lower limb injections or 30 units/kg for bilateral injections. In addition the total DYSPORT dose per treatment session must not exceed 1000 units or 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 5 for recommended dosing for individual muscles.

Table 5: DYSPORT Dosing by Muscle for Paediatric Lower Limb Spasticity

Muscle	**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.

Method of administration
When treating spasticity of the lower limbs in children, DYSPORT is reconstituted with sodium chloride injection B.P. (0.9% w/v) and is administered by intramuscular injection as detailed above.

Focal spasticity of upper and lower limbs in children aged 2 years and older
When treating combined upper and lower limb spasticity in children aged 2 years or older refer to the above sections for the individual indication, i.e. treatment of focal spasticity of the upper limbs or lower limbs in children 2 years of age and older. The dose of DYSPORT to be injected for concomitant treatment should not exceed a total dose per treatment session of 30 U/kg or 1000 U, whichever is lower.

Retreatment of the upper and lower limbs combined should be considered no sooner than a 12 to 16-week window after the previous treatment session. The optimal time to retreatment should be selected based on individuals progress and response to treatment.

Spasmodic torticollis
Dosage
Adults and elderly: The doses recommended for torticollis are applicable to adults of all ages providing the adults are of normal weight with no evidence of low neck muscle mass. A reduced

dose may be appropriate if the patient is markedly underweight or in the elderly, where reduced muscle mass may exist.

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

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

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

For retrocollis distribute the 500 units by administering 250 units into each of the splenius capitis muscles. This may be followed by bilateral trapezius injections (up to 250 units per muscle) after 6 weeks, if there is insufficient response. Bilateral splenii injections may increase the risk of neck muscle weakness.

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

On subsequent administration, the doses may be adjusted according to the clinical response and side effects observed. Doses within the range of 250-1000 units are recommended, although the higher doses may be accompanied by an increase in side effects, particularly dysphagia. 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 twelve weeks or as required to prevent recurrence of symptoms.

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

Method of administration

When treating spasmodic torticollis DYSPORT 500U is reconstituted with 1 mL of sodium chloride injection B.P. (0.9%) and DYSPORT 300U is reconstituted with 0.6 mL of sodium chloride injection BP (0.9%) to yield a solution containing 500 units per mL of DYSPORT. DYSPORT is administered by intramuscular injection as above when treating spasmodic torticollis.

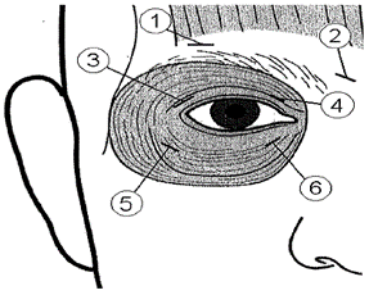
Blepharospasm and hemifacial spasm

Dosage

Adults and elderly: 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.

Injection of 10 units (0.05mL) 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, 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.

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

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 500U is reconstituted with 2.5 mL of sodium chloride injection BP (0.9%) and DYSPORT 300U is reconstituted with 1.5 mL of sodium chloride injection BP (0.9%) to yield a solution containing 200 units per mL of DYSPORT. DYSPORT is administered by subcutaneous injection medially and laterally into the junction between the preseptal and orbital parts of both the upper and lower orbicularis oculi muscles of the eyes.

Axillary hyperhidrosis (excessive sweating).

Dosage

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 48 weeks. The time point for further applications should be determined on an individual basis, when the patient's sweat secretion has returned to an unacceptable level, but not more often than every 12 weeks. There is some evidence for a cumulative effect of repeated doses so the time of each treatment for a given patient should be assessed individually. The maximum dose administered must not exceed 200 units per axilla.

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

Method of administration
When treating axillary hyperhidrosis, DYSPORT 500U is reconstituted with 2.5 mL of sodium chloride injection BP (0.9%) and DYSPORT 300U is reconstituted with 1.5 mL of sodium chloride injection BP (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 hyperhydrosis.

4.3 Contraindications

DYSPORT is contraindicated in individuals with known hypersensitivity to any component of DYSPORT and in pregnancy.

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 should not be exceeded.

Adverse effects resulting from the distribution of the effects of the toxin to sites remote from the site of administration have been reported (see Adverse Effects). Patients treated with therapeutic doses may present with excessive muscle weakness. The risk of occurrence of such undesirable effects may be reduced by using the lowest effective dose and by not exceeding the recommended dose.

For the treatment of spasmodic torticollis and paediatric cerebral palsy spasticity DYSPORT should only be injected by specialists experienced in the diagnosis and management of these conditions and who have received training on the administration of DYSPORT.

DYSPORT should only be used with caution and under close supervision in patients with subclinical or clinical evidence of marked defective neuro-muscular transmission (e.g. myasthenia

gravis). Such patients may have an increased sensitivity to agents such as DYSPORT, which may result in excessive muscle weakness.

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.

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 a context of dysphagia, pneumopathy and/or in patients with significant asthenia have been reported after treatment with botulinum toxin 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.

Antibody formation to botulinum toxin has been noted rarely in patients receiving DYSPORT. Clinically, neutralizing antibodies might be suspected by substantial deterioration in response to therapy and/or a 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 antibodies did not appear to have any significant impact on the efficacy of the drug and was not associated with any unexpected safety concerns.

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

As with any intramuscular injection, DYSPORT should be used only where strictly necessary and with due caution in patients with prolonged bleeding times or infection/inflammation at the proposed injection site.

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

It is essential to study the patient’s facial anatomy prior to administering DYSPORT for correction of glabellar and lateral canthal 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.

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.

Specific precautions must be taken during the preparation and administration of the product and the inactivation and disposal of any unused reconstituted solution.

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

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 NEW ZEALAND 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.

Use in Children
DYSPORT is approved for the symptomatic treatment of upper and lower limb focal spasticity in children aged 2 years and older. For these indications, DYSPORT should only be used in children 2 years of age and older.

Post-marketing reports of possible distant spread of toxin have been very rarely reported in paediatric patients with comorbidities, predominantly with cerebral palsy. In general, the dose used in these cases was in excess of that recommended (see section 4.8 Undesirable effects).

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

4.5 Interaction with other medicines and other forms of interaction

The effects of botulinum toxin may be potentiated by drugs interfering either directly or indirectly with neuromuscular function and such drugs should be used with caution in patients treated with botulinum toxin.

4.6 Fertility, Pregnancy and lactation

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 and Lactation

There are limited data from the use of DYSPORT 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.

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 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 Undesirable effects

Tabulated list of adverse reactions

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1000 to <1/100); Rare (≥1/10,000 to <1/1000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

General

In patients who were treated with DYSPORT suffering from blepharospasm, hemifacial spasm, torticollis or spasticity associated with cerebral palsy, stroke or head injury, axillary hyperhidrosis and glabellar lines, approximately 30% of patients experienced an adverse event.

System Organ Class	Adverse Drug Reaction	Frequency
Nervous system disorders	Neuralgic amyotrophy	Rare
Skin and subcutaneous tissue disorders	Pruritis	Uncommon
	Rash	Rare
General disorders and administration site conditions	Asthenia, fatigue, influenza like illness and injection site reactions (pain / bruising / swelling / reddening)	Common

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

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.

System Organ Class	Adverse Drug Reaction	Frequency
Musculoskeletal and connective tissue disorders	Muscular weakness, musculoskeletal pain, pain in extremity	Common
Gastrointestinal disorders	Dysphagia*	Uncommon
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 adult upper limb spasticity indication.

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.

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, pruritis)	Common
Injury, poisoning and procedural complications	Fall	Common

Focal spasticity affecting the upper and lower limbs in adults.

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.

Focal spasticity of upper limbs in children aged 2 years and older

The following adverse events were observed in paediatric patients treated with DYSPORT for upper limb spasticity.

System Organ Class	Adverse Drug Reaction	Frequency
Musculoskeletal and connective tissue disorders	Muscular weakness, Pain in extremity	Common
	Myalgia	Uncommon
General disorders and administration site conditions	Influenza-like illness, Asthenia, Fatigue, Injection site bruising	Common

System Organ Class	Adverse Drug Reaction	Frequency
	Injection site eczema, Injection site pain, Injection site rash, Injection site swelling	Uncommon
Skin and subcutaneous tissue disorders	Rash	Common

Focal Spasticity affecting the lower limbs in children aged 2 years and older

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

System Organ Class	Adverse Drug Reaction	Frequency
Musculoskeletal and connective tissue disorders	Myalgia, Muscular weakness	Common
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

Focal spasticity of upper and lower limbs in children aged 2 years and older

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

Spasmodic torticollis

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	Uncommon
Respiratory, thoracic and mediastinal disorders	Dysphonia, dyspnoea	Common
	Aspiration, pharyngitis	Rare
Gastrointestinal disorders	Dysphagia, dry mouth	Very common
	Nausea	Uncommon

System Organ Class	Adverse Drug Reaction	Frequency
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.

Blepharospasm and hemifacial spasm

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 eyes, lacrimation increased	Common
	Opthalmoplegia	Rare
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.

Axillary hyperhydrosis

The following adverse events were observed in patients treated with DYSPORT for hyperhydrosis:

System Organ Class	Adverse Drug Reaction	Frequency
Skin and subcutaneous tissue disorders	Compensatory sweating	Common

Glabellar lines

The following adverse events were observed in patients that were administered DYSPORT for the temporary improvement in the appearance of moderate to severe glabellar lines.

System Organ Class	Adverse Drug Reaction	Frequency
Immune system disorders	Hypersensitivity	Uncommon
Nervous system disorders	Headache	Very common
	Facial paresis	Common
	Dizziness	Uncommon

System Organ Class	Adverse Drug Reaction	Frequency
Eye disorders	Asthenopia, eyelid ptosis, eyelid oedema, lacrimation increased, dry eye, muscle twitching	Common
	Visual impairment, vision blurred, diplopia	Uncommon
	Eye movement disorders (excluding diplopia)	Rare
Skin and subcutaneous tissue disorders	Skin rash, pruritus	Uncommon
	Urticaria	Rare
Musculoskeletal and connective tissue system disorders	Muscular weakness of adjacent muscle to the area of injection.*	Common
General disorders and administration site conditions	Injection site reactions (including pain, bruising, pruritis, paraesthesia, erythema, rash). Note these events were also frequently seen in placebo group.	Very common

* This may commonly lead to eyelid ptosis, asthenopia or uncommonly to paresis of facial muscles or visual disturbances.

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.

System Organ Class	Adverse Drug Reaction	Frequency
Nervous system disorders	Headache, facial paresis	Common
Eye disorders	Eyelid oedema, eyelid ptosis	Common
	Dry eye	Uncommon
General disorders and administration site conditions	Injection site reactions (e.g. haematoma, pruritus and swelling)	Common
Injury, poisoning and procedural complications	Periorbital haematoma	Common

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

System Organ Class	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: 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 leading to aspiration pneumonia that may be fatal).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://nzphvc.otago.ac.nz/reporting/.

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. deglutition and dysphonia). Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. General supportive care is advised.

In the event of overdose the patient should be medically monitored for 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 person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or muscle paralysis.

Contact the Poisons Information Centre on 0800 764766 for advice on management of overdose.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other muscle relaxants, peripherally acting agents.
ATC code: M03AX01

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

are triggered by Ca^{2+} which culminate in transmitter release. It does not affect 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 Ca^{2+} mediated acetylcholine release mechanism, thereby diminishing the endplate potential and causing paralysis.

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

Clinical Trials

The Modified Ashworth Scale (MAS) is the most commonly used measure of efficacy in the reduction of 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 limb joints. 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 inflexion 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.

Focal spasticity affecting the upper limbs 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) 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 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 6. 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 2. 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 localisation for injection. Patients were followed for up to 24 weeks.

Table 6: 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 primary targeted muscle group muscle tone at week 4, as measured by the 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).

Table 7: 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)
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**
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)
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)
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)
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 8: 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 p =0.0001	-0.8 n=76 p <0.0001
LS Mean PGA of Response to Treatment	0.4 n=75	0.5 n=76 p=0.537	1.0 n=75 p=0.0011
LS Mean Change from Baseline in Wrist Flexor Muscle Tone on the MAS	-0.3 n=52	-0.7 n=54 p=0.038	-0.9 n=56 p=0.0043
LS Mean Change from Baseline in Finger Flexor Muscle Tone on the MAS	-0.1 n=67	-0.4 n=62 p=0.035	-0.6 n=70 p=0.0005
LS Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS	-0.3 n=53	-0.7 n=58 p= 0.0072	-0.8 n=46 p= 0.0002
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≤0.0004; ** 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. 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 PTT at week 4 and 12 (Table 9).

Table 9: Disability Assessment Scale* Score Responders for the Principal Target of Treatment - ITT Population

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

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

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), wrist (+35.2 degrees) and finger muscles (+11.8 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.

In a dose-finding study (n=82) conducted in 11 European centres (6 in the UK, 4 in Germany and 1 in Austria), doses of 500 units (n=22), 1000 units (n=22) and 1500 units (n=19) of DYSPORT were compared with placebo (n=19) in a randomised, double blind, parallel group study in male and female patients aged 18 years or over with upper limb spasticity following a stroke. All doses of DYSPORT studied showed a significant reduction in spasticity measured by Modified Ashworth Scale (MAS) at week 4 compared with placebo. The MAS was also significantly reduced for all DYSPORT doses over 16 weeks in the elbow and wrist areas, and also for the fingers in the 1000 unit DYSPORT group ($p<0.05$). The number of patients who showed a response (reduction in MAS of at least 1 point on the timepoint scale) in at least 2 of the joint areas studied was significantly higher in the 500 units and 1000 units DYSPORT groups compared with placebo. Effects on function and range of movement for DYSPORT and placebo were not statistically different.

In a placebo-controlled study (n=59) performed in 7 European centres (3 in the UK, 1 in Ireland and 3 in Germany), DYSPORT (1000 units; n=27) was compared with placebo (n=32) in a randomised, double-blind study in male and female patients aged over the legal age of consent with upper limb spasticity following a stroke. The best improvement in spasticity of elbow, wrist and finger joints as measured by the MAS was significantly better in DYSPORT treated patients than the placebo group ($p=0.004$). The magnitude of benefit in MAS score over the 16 week study period was also significantly higher in DYSPORT treated patients in the wrist ($p=0.004$) and finger joints ($p=0.001$) when compared to the placebo group. Passive range of movement over the 16 week study period in the elbow was marginally but significantly improved in DYSPORT treated patients compared to placebo ($p=0.036$).

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

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.

Another double-blind placebo controlled study was conducted for the treatment of hip adductor spasticity in 74 subjects with multiple sclerosis receiving either placebo, DYSPORT 500U, DYSPORT 1000U or DYSPORT 1500U. Active product or placebo was distributed between the adductor magnus, adductor brevis and adductor longus of both legs. Distance between knees was statistically significantly improved in the DYSPORT 1500U group as compared to placebo.

Focal spasticity affecting upper limbs in children aged two years and older

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

After the initial treatment, up to 3 further treatments of DYSPORT could be administered at planned doses of either 8 U/kg or 16 U/kg, although the investigator could elect to increase or decrease the dose (but not exceeding 16 U/kg).

The total dose of DYSPORT was injected intramuscularly into the affected upper limb muscles which included the PTMG of either elbow flexors or wrist flexors as well as other upper limb muscles according to the disease presentation. No more than 0.5 mL was allowed to be administered per injection site. However, more than one injection site per muscle was permitted.

An electrical stimulation (ES) and/or ultrasound was used to assist muscle localisation 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. As shown in Table 10, statistically significant improvements were demonstrated in MAS; improvements in PGA and GAS were not statistically significant.

Table 10: 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≤ 0.05; **p≤ 0.001; *** p≤ 0.0001; compared to 2 U/kg dose group [a] The four most commonly selected primary goals were Reaching, Grasp and release, Use of limb as a helping hand to stabilise and Involving affected arm more in daily activities.			

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

Parents completed the condition-specific Module for Cerebral Palsy for the Paediatric Quality of Life Inventory. At week 16, there was a statistically significant improvement from Baseline in fatigue (p=0.0443) in the DYSPORT 8 U/kg group and, in movement and balance (p=0.0068) in the 16 U/kg group compared with the DYSPORT 2 U/kg group. No other statistically significant improvements were observed in the other subscales.

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

Lower limb focal spasticity in children aged 2 year or older

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

Table 11: MAS Change from Baseline at week 4 and week 12, PGA and GAS at week 4 and week 12 (ITT Population)

Parameter	Placebo (N=77)	DYSPORT	
		10 U/kg/leg (N=79)	15 U/kg/leg (N=79)
LS mean change from baseline in ankle plantar MAS score			
Week 4	-0.5	-0.9 **	-1.0 ***
Week 12	-0.5	-0.8*	-1.0 ***
LS mean score for PGA response to treatment [b]			
Week 4	0.7	1.5***	1.5***
Week 12	0.4	0.8*	1.0**
LS mean GAS score [a			
Week 4	46.2	51.5***	50.9**
Week 12	45.9	52.5***	50.5*

* p≤ 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 DYSPORT 10 U/kg/leg and 15 U/kg/leg treatment groups at week 4 and week 12, and the angle of catch (Xv3) was significant for the DYSPORT 10 U/kg/leg group at week 12 and at both week 4 and week 12 for the DYSPORT 15 U/kg/leg 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 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 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.

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 the other botulinum toxin preparation for the treatment of spasmodic torticollis within the therapeutic dose range (250 to 1000 units).

Blepharospasm and hemifacial spasm in adults

A Phase II, multi-centre, randomized, double-blind, parallel group, placebo-controlled study 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

A total of 812 patients were selected in the four botulinum type A toxin (DYSPORT) trials: 119 in Study 2-54-52120-009, 373 in Study Y-97-52120-717, 100 in Study 2-54-52120-046 and 220 in Study A-94-52120-710. These four double-blind, placebo controlled studies consistently demonstrated the efficacy of DYSPORT administered in single total doses of 20, 25, 30, 50 or 75 units to reduce the severity of glabellar lines. This was true whether the investigators' objective criteria or the patients' subjective assessments were considered in the evaluations. Considering results across all studies, the recommended effective dose is 50 units and there is no statistically robust evidence to support the use of doses higher than this.

Based on the objectively assessed responder rate, the treatment effect appeared as early as 7-14 days after treatment. In Studies 2-54-52120-009 and Y-97-52120-717 which investigated the doses of 50 units and 75 units of DYSPORT, the treatment effect was fully developed after one month, and was still statistically significant after four months for both doses in Study Y-97-52120-717. The patients' satisfaction with the treatment remained highly significant for periods even exceeding four months after treatment. From the consensual decision of the

investigator and the patient, it was estimated that treatment could be repeated after a time interval of 3 to 4 months. The second treatment was as effective as the first one.

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

Pharmacokinetic studies with botulinum toxin pose problems in animals because of the high potency, the minute doses involved, the large molecular weight of the compound and the difficulty of labelling toxin to produce sufficiently high specific activity. Studies using I^{125} labelled toxin have shown that the receptor binding is specific and saturable, and the high density of toxin receptors is a contributory factor to the high potency. Dose and time responses in monkeys showed that at low doses there was a delay of 2-3 days with peak effect seen 5-6 days after injection. The duration of action, measured by changes of ocular alignment and muscle paralysis, varied between 2 weeks and 8 months. This pattern is also seen in man, and is attributed to the process of binding, internalisation and changes at the neuromuscular junction.

5.3 Preclinical safety data

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 effects were observed in the pre- and post-natal study on the F1 generation in rats. Fertility of the males and females was decreased due to reduced mating secondary to muscle paralysis at high doses.

In a juvenile toxicity study, rats treated weekly from the age of weaning on Postnatal day 21 up to 13 weeks of age comparable to children of 2 years old, to young adulthood (11 administrations over 10 weeks, up to total dose of approximately 33U/kg) do not show adverse effects on postnatal growth (including skeletal evaluation), reproductive, neurological and neurobehavioral development.

In a chronic toxicity study performed in rats up to 12 units/animal, there was no indication of systemic toxicity. Effects in reproduction 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Albumin and lactose.

6.2 Incompatibilities

DYSPORT should not be mixed with other medicinal products except those mentioned in the Dosage and Administration section.

6.3 Shelf life

The shelf life of the packaged product is 24 months when stored at 2-8°C. Maximum storage time of reconstituted product is 24 hours at 2-8ºC.

The product does not contain an anti-microbial agent. The reconstituted product should therefore be used as soon as possible.

6.4 Special precautions for storage

Unopened vials must be maintained at temperatures between 2ºC and 8ºC. DYSPORT must be stored in a refrigerator protected from light at the hospital where the injections are to be carried out and should not be given to the patient to store.

Reconstituted DYSPORT may be stored in a refrigerator (2-8ºC) protected from light for up to 24 hours prior to use. DYSPORT should not be frozen.

6.5 Nature and contents of container

DYSPORT is available in packs of 2 x 3 mL vials each containing 500 units Clostridium botulinum type A toxin-haemagglutinin complex.

DYSPORT is available in packs of 1 x 3 mL vials each containing 300 units Clostridium botulinum type A toxin-haemagglutinin complex.

6.6 Special precautions for use and disposal

Botulinum toxin is very susceptible to heat and certain chemical products. Any spills of the freeze-dried product must be wiped up:

- Either using absorbent material impregnated with a solution of sodium hypochlorite (bleach) in case of freeze-dried product.
- Or with dry, absorbent material in case of reconstituted product.

Gloves should be worn when cleaning product spills.

The contaminated surfaces should be cleaned using absorbent material impregnated with a solution of sodium hypochlorite (bleach), then dried.

If a vial is broken, proceed as indicated above. Carefully collect the pieces of broken glass and wipe up the product, avoiding any cuts to the skin.

If the product makes contact with the skin, wash with a solution of sodium hypochlorite (bleach) then rinse abundantly with water.

If the product makes contact with the eyes, rinse abundantly with water or with a dedicated eye-rinsing solution.

In the event of injury to the handler (cut or self-injection), proceed as indicated above and take the appropriate medical measures depending on the dose injected.

<u>Recommendations for the disposal of contaminated materials</u>

The needles, syringes and vials - which should not be emptied - must be placed in suitable containers intended for incineration after use.

Contaminated materials (absorbent cloth, gloves, ampoule debris) should be placed in an unpierceable bag for disposal by incineration.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

Toll-Free Phone: 0800 947 486

9 DATE OF FIRST APPROVAL

500 units: 16 April 1992
300 units: 19 November 2015

10 DATE OF REVISION OF THE TEXT

02 February 2023

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of precautions for: dry eye, excessive muscle weakness or atrophy.
4.8	Addition of dizziness for use in glabellar lines. Addition of facial paresis and eyelid ptosis for use in lateral canthal lines. Addition of post-marketing reports of hypersensitivity, hypoaesthesia and muscle atrophy. Reformat adverse effects section into tabular format.
8	Sponsor name corrected.

DYSPORT is a registered trademark.