PRODUCT MONOGRAPH

PrDYSPORT 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
Wrexham, LL13 9UF, UK
http://www.ipsen.com/en

Distributed by: Ipsen Biopharmaceuticals Canada Inc.
Suite 502,
5060 Spectrum Way,
Mississauga, Ontario
L4W 5N5

Submission Control No: 199537 Date of Approval: January 3, 2017

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Table of Contents

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:

- To reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults
- For the symptomatic treatment of focal spasticity affecting the upper limbs in adults

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

Pediatrics (< 18 years of age):
DYSPORT THERAPEUTIC™ is not recommended for use in pediatric patients less than 18 years of age.

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 of the product monograph.
- 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**).

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.

Very rare cases of death, occasionally in the context of dysphagia, pneumopathy (including but not limited to dyspnoea, 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.

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.

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) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Carcinogenesis and Mutagenesis
Animal studies to evaluate the carcinogenic and genotoxic potential of DYSPORT THERAPEUTIC™ have not been conducted. (See TOXICOLOGY section for more information).

Cardiovascular
In study 06-01, 79 subjects were assessed by EKG for treatment-related QT interval changes. Following the use of DYSPORT AESTHETIC™ for the treatment of glabellar lines, no QT/QTc prolongation was observed.

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. 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 of the clinical impact of developing antibodies are limited (see ADVERSE REACTIONS section). As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.

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 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): DYSPORT THERAPEUTIC™ is not recommended for use in children.

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*.

Upper Limb 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 1 lists the most frequently reported treatment adverse events (≥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 1: All Treatment-Emergent Adverse Events Observed in At Least 2% of 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	**4**	**9**	5
Fall	2	3	2
Respiratory, thoracic and mediastinal disorders	**5**	**5**	**3**
Cough	1	2	1
Psychiatric disorders	**2**	**5**	**3**
Depression	2	3	1

Injection Site Reactions

As expected for any injection procedure, injection site reactions (e.g. pain, bruising, haemorrhage, injection site erythema/haematoma etc.) have been reported following administration of DYSPORT THERAPEUTIC™.

Less Common Adverse Drug Reactions

In pooled analysis of double blind placebo-controlled clinical studies adverse drug reactions with an incidence of less than 2% reported in DYSPORT THERAPEUTIC™ treatment groups included event of fatigue.

Cervical Dystonia

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 18–79years). Most patients (87.3%) were less than 65 years of age; 59% were women.

Table 2 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 2: Most Common TEAEs (>5%) and Greater than Placebo: Double-blind Phase of Clinical Trials

	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.

Testing for antibodies to DYSPORT THERAPEUTIC™ was performed in subjects treated with DYSPORT THERAPEUTIC™, 281 subjects in AUL clinical trials and 211 subjects in CD clinical trials. About 3% of subjects developed neutralizing antibodies over time with DYSPORT THERAPEUTIC™ treatment.

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).

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 neurotoxin 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 3: 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.**

- **The potency units of DYSPORT THERAPEUTIC™ are specific to the preparation and assay method utilized. They 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.**

- **Injection intervals of DYSPORT THERAPEUTIC™ should be no more frequent than every three months.**

Recommended Dose and Dosage Adjustment

Upper Limb 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 DYSPORT THERAPEUTIC™. In the pivotal trial, doses of 500 Units, 1000 Units were divided among selected muscles, (see Table 4) at a given treatment session. No more than 1 mL should generally be administered at any single injection site.

Table 4: DYSPORT THERAPEUTIC™ Dosing by Muscle for Upper Limb Spasticity

Muscles Injected	Recommended Dose DYSPORT THERAPEUTIC™
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

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 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™.

Cervical Dystonia
The recommended initial dose of DYSPORT THERAPEUTIC™ for the treatment of cervical dystonia 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 10 of PART II – CLINICAL TRIALS). 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. Simultaneous EMG-guided application of DYSPORT THERAPEUTIC™ may be helpful in locating active muscles not identified by physical examination alone.

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). Dose exceeding 1000 Units is not recommended.

Administration
Reconstitution instructions are specific for the 300 Unit dose vial and the 500 Unit dose vial. These volumes yield concentrations specific for the use for each indication (Table 5).

Table 5: Recommended Reconstitution Volumes

Target concentration Units/0.1 mL	Diluent* volume	
	300 Unit Dose	500 Unit Dose
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

Reconstitution:
Parenteral Products:

Upper Limb Spasticity
DYSPORT THERAPEUTIC™ is supplied as a single-use vial. The recommended concentration is 100 Units/ mL or 200 Units/ mL with 0.9% Sodium Chloride Injection USP (without preservative) (see Table 5).

Using an appropriately sized sterile syringe, needle and aseptic technique, draw up the required volume (Table 5) 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. No more than 2.5 mL of saline should be introduced into the vial. 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 discoloration prior to administration.

Reconstituted DYSPORT THERAPEUTIC™ should be a clear, colorless 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.

** When using 5 mL of diluent for a 500 Unit vial of DYSPORT THERAPEUTIC™, complete the following steps.

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.

Cervical Dystonia

Each 500 Unit vial of DYSPORT THERAPEUTIC™ is to be reconstituted with 1 mL of 0.9% Sodium Chloride Injection USP (without preservative) to yield a solution of 50.0 Units per 0.1 mL. Each 300 Unit vial of DYSPORT THERAPEUTIC™ is to be reconstituted with 0.6 mL of 0.9% Sodium Chloride Injection USP (without preservative) to yield a solution equivalent to 50.0 Units per 0.1 mL (see Table 5).

Using an appropriately sized sterile syringe, needle and aseptic technique, draw up 1.0 mL or 0.6 mL of sterile, 0.9% Sodium Chloride Injection USP (without preservative) for 500 and 300 Unit vials, respectively. 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 no vacuum is observed. Swirl gently to dissolve. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Reconstituted DYSPORT THERAPEUTIC™ should be a clear, colorless 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.

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 to process a request for antitoxin. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration.

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 three months. 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 micrograms lactose.

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 produced as a 150 kDa single polypeptide chain composed of 1296 amino acid residues (1295 after cleavage of the N-terminal methionine). 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.

One unit of DYSPORT THERAPEUTIC™ corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. The method for performing the assay is specific to Ipsen's product DYSPORT THERAPEUTIC™. Due to differences in specific details such as vehicle, dilution scheme and laboratory protocols for various mouse LD50 assays, 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

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™ 500 Units (N=80), DYSPORT THERAPEUTIC™ 1000 Units (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 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. Additional muscles suggested to the investigator are listed in Table 6. 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 6: Dose Range per Muscle

Muscles Injected	Volume (mL)	DYSPORT THERAPEUTIC™ 500 U	DYSPORT THERAPEUTIC™ 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 (PTMG) muscle tone at week 4, as measured by the MAS (Table 7). 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 7: Primary Endpoint [MAS in the Primary Targeted Muscle Group (PTMG)] and Secondary Endpoint (PGA) at Week 4

	Placebo (N=79)	DYSPORT THERAPEUTIC™	
		(500 units) (N=80)	(1000 units) (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 8.

Table 8: Change from Baseline in MAS for each muscle group at Week 4

	Placebo (N=79)	DYSPORT THERAPEUTIC™	
		(500 units) (N=80)	(1000 units) (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.

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 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 500 Units 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 9). These clinical trials were followed by open label repeated treatment studies where retreatment was determined by clinical need after a minimum of 12 weeks.

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 9).

Table 9: 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 10 indicates the average DYSPORT THERAPEUTIC™ dose, and percentage of total dose, injected into specific muscles in the pivotal clinical trials.

Table 10: 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

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.

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 16 Units in females, and 10 Units in males. There were no effects upon implantation parameters at doses up to and including 8 Units. Mating was impaired at the high dose (10 Units for males and 16 Units 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 8 Units/week for females and 5 Units/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 5 Units daily from Gestation Days 6-17. Additional groups of animals received intermittent doses of 10 Units on Days 6 and 12 of gestation. There was a slight increase in fetal resorptions at the high doses of 5 Units daily and 10 Units intermittently. In rabbits, DYSPORT THERAPEUTIC™ was administered at doses of 1, 10 and 20 Units daily from Gestation Days 6-19. Additional groups of animals received intermittent doses of 40 Units on Days 6 and 13 of gestation. All animals treated at 20 Units 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 10 Units 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 6 Units. 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 6 Units and 2 Units, 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 2 Units, but fiber size reductions were still evident for animals treated with 6 Units. 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 12 Units given as injections at four week intervals for six injections. A fourth group of male and female animals receiving 12 U/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 12 Units following the first injection, but generally not evident at 1 Unit 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 12 Units. Animals treated at 12 Units 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 12 Units and terminated one month after the fifth injection.

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 described toxicity 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 subjective symptoms and objective signs of cervical dystonia in adults
- for the symptomatic treatment of focal spasticity affecting the upper limbs in adults

What it does:
DYSPORT THERAPEUTIC™ is a drug that also 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
- you have an infection in the muscles where it would normally be injected
- you are allergic to cow's milk protein
- you have any muscle disorders in other parts of your body, including myasthenia gravis, Eaton Lambert 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

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

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

Seek immediate medical attention if swallowing, speech or respiratory problems arise.

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, netilmicin, 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:
Overdose with DYSPORT THERAPEUTIC™ is a relative term that can reflect undesired aesthetic effect. 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 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

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

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, difficulty in speaking, and reduced visual acuity and accommodation).

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 adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:
    Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, contact your health professional. 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.

This leaflet was prepared by Ipsen Biopharm Ltd.

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Last revised: November 30, 2016