PRODUCT MONOGRAPH

[Pr]DYSPORT THERAPEUTIC™

abobotulinumtoxinA for injection Ph. Eur.

Sterile lyophilized powder for solution for injection

300 and 500 Units per vial

Neuromuscular Blocking Agent

Manufactured by: Ipsen Biopharm Limited
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PrDYSPORT THERAPEUTIC™

abobotulinumtoxinA for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non medicinal Ingredients
Intramuscular	Sterile, lyophilized powder for reconstitution; 300 and 500 Units per vial	Human Serum Albumin *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

DYSPORT THERAPEUTIC™ (abobotulinumtoxinA**)** is indicated:

Cervical Dystonia

- To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults

Focal Spasticity

- For the symptomatic treatment of focal spasticity affecting the upper and lower limbs in patients 2 years of age and older

Geriatrics (> 65 years of age):
The clinical data for subjects > 65 years of age are limited.

Pediatrics (< 18 years of age):
Safety and effectiveness in pediatric patients below 2 years of age have not been evaluated.

DYSPORT THERAPEUTIC™ is not recommended for use in pediatric patients less than 18 years of age in the treatment of cervical dystonia.

CONTRAINDICATIONS

DYSPORT THERAPEUTIC™ is contraindicated in patients:

- who are hypersensitive to abobotulinumtoxinA or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section.
- with infection at the proposed injection sites.
- known to be allergic to cow's milk protein.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The term "Unit" upon which dosing is based, is a specific measurement of toxin activity that is unique to Ipsen's formulation of abobotulinumtoxinA. Therefore, the units used to describe DYSPORT THERAPEUTIC™ activity are different from those used to describe that of other botulinum toxin preparations and the units representing DYSPORT THERAPEUTIC™ activity are not interchangeable with other products.
- DYSPORT THERAPEUTIC™ should only be administered by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.
- Follow the recommended dosage and frequency of administration for DYSPORT THERAPEUTIC™ (See **WARNINGS AND PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**).
- DISTANT SPREAD OF TOXIN EFFECT: The effects of DYSPORT THERAPEUTIC™ and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

General

Use DYSPORT THERAPEUTIC™ only as directed.

Do not use dosage recommendations and potency units applied to other botulinum toxin products when using DYSPORT THERAPEUTIC™. Do not exceed the recommended dosage and frequency of administration of DYSPORT THERAPEUTIC™.

The safe and effective use of DYSPORT THERAPEUTIC™ depends upon proper storage of the product, selection of the correct dose, reconstitution, and injection technique.

Injection intervals of DYSPORT THERAPEUTIC™ should be no more frequent than every 12 weeks. Indication-specific dosage and administration recommendations should be followed.

As with any intramuscular injection, DYSPORT THERAPEUTIC™ should only be used where strictly necessary in patients with prolonged bleeding times.

Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnea, respiratory failure, respiratory arrest) and/or in patients with significant asthenia have been reported following treatment with botulinum toxin A or B. Patients with disorders resulting in defective neuromuscular transmission, difficulty in swallowing or breathing are more at risk of experiencing these effects. In these patients, treatment must be administered under the control of a specialist and only if the benefit of treatment outweighs the

risk.

Caution should be exercised when treating patients, especially the elderly, with focal spasticity affecting the lower limbs, who may be at increased risk of fall.

Injection site-specific dosage and administration recommendations for each indication should be followed. When combining indications, the maximum cumulative body dose in a 12-week interval should not exceed 1500 Units in adult patients. When combining indications, the maximum cumulative body dose in a 16-week interval should not exceed 30 Units/kg or 1000 Units, whichever is lower, in pediatric patients (see DOSAGE AND ADMINISTRATION).

DYSPORT THERAPEUTIC™ should be administered with caution to patients with pre-existing swallowing or breathing problems as these can worsen following the distribution of the effect of toxin into the relevant muscles (see Gastrointestinal/Respiratory subsection below).

This product contains human serum albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. The theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

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.

Carcinogenesis and Mutagenesis

Animal studies to evaluate the carcinogenic and genotoxic potential of DYSPORT THERAPEUTIC™ have not been conducted (see TOXICOLOGY).

Driving and Operating Machinery

Adverse events such as muscle weakness occurred in DYSPORT THERAPEUTIC™-treated patients. Caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Gastrointestinal/Respiratory

DYSPORT THERAPEUTIC™ should be administered with caution to patients with pre-existing swallowing or breathing problems as these can worsen following the distribution of the effect of toxin into the relevant muscles. Aspiration has occurred in rare cases and is a risk when treating patients who have a chronic respiratory disorder. Patients and their care-givers must be warned of the necessity to seek immediate medical treatment in case of problems with swallowing, speech or respiratory problems.

Immune

The data to assess the clinical impact of developing antibodies are limited. As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.

In clinical trial studies, about 3% of adult subjects and 2.1% of pediatric subjects developed neutralizing antibodies over time following DYSPORT THERAPEUTIC™ treatment. The clinical relevance of this observation is unknown (see Clinical Trial Adverse Drug Reactions).

Neurologic

Caution should be exercised when administering DYSPORT THERAPEUTIC™ to individuals with peripheral motor neuropathy (e.g., amyotrophic lateral sclerosis or motor neuropathy), facial palsy or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at an increased risk of excessive muscle weakness and clinically significant systemic effects such as severe dysphagia and respiratory compromise.

Skin

Caution should be exercised when administering DYSPORT THERAPEUTIC™ to patients with inflammation at the injection site(s), deep dermal scarring, or thick sebaceous skin.

Special Populations

Pregnant Women: There are limited data from the use of abobotulinumtoxinA in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development other than at high doses causing maternal toxicity. The potential risk to pregnant women is unknown. DYSPORT THERAPEUTIC™ 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.

Nursing Women: It is not known whether this drug is excreted in human milk. The excretion of DYSPORT THERAPEUTIC™ in milk has not been studied in animals. The use of DYSPORT THERAPEUTIC™ during lactation is not recommended.

Pediatrics (< 18 years of age):

There have been some spontaneous reports of death associated with severe adverse reactions in children with severe cerebral palsy after treatment with a botulinum toxin product. Extreme caution should be exercised when treating pediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease (see Post-Market Adverse Drug Reactions in ADVERSE REACTIONS).

Safety and effectiveness in pediatric patients below 2 years of age have not been evaluated.

DYSPORT THERAPEUTIC™ is not recommended for use in children less than 18 years of age in the treatment of cervical dystonia.

Geriatrics (> 65 years of age): The clinical data for subjects > 65 years of age are limited. No clinical trials specifically designed for elderly patients have been performed. In general, elderly patients should be observed to evaluate their tolerability of DYSPORT THERAPEUTIC™, due to the greater frequency of concomitant diseases and other drug therapies.

Monitoring and Laboratory Tests

There are no specific requirements for laboratory test monitoring when patients are treated with DYSPORT THERAPEUTIC™.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions may occur within the first few days following injection and while generally transient may have a duration of several months.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue; however, weakness of adjacent muscles associated with local diffusion and/or injection technique has been reported.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Cervical Dystonia (CD)

In four clinical studies, 173 patients with cervical dystonia had received treatment with DYSPORT THERAPEUTIC™ at the dose of 500 Units. Two of these studies were phase III randomized, double-blind and placebo-controlled clinical trials involving 252 patients (121 in DYSPORT THERAPEUTIC™ group, 131 in placebo group).

The DYSPORT THERAPEUTIC™ 500 Unit population was almost entirely Caucasian (99.4%) with a median age of 51 years (range 18–79 years). Most patients (87.3%) were less than 65 years of age; 59% were women.

Table 1 compares the incidence of the most frequent treatment-emergent adverse events (TEAEs) from a single treatment cycle of 500 Units of DYSPORT THERAPEUTIC™ compared to placebo (see CLINICAL TRIALS).

Table 1: Most Common TEAEs (>5%) and Greater than Placebo: Double-Blind Phase of Clinical Trials in Patients with CD

	Double-blind Phase	
System Organ Class Preferred Term	**DYSPORT THERAPEUTIC™ 500 Units (N=173)**	**Placebo (N=182)**
	%	**%**
Any TEAE	**61**	**51**
General disorders and administration site conditions	**30**	**23**
Injection site discomfort	13	8
Fatigue	12	10
Injection site pain	5	4
Musculoskeletal and connective tissue disorders	**30**	**18**
Muscular weakness	16	4

Musculoskeletal pain	7	3
Gastrointestinal disorders	**28**	**15**
Dysphagia	15	4
Dry mouth	13	7
Nervous system disorders	**16**	**13**
Headache	11	9
Infections and infestations	**13**	**9**
Respiratory, thoracic and mediastinal disorders	**12**	**8**
Dysphonia	6	2
Eye Disorders[a]	**7**	**2**

a. The following preferred terms were reported: vision blurred, diplopia, visual acuity reduced, eye pain, eyelid disorder, accommodation disorder, dry eye, eye pruritus.

Spasticity in Adults

Safety results from pooled controlled studies in adults are reported here.

Injection Site Reactions

Injection site reactions (e.g. pain, bruising, hemorrhage, erythema etc.) have occurred following administration of DYSPORT THERAPEUTIC™ in adults with both upper and lower limb spasticity.

Adult Upper Limb (AUL) Spasticity

The safety data was evaluated from six double-blind placebo-controlled studies and three open label studies. In six pooled double-blind placebo-controlled studies, 398 subjects with upper limb spasticity received DYSPORT THERAPEUTIC™, (187 subjects received 500 U and 194 received 1000 U) and 269 patients received placebo.

Table 2 lists the most frequently reported TEAEs (≥2%) in any DYSPORT THERAPEUTIC™ dose group and more than placebo in double-blind studies investigating the treatment of upper limb spasticity in adults with DYSPORT THERAPEUTIC™.

Table 2: All TEAEs Observed in At Least 2% of AUL Spasticity Subjects In Any DYSPORT THERAPEUTIC™ Dose Group and More Frequent Than Placebo (Pooled Double-Blind Studies)

System Organ Class Preferred Term, n (%)	DYSPORT THERAPEUTIC™ 500 Units (N=187) %	 1000 Units (N=194) %	Placebo (N=269) %
Any TEAE	**40**	**49**	**37**
Infections and infestations	**13**	**13**	**9**
Nasopharyngitis	4	1	1
Urinary tract infection	3	1	2
Influenza	1	2	1
Infection	1	2	1
Musculoskeletal and connective tissue disorders	**8**	**14**	**8**
Muscular weakness	2	4	1
Pain in extremity	0	2	1
Musculoskeletal pain	3	2	2
Nervous system disorders	**11**	**14**	**12**
Headache	1	2	1
Dizziness	3	1	2
General disorders and administration site conditions	**9**	**7**	**7**

Asthenia	2	1	0
Injury, poisoning and procedural complications Fall	**4** 2	**9** 3	5 2
Respiratory, thoracic and mediastinal disorders Cough	**5** 1	**5** 2	**3** 1
Psychiatric disorders Depression	**2** 2	**5** 3	**3** 1

Adult Lower Limb (ALL) Spasticity

Table 3 lists the most frequently reported adverse reactions (≥2%) from six double-blind placebo-controlled studies. Among adult patients with lower limb spasticity who received DYSPORT THERAPEUTIC™; 234 patients received 1000 U, 277 received 1500 U and 350 patients received placebo. The most commonly observed adverse reactions were falls, muscular weakness and myalgia.

Table 3: Adverse Reactions Observed in at Least 2% of Patients Treated in Pooled, Double-Blind Trials of ALL Spasticity and Reported More Frequently than with Placebo

System Organ Class/ Preferred Term	**Placebo (N=350) %**	**DYSPORT THERAPEUTIC™ 1000U (N=234) %**	**DYSPORT THERAPEUTIC™ 1500U (N=277) %**
Musculoskeletal and connective tissue disorders			
Muscular weakness	2	3	7
Myalgia	5	6	7
Injury, poisoning and procedural complications			
Fall	4	6	9
General disorders and administration site conditions			
Fatigue	1	1	3
Asthenia	1	1	2
Influenza like illness	1	2	1
Gastrointestinal disorders			
Dysphagia	1	1	3

When treating upper and lower limbs in adult patients concomitantly with DYSPORT THERAPEUTIC™ at a total dose of up to 1500 Units, there were no safety findings in addition to those expected from treating either upper limb or lower limb muscles alone.

Spasticity in Pediatric Patients

Pediatric Upper Limb (PUL) Spasticity

Table 4 reflects exposure to DYSPORT THERAPEUTIC™ in 210 patients, 2 to 17 years of age, who were evaluated in a double-blind, active-controlled, multicenter study in patients treated for upper limb spasticity due to cerebral palsy (see CLINICAL TRIALS). The most commonly observed adverse reaction (≥10% of patients) was: upper respiratory tract infections. The incidence of all treatment-related TEAEs occurring in patients treated with DYSPORT THERAPEUTIC™ in treatment cycle 1 are presented in Table 4. Patients received either DYSPORT THERAPEUTIC™ 2 Units/kg (low dose control), 8 Units/kg or 16 Units/kg.

Table 4: Treatment-Related TEAEs Observed in ≥ 3% of Patients Treated in a Double-Blind Study of Cerebral Palsy Patients with PUL Spasticity and Reported More Frequently than in the Control Group

Treatment-Related TEAEs	DYSPORT 2 Units/kg (N=70) (%)	DYSPORT 8 Units/kg (N=70) (%)	DYSPORT 16 Units/kg (N=70) (%)
Infections and infestations			
Upper respiratory tract infection	7	9	11
Influenza	1	1	3
Tonsillitis	1	3	1
Urinary tract infection	0	4	0
Pharyngitis streptococcal	0	0	3
Gastrointestinal disorders			
Vomiting	3	4	1
Nausea	0	3	1
Salivary hypersecretion	0	3	0
Musculoskeletal and connective tissue disorders			
Muscular weakness	1	4	6
Arthralgia	1	3	1
Nervous system disorders			
Headache	0	6	3
Seizure	3	4	0
Epilepsy	1	0	4
General disorders and administration site conditions			
Pyrexia	3	6	3
Asthenia	0	3	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	0	7	1
Skin and subcutaneous tissue disorders			
Rash	0	4	0
Psychiatric disorders			
Anxiety	0	3	0

Pediatric Lower Limb (PLL) Spasticity

Table 5 lists the most frequently reported adverse drug reactions in 280 patients, 2 to 17 years of age, in the pooled, randomized, placebo-controlled clinical studies that assessed the use of DYSPORT THERAPEUTIC™ for the treatment of unilateral or bilateral lower limb spasticity in pediatric cerebral palsy patients (see CLINICAL TRIALS). The most commonly observed adverse reactions (≥5% of patients) were: influenza-like illness, myalgia and muscular weakness.

The adverse reactions (≥2.0%) in any DYSPORT THERAPEUTIC™ dose group and occurring at a frequency greater than placebo in the pooled double-blind studies for the treatment of lower limb spasticity in pediatric patients with cerebral palsy are listed in Table 5.

Table 5: Adverse Reactions Observed in ≥ 2% of Patients Treated in Pooled, Double-Blind Trials of Cerebral Palsy Patients with PLL Spasticity and Reported More Frequently than with Placebo

	Placebo	DYSPORT THERAPEUTIC™ Unilateral Injections		DYSPORT THERAPEUTIC™ Bilateral Injections	
System Organ Class (SOC)/Preferred Term (PT)	(N=136) %	10 U/kg (N=43) %	15 U/kg (N=52) %	20 U/kg (N=64) %	30 U/kg (N=84) %
General disorders and administration site conditions					
Influenza-like illness	5	0	10	9	2
Injection site reaction	1	2	2	3	1
Fatigue	0	0	0	3	0
Gait disturbance	0	2	0	0	2
Asthenia	0	0	0	2	0
Musculoskeletal and connective tissue disorders					
Myalgia	5	2	2	3	8
Muscular weakness	1	5	0	0	1
Renal and urinary disorders					
Urinary incontinence	0	2	0	0	1
Injury, poisoning and procedural complications					
Fall	1	0	0	3	4

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

Neutralizing Antibody Production

Testing for antibodies to DYSPORT THERAPEUTIC™ was performed in subjects treated with DYSPORT THERAPEUTIC™, 281 subjects in AUL clinical trials, 452 subjects in ALL clinical trials, 211 subjects in CD clinical trials, 178 pediatric subjects in PUL trials and 429 pediatric subjects in PLL trials. About 3% of adult subjects and 2.1% of pediatric subjects developed neutralizing antibodies over time with DYSPORT THERAPEUTIC™ treatment. The clinical relevance of this observation is unknown.

Post-Market Adverse Drug Reactions

There is extensive post-marketing experience for the treatment of upper facial lines. Adverse reactions are reported voluntarily from a population of uncertain size; thus, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure. The following adverse reactions have been identified during post-approval use, regardless of indication: vertigo, eyelid ptosis, diplopia, vision blurred, photophobia, dysphagia, nausea, injection site pain, malaise, influenza-like illness, hypersensitivity, sinusitis, amyotrophy, burning sensation, facial paresis, dizziness, headache, hypoesthesia, erythema, and excessive granulation tissue.

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).

There have been some spontaneous reports of death associated with severe adverse reactions including aspiration pneumonia in children with severe cerebral palsy after treatment with a botulinum toxin product. A causal association to botulinum toxin product was not firmly established in these cases.

DRUG INTERACTIONS

No specific interactions have been reported.

Overview

No formal drug interaction studies have been conducted with DYSPORT THERAPEUTIC™.

Patients treated concomitantly with botulinum toxins and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents) should be observed closely because the effect of the botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of DYSPORT THERAPEUTIC™ may potentiate systemic anticholinergic effects such as blurred vision.

The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Drug-Drug Interactions

Table 6: Potential Drug-Drug Interactions

Proper name of drug	Ref	Effect	Clinical comment
aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission (e.g., curare-like agents, lincosamides, polymyxins, and anticholinesterases).	T	Theoretically, the effect of botulinum toxin may be potentiated.	The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission. Caution should be exercised when DYSPORT THERAPEUTIC™ is used with aminoglycosides or any other drugs that interfere with neuromuscular transmission.
Different botulinum neurotoxin serotypes	T	Unknown	The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Legend: T = Theoretical

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- **For Intramuscular Use Only.**
- **Although actual location of the injection sites in a muscle 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.**
- **The potency units of DYSPORT THERAPEUTIC™ are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT THERAPEUTIC™ cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.**
- **Treatment should be administered at the recommended dose for each treatment area.**
- **In the treatment of spasticity, 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.**
- **Injection intervals of DYSPORT THERAPEUTIC™ should be no more frequent than every 12 weeks in adult patients and in pediatric patients with lower limb spasticity; and every 16 weeks in pediatric patients with upper limb spasticity.**
- **When combining indications, the maximum cumulative body dose in a 12-week interval should not exceed 1500 Units in adult patients.**
- **When combining indications, the maximum cumulative body dose in a 16-week interval should not exceed 30 Units/kg or 1000 Units, whichever is lower, in pediatric patients.**

Recommended Dose and Dosage Adjustment

Cervical Dystonia
The recommended initial dose of DYSPORT THERAPEUTIC™ for the treatment of cervical dystonia in adults is 500 Units given intramuscularly as a divided dose among affected muscles in patients with or without a history of prior treatment with botulinum toxin. (A description of the average DYSPORT THERAPEUTIC™ dose and percentage of total dose injected into specific muscles in the pivotal clinical trials can be found in Table 13). Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Clinical

studies with DYSPORT THERAPEUTIC™ in cervical dystonia suggest that the peak effect occurs between two and four weeks after injection.

In uncontrolled open label clinical trials, the repeated treatment of cervical dystonia with DYSPORT THERAPEUTIC™ was studied based on return of clinical symptoms. Doses were within the range of 250-1000 Units. Re-treatment, if needed, should not occur in intervals of less than 12 weeks (see CLINICAL TRIALS). Doses exceeding 1000 Units is not recommended.

Spasticity in Adults
No more than 1 mL should generally be administered at any single injection site. The maximum recommended total body dose of DYSPORT THERAPEUTIC™ for the treatment of spasticity (upper and lower limb combined) in adults is 1500 Units per treatment session.

Adult Upper Limb Spasticity
In the pivotal trial, doses of 500 and 1000 Units were divided among selected muscles (Table 7), at a given treatment session.

Table 7: DYSPORT THERAPEUTIC™ Dosing by Muscle for AUL Spasticity

Muscles Injected	Recommended DYSPORT THERAPEUTIC™ Dose
Flexor carpi radialis (FCR)	100-200 U
Flexor carpi ulnaris (FCU)	100-200 U
Flexor digitorum profundus (FDP)	100-200 U
Flexor digitorum superficialis (FDS)	100-200 U
Flexor pollicis longus	100-200 U
Adductor pollicis	25-50 U
Brachialis	200-400 U
Brachioradialis	100-200 U
Biceps brachii (BB)	200-400 U
Pronator teres	100-200 U
Triceps brachii (long head)	150-300 U
Pectoralis major	150-300 U
Subscapularis	150-300 U
Latissimus dorsi	150-300 U

Repeat DYSPORT THERAPEUTIC™ 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 THERAPEUTIC™ and muscles to be injected. Clinical improvement may be expected one week after administration of DYSPORT THERAPEUTIC™.

Adult Lower Limb Spasticity
In the pivotal clinical trial, doses of 1000 and 1500 Units were divided among selected muscles at a given treatment session (Table 8).

Table 8: DYSPORT THERAPEUTIC™ Dosing by Muscle for ALL Spasticity

Muscles Injected	Recommended DYSPORT THERAPEUTIC™ Dose	Recommended Number of Injection Sites per Muscle
Distal Muscles		
Gastrocnemius		
Gastrocnemius medial head	100 Units to150 Units	1
Gastrocnemius lateral head	100 Units to 150 Units	1
Soleus	330 Units to 500 Units	3
Tibialis posterior	200 Units to 300 Units	2
Flexor digitorum longus	130 Units to 200 Units	1-2
Flexor digitorum brevis	67 Units to 100 Units	1
Flexor hallucis longus	70 Units to 200 Units	1
Flexor hallucis brevis	100 Units	1

Repeat DYSPORT THERAPEUTIC™ 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, or longer. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of DYSPORT THERAPEUTIC™ and muscles to be injected.

Spasticity in Pediatric Patients

For treatment in combined indications, the dose of DYSPORT THERAPEUTIC™ to be injected in each location should similarly be tailored to individual needs, without exceeding a total dose of 30 Units/kg or 1000 Units, whichever is lower, per treatment session in a 16-week interval. DYSPORT THERAPEUTIC™ dosing for spasticity in pediatric patients is based on Units per kilogram of body weight. To calculate the total units of DYSPORT THERAPEUTIC™ required for treatment of one limb, select the dose of DYSPORT THERAPEUTIC™ in Units/kg and the body weight (kg) of the patient (Tables 9 and 10).

The total dose administered should be divided between the affected spastic muscles of the upper or lower limb(s) and should be distributed across more than 1 injection site in any single muscle.

No more than 0.5 mL should generally be administered at any single injection site.

Pediatric Upper Limb Spasticity

In the pivotal clinical trial, doses of 8 Units/kg and 16 Units/kg were divided among selected muscles of the target upper limb at a given treatment session (Table 9).

Table 9: DYSPORT THERAPEUTIC™ Dosing by Muscle for PUL Spasticity

Muscle	Recommended DYSPORT THERAPEUTIC™ Dose (Units/kg Body Weight)	Recommended Number of Injection Sites per Muscle
Brachialis	3 to 6 Units/kg	Up to 2
Brachioradialis	1.5 to 3 Units/kg	1
Biceps brachii	3 to 6 Units/kg	Up to 2
Pronator teres	1 to 2 Units/kg	1
Pronator quadratus	0.5 to 1 Unit/kg	1

Flexor carpi radialis (FCR)	2 to 4 Units/kg	Up to 2
Flexor carpi ulnaris (FCU)	1.5 to 3 Units/kg	1
Flexor digitorum profundus (FDP)	1 to 2 Units/kg	1
Flexor digitorum superficialis (FDS)	1.5 to 3 Units/kg	Up to 4
Flexor pollicis brevis/opponens pollicis	0.5 to 1 Unit/kg	1
Adductor pollicis	0.5 to 1 Unit/kg	1
Total dose*	**Up to 16 Units/kg in a single upper limb (and not exceeding 21 Units/kg if both upper limbs injected)**	

*The total dose must not exceed 16 Units/kg or 640 Units, whichever is lower for unilateral injections or 21 Units/kg or 840 Units, whichever is lower for bilateral injections.

Repeat DYSPORT THERAPEUTIC™ 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.

Pediatric Lower Limb Spasticity

In the pivotal clinical trial, doses of 10 Units/kg and 15 Units/kg were divided among selected muscles of the target lower limb at a given treatment session (Table 10).

Table 10: DYSPORT THERAPEUTIC™ Dosing by Muscle for PLL Spasticity

Muscle Injected	Recommended DYSPORT THERAPEUTIC™ Dose (Units/kg Body Weight)	Recommended Number of Injection Sites per Muscle
Gastrocnemius	6 to 9 U/kg[a]	Up to 4
Soleus	4 to 6 U/kg[a]	Up to 2
Total dose*	**10 to 15 U/kg divided across both muscles**	**Up to 6**

[a]The listed individual doses to be injected in the muscles can be used within the range mentioned without exceeding 15U/kg total dose for unilateral injection or 30U/kg for bilateral injections or 1000 Units, whichever is lower.
*The total dose must not exceed 15 Units/kg for unilateral lower limb injections or 30 Units/kg for bilateral lower limb injections or 1000 units, whichever is lower.

Repeat DYSPORT THERAPEUTIC™ 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 the 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 THERAPEUTIC™ and muscles to be injected.

Reconstiution

DYSPORT THERAPEUTIC™ is supplied as a dry powder, in single-dose 300 Unit and 500 Unit vials, which must be reconstituted with preservative-free 0.9% Sodium Chloride Injection, USP using aseptic technique prior to intramuscular injection. Table 11 provides dilution instructions for the 300 and 500 Unit vials, depending on the desired final concentration. The desired final concentration varies depending on the indication (Table 11).

Table 11: Recommended Reconstitution Volumes

Target concentration (Units/0.1 mL)	Diluent* volume 300 Unit Vial	500 Unit Vial
10.0	3.0 mL	5.0 mL**
20.0	1.5 mL	2.5 mL
50.0	0.6 mL	1.0 mL

* Preservative-free 0.9% Sodium Chloride Injection
**For 5.0 mL reconstituation volume only, please see steps below.

Using an appropriately sized sterile syringe, needle and aseptic technique, draw up the required volume (Table 11) of 0.9% Sodium Chloride Injection USP (without preservative).

Insert the needle into the DYSPORT THERAPEUTIC™ vial. The partial vacuum will begin to pull the saline into the vial. Any remaining required saline should be expressed into the vial manually. Do not use the vial if a vacuum is absent. Gently swirl to dissolve. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Reconstituted DYSPORT THERAPEUTIC™ should be a clear, colourless solution, free of particulate matter; otherwise it should not be injected. Expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach an appropriately sized new sterile needle.

**To reconstitute a 500 Unit vial for 10 Units/0.1 mL concentration, complete the following steps:

When using 5.0 mL of diluent for a 500 Unit vial of DYSPORT THERAPEUTIC™, no more than 2.5 mL of saline should be introduced into the vial.

1. Reconstitute a 500 Unit vial of DYSPORT THERAPEUTIC™ with 2.5 mL of Preservative-free 0.9% Sodium Chloride Injection, USP, gently mix, and set the vial aside.
2. Withdraw 2.5 mL of Preservative-free 0.9% Sodium Chloride Injection, USP, into a 5 mL syringe.
3. Take the 5 mL syringe with 2.5 mL Preservative-free 0.9% Sodium Chloride Injection, USP, and draw up the DYSPORT THERAPEUTIC™ solution from the reconstituted vial without inverting and mix gently. The resulting concentration will be 10 units/0.1 mL.
4. Dispose of any unused saline.

Once reconstituted, DYSPORT THERAPEUTIC™ should be stored in a refrigerator at 2–8°C protected from light and used within 24 hours. Do not freeze reconstituted DYSPORT THERAPEUTIC™. Discard the vial and needle in accordance with local regulations.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Excessive doses of DYSPORT THERAPEUTIC™ may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary.

Symptoms of overdose are not likely to be 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 paralysis.

There is no significant information regarding overdose from clinical studies.

In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local Health Department.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

DYSPORT THERAPEUTIC™ inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings. Toxin activity occurs in the following sequence: Toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor mediated endocytosis, pH-induced translocation of the toxin light chain to the cell cytosol and cleavage of SNAP25 leading to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves.

Recovery of transmission occurs gradually as the neuromuscular junction recovers from SNAP25 cleavage and as new nerve endings are formed.

Pharmacodynamics

The primary pharmacodynamic effect of DYSPORT THERAPEUTIC™ is due to chemical denervation of the treated muscle resulting in a measurable decrease of the compound muscle action potential, causing a localized reduction of muscle activity.

Pharmacokinetics

DYSPORT THERAPEUTIC™ is not expected to be present in the peripheral blood at measurable levels following intramuscular injection at the recommended doses. Using currently available analytical technology, it is not possible to detect DYSPORT THERAPEUTIC™ in the peripheral blood following intramuscular injection at the recommended doses.

Duration of Effect

The clinical effect of DYSPORT THERAPEUTIC™ may last up to 20 weeks. DYSPORT THERAPEUTIC™ should not be administered more frequently than every 12 weeks in adult patients and pediatric patients with lower limb spasticity; and every 16 weeks in pediatric patients with upper limb spasticity between two treatment sessions. When combining indications, the injection intervals should be no more frequent than every 12 weeks in adult patients and 16 weeks in pediatric patients. When used for re-treatment, DYSPORT THERAPEUTIC™ should be reconstituted and injected using the same techniques as the initial treatment.

STORAGE AND STABILITY

DYSPORT THERAPEUTIC™ must be stored under refrigeration at 2–8°C. Protect from light.

Administer DYSPORT THERAPEUTIC™ within 24 hours of reconstitution; during this period reconstituted DYSPORT THERAPEUTIC™ should be stored under refrigeration at 2–8°C. Do not freeze after reconstitution.

Do not use after the expiration date on the vial.

SPECIAL HANDLING INSTRUCTIONS

All vials, including expired vials, or equipment used with DYSPORT THERAPEUTIC™ should be disposed of carefully as is done with all medical waste.

DOSAGE FORMS, COMPOSITION AND PACKAGING

DYSPORT THERAPEUTIC™ is supplied as a single-use sterile 300 Unit vial and a single-use sterile 500 Unit vial for reconstitution with 0.9% Sodium Chloride Injection USP (without preservative). Each vial contains 300 Units of lyophilized abobotulinumtoxinA, 125 micrograms human serum albumin and 2.5 mg lactose; or 500 Units of lyophilized abobotulinumtoxinA, 125 micrograms human serum albumin and 2.5 mg lactose.

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: abobotulinumtoxinA

Structural formula: AbobotulinumtoxinA (Botulinum toxin type A), the active ingredient in DYSPORT THERAPEUTIC™ is a purified neurotoxin type A complex produced by fermentation of the bacterium *Clostridium botulinum* type A, Hall Strain. It is purified from the culture supernatant by a series of precipitation, dialysis, and chromatography steps.

AbobotulinumtoxinA is a complex which includes a 150 kDa neurotoxin composed of 1296 amino acid residues (1295 after cleavage of the N-terminal methionine). The 150 kDa neurotoxin is produced as a single-chain polypetide. After synthesis, the neurotoxin is proteolytically cleaved to generate a di-chain protein composed of a heavy chain (~80 kDa) and light chain (~50 kDa). On a genetic level, the toxin gene occurs in a cluster of genes which also encode for the non-toxic non-hemagglutinin protein (NTNH), a regulator protein and the hemagglutinin (HA) proteins (HA70, HA34 and HA17). These proteins and their derivatives, except for the regulator protein, form the components of the neurotoxin type A complex. According to published literature, DYSPORT THERAPEUTIC™ delivers approximately 5 picograms (pg) of 150 kDa active neurotoxin per unit of abobotulinumtoxinA.

DYSPORT THERAPEUTIC™ uses a cell-based assay to determine the potency of the product relative to a reference material. The assay and reference material are specific to DYSPORT THERAPEUTIC™. One unit of DYSPORT THERAPEUTIC™ corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. Due to specific details of the assay system, such as vehicle, dilution scheme and laboratory protocols, units of biological activity of DYSPORT THERAPEUTIC™ are not interchangeable with units of any other botulinum toxin or any toxin assessed with any other specific assay method.

CLINICAL TRIALS

Cervical Dystonia
The efficacy of DYSPORT THERAPEUTIC™ was evaluated in two well-controlled, randomized, double-blind, placebo controlled, single dose, parallel group studies in treatment-naïve and previously treated cervical dystonia patients at dose of 500U. The principal analyses from these trials provide the primary demonstration of efficacy involving 252 patients (121 on DYSPORT THERAPEUTIC™, 131 on placebo) with 36% male and 64% female. Ninety-nine percent of the patients were Caucasian.

In both placebo controlled studies (Study 051 and Study 045), a dose of 500U DYSPORT THERAPEUTIC™ was given by intramuscular injection divided among two to four affected muscles. The primary assessment of efficacy was based on the total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) change from baseline at Week 4 for both studies. The scale evaluates the severity of dystonia, patient perceived disability from dystonia, and pain. The adjusted mean change from baseline in the TWSTRS total score was statistically significantly greater for the DYSPORT THERAPEUTIC™ group than the placebo group at Weeks 4 in both studies (see Table 12). These clinical trials were followed by open label repeated treatment studies where retreatment was determined by clinical need after a minimum of 12 weeks.

Table 12: TWSTRS Total Score Efficacy Outcome from the Phase 3 Cervical Dystonia Studies Intent to Treat Population

	Study 051		**Study 045**	
	DYSPORT THERAPEUTIC™ 500 Units n=55	**Placebo n=61**	**DYSPORT THERAPEUTIC™ 500 Units n=37**	**Placebo n=43**
Baseline (week 0)_ Mean (SD)	43.8 (8.0)	45.8 (8.9)	45.1 (8.7)	46.2 (9.4)
Week 4 Mean (SD)	30.0 (12.7)	40.2 (11.8)	35.2 (13.8)	42.4 (12.2)
Change from Baseline[ab]	-15.6 (2.0)	-6.7 (2.0)	-9.6 (2.0)	-3.7 (1.8)
Treatment difference	-8.9[c]		-5.9[c]	
95% confidence interval	[-12.9 to -4.7]		[-10.6 to -1.3]	
p value	<0.0001		0.013	
Week 8 Mean (SD)	29.3 (11.0)	39.6 (13.5)		
Change from Baseline[ab]	-14.7 (2.0)	-5.9 (2.0)		
Treatment difference	-8.8[c]			
95% confidence interval	[-12.9 to -4.7]			
p value	<0.0001			

a. Change from baseline is expressed as adjusted least squares mean (SE)
b. For Study 051, the type I error rate was controlled using a hierarchical testing procedure
c. Treatment difference and corresponding confidence intervals are obtained from an analysis of covariance on the change from baseline with treatment, baseline TWSTRS total score, BTX status at baseline and centre as explanatory variables.
Abbreviations: BTX=botulinum toxin; SD=standard deviation; SE=standard error

Analyses by gender, weight, geographic region, underlying pain, cervical dystonia severity at baseline and history of treatment with botulinum toxin did not show any meaningful differences between groups.

Table 13 indicates the average DYSPORT THERAPEUTIC™ dose, and percentage of total dose, injected into specific muscles in the pivotal clinical trials.

Table 13: DYSPORT THERAPEUTIC™ 500 Units Starting Dose (units and % of the total dose) by Unilateral Muscle Injected During Double-Blind Pivotal Phase 3 Studies 045 and 051 (Combined) in CD

Number of patients injected per muscle[a]		DYSPORT THERAPEUTIC™ Dose Injected		Percentage of the total DYSPORT THERAPEUTIC™ Dose Injected	
		Median [DYSPORT THERAPEUTIC™ Units] (min, max)	75th percentile [DYSPORT THERAPEUTIC™ Units]	Median [%] (min, max)	75th percentile [%]
Sternocleidomastoid	90	125 Units (50, 350)	150 Units	26.5% (10, 70)	30.0%
Splenius capitis	85	200 Units (75, 450)	250 Units	40.0% (15, 90)	50.0%
Trapezius	50	102.6 Units (50, 300)	150 Units	20.6% (10, 60)	30.0%
Levator scapulae	35	105.3 Units (50, 200)	125 Units	21.1% (10, 40)	25.0%
Scalenus (medius and anterior)	26	115.5 Units (50, 300)	150 Units	23.1% (10, 60)	30.0%
Semispinalis capitis	21	131.6 Units (50, 250)	175 Units	29.4% (10, 50)	35.0%
Longissimus	3	150 Units (100, 200)	200 Units	30.0% (20, 40)	40.0%

a. Total number of patients in combined studies 045 and 051 who received initial treatment = 121

Retreatment was studied in the clinical trials e.g., in an open label study, a total of 131, 121, 111 subjects with cervical dystonia received retreatment with DYSPORT THERAPEUTIC™ in Cycles 1, 2, and 3, respectively. The dose of DYSPORT THERAPEUTIC™ administered at the first treatment was 500 Units, DYSPORT THERAPEUTIC™ given at the second and third treatments were titrated for individual patients (range from 250 to 1000 Units). The median time to retreatment was 14 weeks, with one in four subjects being greater than 20 weeks and one in ten subjects being greater than 35 weeks. DYSPORT THERAPEUTIC™ was effective and well tolerated in the repeated treatments in patients with cervical dystonia.

Spasticity in Adults

Adult Upper Limb Spasticity

The efficacy and safety of DYSPORT THERAPEUTIC™ for the treatment of upper limb spasticity was evaluated in a randomized, multi-center, double-blind, placebo-controlled study that included 238 patients (159 DYSPORT THERAPEUTIC™ and 79 placebo) with upper limb spasticity (Modified Ashworth Scale (MAS) score ≥2 in the primary targeted muscle group for toxin naive subjects or MAS score ≥3 in the primary targeted muscle group for toxin non-naive subjects at least 4 months after the last BTX 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 THERAPEUTIC™ 500U (n=80), DYSPORT

THERAPEUTIC™ 1000U (n=79), or placebo (n=79) was injected intramuscularly into the affected upper limb muscles. The volume of either DYSPORT THERAPEUTIC™ or placebo injected in the primary targeted muscle groups (PTMG) is presented in Table 14. 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. Additional muscles suggested to the investigator are listed in Table 14. No more than 1.0 mL was allowed to be administered per injection site. However, more than one injection site per muscle was permitted.

Table 14: Dose Range per Muscle for AUL Spasticity

Muscles Injected	Volume (mL)	DYSPORT THERAPEUTIC™ 500U	DYSPORT THERAPEUTIC™ 1000U
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 muscle tone at week 4, as measured by the MAS (Table 15). The PTMG was selected among the following muscle groups: extrinsic finger flexors or wrist flexors or elbow flexors. MAS is a 5-point scale consisting of 6 grades: 0, 1, 1+, 2, 3, or 4 and can be applied to muscles of both upper and lower limbs. 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 15: Primary Endpoint [MAS in the Primary Targeted Muscle Group (PTMG)] and Secondary Endpoint (PGA) at Week 4 in AUL Spasticity

	Placebo (N=79)	DYSPORT THERAPEUTIC™	
		500U (n=80)	1000U (n=79)
LS Mean Change from Baseline in PTMG Muscle Tone on the MAS	0.12	-0.98**	-1.10**

LS Mean PGA of Response to Treatment		1.30**	1.71**
** p<0.0001			

- N= number of subjects taken into account for the analyses.
- LS Mean = Least Squares Mean
- For both the primary and secondary endpoints, change from baseline values were ranked prior to analysis. An analysis of variance was then applied to the ranked values with treatment, BTX treatment status at baseline and centre as explanatory variables.
- Type I error control was achieved by use of a closed test hierarchical procedure

As a tertiary endpoint, the percentage of MAS responders (at least one grade reduction from baseline on the MAS in the PTMG) assessed for the PTMG at Weeks 1, 4 and 12, respectively were 15.2%, 22.8% and 13.9% in the placebo group, compared with 52.5%, 73.8% and 42.5% in the DYSPORT THERAPEUTIC™ 500 U group and with 67.1%, 78.5% and 48.1% in the DYSPORT THERAPEUTIC™ 1000 U group. MAS scores for each muscle group are provided in Table 16.

Table 16: Change from Baseline in MAS for each muscle group at Week 4 in AUL Spasticity

	Placebo (N=79)	**DYSPORT THERAPEUTIC™**	
		500U (n=80)	**1000U (n=79)**
LS* Mean Change from Baseline in Wrist Flexor Muscle Tone on the MAS	-0.25 (n=54)	-1.08 (n=57)	-1.29 (n=58)
LS Mean Change from Baseline in Finger Flexor Muscle Tone on the MAS	-0.27 (n=70)	-0.76 (n=66)	-0.86 (n=73)
LS Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS	-0.27 (n=56)	-0.79 (n=61)	-0.96 (n=48)

* LS =Least Square

The efficacy of DYSPORT THERAPEUTIC™ on upper limb passive function was assessed using the Principal Target of Treatment (PTT) chosen from the following domains, hygiene, limb position, dressing and pain, of the Disability Assessment Scale (DAS). The LS mean change from baseline to Week 4 in DAS scores for the PTT was -0.5 in the placebo group, -0.6 in the DYSPORT THERAPEUTIC™ 500U group and -0.7 in the DYSPORT THERAPEUTIC™ 1000U group.

Tardieu Scale assessing spasticity was analyzed in patients having a spasticity angle greater than 10° in their finger, wrist or elbow flexors.

- In the finger flexors, change from baseline in spasticity angle at week 4 was -7.5°, -28.9° and -31.0° while for spasticity grade was -0.2, -0.4 and -0.5, in the placebo, DYSPORT THERAPEUTIC™ 500U and DYSPORT THERAPEUTIC™ 1000U groups, respectively.
- In the wrist flexors, change from baseline in spasticity angle at week 4 was -0.7°, -17.2° and – 24.9° while for spasticity grade was -0.2, -0.6 and -0.8, in the placebo, DYSPORT THERAPEUTIC™ 500U and DYSPORT THERAPEUTIC™ 1000U groups, respectively.

- In the elbow flexors, change from baseline in spasticity angle at week 4 was -5.5°, -17.1° and – 23.7° while for spasticity grade was -0.1, -0.3 and -0.3, in the placebo, DYSPORT THERAPEUTIC™ 500U and DYSPORT THERAPEUTIC™ 1000U groups, respectively.

Active Range of Motion was assessed in the chosen PTMG (finger, wrist or elbow flexors) for each individual patient.

- In the finger flexors, change from baseline in AROM at week 4 was -6.2°, +25.7° and +11.8° in the placebo, DYSPORT THERAPEUTIC™ 500U and DYSPORT THERAPEUTIC™ 1000U groups, respectively.
- In the wrist flexors, change from baseline in AROM at week 4 was -5.6°, +10.8° and +35.2° in the placebo, DYSPORT THERAPEUTIC™ 500U and DYSPORT THERAPEUTIC™ 1000U groups, respectively.
- In the elbow flexors, change from baseline in AROM at week 4 was +5.9°, +10.4° and +18.3° in the placebo, DYSPORT THERAPEUTIC™ 500U and DYSPORT THERAPEUTIC™ 1000U groups, respectively.

In a repeated dose clinical trial, a total of 51, 46 and 42 patients received repeat doses of up to 1000 units in cycles 1, 2 and 3 respectively. Re-treatment was determined by clinical need after a minimum of 12 weeks. DYSPORT THERAPEUTIC™ was effective and well tolerated in the repeated treatments in patients with upper limb spasticity.

Adult Lower Limb Spasticity

The efficacy and safety of DYSPORT THERAPEUTIC™ for the treatment of lower limb spasticity was evaluated in a prospective, phase 3, randomized, multicentre, double-blind, placebo-controlled study and in its extension open label study. Patients had lower limb spasticity (MAS score ≥2 in the affected ankle joint for toxin naive patients or MAS score ≥3 in the affected ankle joint for toxin non-naive patients at least 4 months since the last botulinum toxin injection in the affected lower limb) and were at least 6 months post-stroke or post-traumatic brain injury.

The total DYSPORT THERAPEUTIC™ dose was injected intramuscularly into the gastrocnemius and soleus muscles and at least one additional lower limb muscle, according to the clinical presentation. Table 17 provides the median DYSPORT THERAPEUTIC™ doses injected and the number of injections into specific muscles of the lower limb as reported in the double-blind study, safety population.

Table 17: DYSPORT THERAPEUTIC™ Dose Injected and Number of Injections per Muscle in ALL Spasticity (Safety Population) - Median for the 1000U and 1500U Dose Groups

Injected Muscle	DYSPORT THERAPEUTIC™ Units Injected	Number Of Injection Sites
Gastrocnemius		
Lateral	100 Units to 150 Units	1
Medial	100 Units to 150 Units	1
Soleus	333 Units to 500 Units	3
Tibialis posterior	200 Units to 300 Units	2
Flexor digitorum longus	133 Units to 200 Units	1 to 2
Flexor digitorum brevis	67 Units to 100 Units	1

Flexor hallucis longus	67 Units to 200 Units	1
Flexor hallucis brevis	100 Units	1

The primary efficacy variable was muscle tone assessed by the MAS at the ankle joint (with the knee extended) at week 4 (MAS is a 5-point scale consisting of 6 grades: 0, 1, 1+, 2, 3, or 4). The first secondary endpoint was the PGA at week 4 (Table 18).

Table 18: Change from Baseline in MAS and PGA at Week 4 in ALL Spasticity (Intent-to-Treat Population)

Week 4	DYSPORT THERAPEUTIC™ 1000U (n=125)	DYSPORT THERAPEUTIC™ 1500U (n=128)	Placebo (n=128)
LS Mean Change from Baseline in Ankle plantar flexor Muscle Tone on the MAS [LS mean 95% CI]	-0.6 [-0.8 to -0.5]	-0.8 [-0.9 to -0.7]	-0.5 [-0.7 to -0.4]
P value (Comparison to Placebo)	0.2859	0.0091	N/A
LS Mean PGA of Response to Treatment	0.9 [0.7 to 1.1]	0.9 [0.7 to 1.1]	0.7 [0.5 to 0.9]
P-value (Comparison to Placebo)	0.0640	0.0665	N/A

N=number of subjects taken into account for the analysis. LS Mean = Least Squared Mean. CI = confidence interval.

When assessing MAS at the ankle with the knee flexed as a tertiary endpoint, the LS mean change from baseline to Week 4 in MAS scores were -0.4 in the placebo group, -0.7 in the DYSPORT THERAPEUTIC™ 1000U group and -0.8 in the DYSPORT THERAPEUTIC™ 1500U group.

On completion of this study, 352 patients entered an open-label extension study in which re-treatment with DYSPORT THERAPEUTIC™ 1000U or 1500U was determined by clinical need. A total of 345, 297, 224 and 139 subjects received retreatment with DYSPORT THERAPEUTIC™ in Cycles 1, 2, 3, and 4 respectively. DYSPORT THERAPEUTIC™ was effective and well tolerated in the repeated treatments in patients with lower limb spasticity. A total of 165 subjects with co-existing upper limb spasticity were able to receive injections of DYSPORT THERAPEUTIC™ 500U into the affected upper limb in addition to 1000U in the lower limb, with a maximum total dose of 1500U in cycles 3 and 4.

Spasticity in Pediatric Patients

Pediatric Upper Limb Spasticity

The efficacy and safety of DYSPORT THERAPEUTIC™ was evaluated in a double-blind, low-dose, controlled, multicenter study in patients 2 to 17 years of age treated for upper limb spasticity due to cerebral palsy. A total of 208 toxin naive or non-naive patients with a MAS of grade 2 or greater at the PTMG were enrolled and received DYSPORT THERAPEUTIC™ 8U/kg (n=69), DYSPORT THERAPEUTIC™ 16U/kg (n=70) or DYSPORT THERAPEUTIC™ 2U/kg (n=69) injected into the study upper limb. In the study, 60% of the patients were male and 75% were white. All patients had baseline MAS score ≥2 in PTMG in the study upper limb (elbow

flexors or wrist flexors), in which 89% of the patients had baseline MAS score 2 and no patient having baseline MAS score 4. All patients had physical therapies such as occupational therapy at least 30 days prior to treatment.The primary efficacy endpoint was the mean change from baseline in MAS in the PTMG at Week 6; a co-primary endpoint was the mean Physician's Global Assessment (PGA) score at Week 6. Efficacy results are shown in Table 19.

Table 19: MAS and PGA Change from Baseline in PUL Spasticity (mITT Population)

		Control 2U/kg (n=69)	**DYSPORT THERAPEUTIC™ 8U/kg (n=69)**	**DYSPORT THERAPEUTIC™ 16U/kg (n=70)**
LS Mean Change from Baseline in PTMG Muscle Tone on the MAS	Week 6	-1.6	-2.0*	-2.3*
LS Mean PGA score	Week 6	1.8	2.0	2.0

N= number of subjects
LS=Least Square
* p≤0.05 compared to 2U/kg dose group

At Week 16 the LS mean reduction in MAS was -1.2 and -1.5 in the DYSPORT THERAPEUTIC™ 8 and 16 U/kg/leg dose groups, respectively, compared to -0.9 in the control group. The LS mean PGA scores at Week 16 were 1.7 and 1.9 in the DYSPORT THERAPEUTIC™ 8 and 16 U/kg/leg dose groups, compared to 1.8 in the control group.

Pediatric Lower Limb Spasticity

The efficacy of DYSPORT THERAPEUTIC™ in cerebral palsy patients 2 to 17 years of age with dynamic equinus foot deformity due to spasticity was evaluated in a double-blind, placebo-controlled multicenter study (Study 141). A total of 235 DYSPORT THERAPEUTIC™ (n=158) and placebo (n=77) toxin naïve or non-naïve patients (n=199, 2-9 years old and n=36, 10-17 years old) with a MAS of grade 2 or greater at the ankle plantar flexor were enrolled to receive DYSPORT THERAPEUTIC™ 10U/kg/leg (n=79), DYSPORT THERAPEUTIC™ 15U/kg/leg (n=79) or placebo (n=77) injected into the gastrocnemius and soleus muscles. Forty one percent of patients (n=66) were treated bilaterally and received a total lower limb DYSPORT THERAPEUTIC™ dose of either 20U/kg (n=37) or 30U/kg (n=29). The primary efficacy endpoint was the mean change from baseline in MAS in ankle plantar flexors and the first secondary efficacy endpoint was the mean change from baseline in PGA score. Mean Goal Attainment Scaling (GAS) score at Week 4 was also a pre-specified secondary endpoint. The primary efficacy analyses were conducted at week 4 after the treatment. 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 could enter an open-label extension study (Study 147) where they could receive up to 4 treatments, including injection into other distal and proximal lower limb muscles.

Table 20: MAS, PGA and GAS Change from Baseline to Week 4 in PLL Spasticity (ITT Population)

Week 4	Placebo (N=77)	DYSPORT THERAPEUTIC™ 10 U/kg/leg (n=79)	DYSPORT THERAPEUTIC™ 15 U/kg/leg (n=79)
Mean Change from Baseline in Ankle plantarflexor Muscle Tone on the MAS			
LS mean [LS mean 95% CI] P value (compared to placebo)	-0.48 [-0.69, -0.27] N/A	-0.86 [-1.07, -0.65] 0.0029	-0.97 [-1.18, -0.76] 0.0002
Mean PGA of Response to Treatment			
LS Mean [LS mean 95% CI] P value (compared to placebo)	0.73 [0.46, 0.99] N/A	1.54 [1.28, 1.81] <0.0001	1.50 [1.23, 1.77] <0.0001
Mean GAS Score*			
LS Mean [LS mean 95% CI] P value (compared to placebo)	46.21 [43.70, 48.72] N/A	51.53 [49.05, 54.01] 0.0006	50.86 [48.36, 53.36] 0.0031
* 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%).			

At Week 12 the LS mean reduction in MAS was -0.8 and -1.0 in the DYSPORT THERAPEUTIC™ 10 and 15 U/kg/leg dose groups, respectively, compared to -0.5 in the placebo group. The LS mean PGA scores at Week 12 were 0.8 and 1.0 in the DYSPORT THERAPEUTIC™ 10 and 15 U/kg/leg dose groups, compared to 0.4 in the placebo group. The corresponding LS mean GAS scores were 52.49, 50.47 and 45.85 in the DYSPORT THERAPEUTIC™ 10 U/kg/leg, 15 U/kg/leg and placebo groups.

Retreatment was studied in an open label study where patients could receive retreatment as required, including injection into other distal and proximal lower limb muscles. A total of 207, 175, 86 and 11 pediatric patients with lower limb spasticity ages 2 to 17 years received retreatment with DYSPORT THERAPEUTIC™ (10-15U/kg) in Cycles 1, 2, 3, and 4 respectively. The majority of subjects treated with DYSPORT THERAPEUTIC™ were retreated by Week 22 (62.5% in the DYSPORT THERAPEUTIC™ 10 U/kg/leg group and 68.8% in the DYSPORT THERAPEUTIC™ 15 U/kg/leg group), though more than 20% of subjects in both DYSPORT THERAPEUTIC™ treatment groups had not yet received retreatment by Week 28.

DETAILED PHARMACOLOGY

DYSPORT THERAPEUTIC™ inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings. Toxin activity occurs in the following sequence: Toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor mediated endocytosis, pH-induced translocation of the toxin light chain to the cell cytosol and cleavage of SNAP25 leading to intracellular blockage of neurotransmitter exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves.

Recovery of transmission occurs gradually as the neuromuscular junction recovers from SNAP25 cleavage and as new nerve endings are formed.

TOXICOLOGY

Carcinogenicity

Studies to evaluate the carcinogenic potential of DYSPORT THERAPEUTIC™ have not been conducted.

Mutagenicity

Genotoxicity studies have not been conducted with DYSPORT THERAPEUTIC™.

Fertility and Reproductive Toxicity

DYSPORT THERAPEUTIC™ had no effect upon fertility when administered intramuscularly to rats at weekly doses up to 16U in females, and 10U in males. There were no effects upon implantation parameters at doses up to and including 8U. Mating was impaired at the high dose (10U for males and 16U for females), likely due to impaired hind limb function (result of the pharmacological effect on the muscle). The NOAEL for fertility and general reproduction performance was 8U/week for females and 5U/week for males.

Teratogenic Effects

DYSPORT THERAPEUTIC™ was not teratogenic when evaluated in rats and rabbits. In rats, DYSPORT THERAPEUTIC™ was administered at doses of 0.5, 1.5 and 5U daily from Gestation Days 6-17. Additional groups of animals received intermittent doses of 10U on Days 6 and 12 of gestation. There was a slight increase in fetal resorptions at the high doses of 5U daily and 10U intermittently. In rabbits, DYSPORT THERAPEUTIC™ was administered at doses of 1, 10 and 20U daily from Gestation Days 6-19. Additional groups of animals received intermittent doses of 40U on Days 6 and 13 of gestation. All animals treated at 20U daily died or were sacrificed in a moribund condition, with some animals aborting. C-section data revealed comparable rates of pre-and post-implantation loss across the surviving groups. Fetal survival was not affected.

Reproductive and Developmental Effects

In a study evaluating postnatal effects, pregnant rats were given weekly doses of 1, 2.5, 5 and 10U from Day 6 of gestation through weaning of the litters (21 days postpartum). There was no effect of treatment on *in utero* survival. Evaluation of the offspring showed no effects on survival, body weights, sexual maturation, post-weaning development, mating performance or fertility. All offspring appeared normal.

Animal Toxicity Studies

DYSPORT THERAPEUTIC™ has been evaluated in both single dose and repeated dose studies in rats. In the single dose study, DYSPORT THERAPEUTIC™ was administered as a single intramuscular injection into the left gluteus muscle at doses of 2 or 6U. To evaluate reversibility of effects, subgroups of animals were sacrificed after 7, 30, 60 and 90 days of observation. No adverse systemic signs were observed, and there were no local reactions at the site of injection. Treatment related effects were limited to a reduction in the size and weight of the injected muscle, considered to be a pharmacological effect of the drug. Muscle size reduction was noted at Day 7 and Day 30 for animals treated with 6U and 2U, respectively. This was histologically confirmed as a reduction in muscle fiber size. By 90 days, muscle fiber size and resultant weights were approaching normal levels for animals treated at 2U, but fiber size reductions were still evident for animals treated with 6U. Special evaluations looking at nerves serving these muscles showed the expected disorganization early in the study, but normal nerve-muscle morphology was returning by 90 days.

In a chronic toxicity study in rats, DYSPORT THERAPEUTIC™ was administered at 1, 4 and 12U given as injections at four week intervals for six injections. A fourth group of male and female animals receiving 12U/adm. as 5 injections were subjected to a one month recovery period. Two control groups received the placebo on the same regimens. There was no indication of systemic toxicity at any dose and there were no signs of local irritation at the injection site. Reduced muscle size was evident at 4 and 12U following the first injection, but generally not evident at 1U until the fifth injection. As expected there was histological evidence of atrophy of muscle fibers accompanied by minimal to moderate focal fatty infiltration and slight to minimal focal interstitial fibrosis at 1, 4 and 12Us. Animals treated at 12U showed reduced body weight gain or body weight loss over the two week period following each dose with no evidence of recovery of the muscle in the rats treated at 12U and terminated one month after the fifth injection.

Juvenile Animal Data
A repeat-dose toxicity study in juvenile rats treated weekly from the age of weaning on Postnatal Day 21 to 13 weeks of age, comparable to children of 2 years old to young adulthood, did not show adverse effects on postnatal growth (including skeletal evaluation), reproductive, neurological and neurobehavioral development.

Ocular or Dermal Irritation
A local tolerance study in rabbits showed no adverse effects when instilled into the eye. There was no evidence of local effects at the site of injection in any of the above describedtoxicity and reproduction studies.

PART III: CONSUMER INFORMATION

PrDYSPORT THERAPEUTIC™
(abobotulinumtoxinA)
for injection

This leaflet is part III of a three-part "Product Monograph" published when DYSPORT THERAPEUTIC™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about DYSPORT THERAPEUTIC™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
DYSPORT THERAPEUTIC™ is indicated

- to reduce the symptoms of cervical dystonia in adults
- to temporarily relieve muscle stiffness in patients 2 years of age and older with spasticity

What it does:
DYSPORT THERAPEUTIC™ is a drug that relaxes the muscles.

When it should not be used:
It should not be used if you:

- are allergic or sensitive to any of the ingredients
- have an infection in the muscles where it would normally be injected
- are allergic to cow's milk protein
- have any muscle disorders in other parts of your body, including myasthenia gravis, Lambert-Eaton Syndrome or amyotrophic lateral sclerosis

What the medicinal ingredient is:
abobotulinumtoxinA

What the important non medicinal ingredients are:
Human serum albumin and lactose monohydrate

What dosage forms it comes in:
DYSPORT THERAPEUTIC™ is supplied in a single-use, sterile 300 and 500 Unit vial.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

If you develop swallowing, speech or breathing difficulties, please contact medical emergency services or ask your friend or relatives to do so.

BEFORE you use DYSPORT THERAPEUTIC™ talk to your doctor or pharmacist if you:

- have myasthenia gravis or Lambert-Eaton Syndrome, amyotrophic lateral sclerosis or another muscle disorder
- are allergic or sensitive to any botulinum toxin product
- have an infection at the proposed injection site
- are scheduled to have surgery using a general anesthetic
- are taking or are likely to take antibiotics, especially aminoglycoside antibiotics
- are pregnant or become pregnant while taking this drug.
- are nursing. It is not known whether this drug is excreted in human milk.
- have pre-existing swallowing or breathing difficulties.

DYSPORT THERAPEUTIC™ is for intramuscular use only.

DYSPORT THERAPEUTIC™ should only be given by a physician with the appropriate qualifications and experience in the treatment and use of DYSPORT THERAPEUTIC™. There should be at least a 12 week treatment interval in adult patients and pediatric patients with lower limb spasticity; and a 16 week treatment interval in pediatric patients with upper limb spasticity between two treatment sessions. When combining indications, the injection intervals should be no more frequent than every 12 weeks in adult patients and 16 weeks in pediatric patients.

Side effects may occur from misplaced injections of DYSPORT THERAPEUTIC™ temporarily paralyzing nearby muscle groups. There have been very rare reports of side effects that may be related to the spread of botulinum neurotoxin distant from the injection site. These may include excessive muscle weakness, swallowing and breathing difficulties or accidental swallowing of food or drink into the airways, which can be life threatening or fatal. These symptoms have been reported hours to weeks after injection. Patients who receive the recommended doses may very rarely experience excessive muscle weakness.

Tell your doctor if you experience any difficulties in swallowing food while on DYSPORT THERAPEUTIC™, as it could be related to the dosage. Difficulty in swallowing food, ranging from very mild to severe, can persist for 2–3 weeks after injection, or longer.

Tell your doctor if you are taking other medicines, including those you have bought at your pharmacy, supermarket or health food shop.

INTERACTIONS WITH THIS MEDICATION

The effect of DYSPORT THERAPEUTIC™ may be increased by aminoglycoside antibiotics (e.g., streptomycin, tobramycin, neomycin, gentamicin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin or any other drugs that interfere with neuromuscular transmission.

PROPER USE OF THIS MEDICATION

Usual dose:
DYSPORT THERAPEUTIC™ can only be used by health care professionals experienced in the application of Botulinum toxin.

The optimum dosage and number of injection sites in the treated muscle will be chosen by your doctor.

Overdose:
Symptoms of overdose for this product, as for all botulinum toxins, are related to the dose, the condition being treated and

susceptibility of the patient. Symptoms are not apparent immediately after the injection and may include general weakness, drooping eyelid, double vision, swallowing and speech difficulties, and pneumonia.

In case you feel symptoms of overdose please seek medical emergency services immediately or ask your relatives to do so, and have yourself admitted to a hospital. Medical supervision for up to several days and assisted ventilation may be necessary.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Cervical Dystonia
The most commonly reported side effects (≥ 5%) were muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, neck pain, musculoskeletal pain, difficulty in swallowing, injection site pain, and eye disorders (consisting of blurred vision, reduced visual acuity and accommodation), and difficulty in speaking.

Adult Upper Limb Spasticity
The most commonly reported side effects (≥ 4%) were muscular weakness and nasopharyngitis.

Adult Lower Limb Spasticity
The most commonly reported side effects (≥ 4%) were fall, pain in the extremities and muscular weakness.

Pediatric Upper Limb Spasticity
The most commonly reported side effects (≥ 5%) were upper respiratory tract infections, muscular weakness, headache, fever and rhinorrhea.

Pediatric Lower Limb Spasticity
The most commonly observed adverse reactions (≥ 5% of patients) were influenza-like illness, myalgia and muscular weakness.

This is not a complete list of side effects. For any unexpected effects while taking **DYSPORT THERAPEUTIC™,** *contact your doctor or pharmacist.*

HOW TO STORE IT

Keep out of the reach and sight of children.

DYSPORT THERAPEUTIC™ must be stored under refrigeration at 2-8ºC. Protect from light. Once reconstituted, it can be stored under refrigeration at 2-8ºC for up to 24 hours. Do not freeze after reconstitution.

Reporting Suspected Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

Ipsen Biopharmaceuticals Canada Inc. at 5060 Spectrum Way Mississauga ON L4W 5N5, www.DysportCanada.ca
or by calling 1-855-215-2288.

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