

PRODUCT MONOGRAPH

PrDYSPORT AESTHETIC™

abobotulinumtoxinA for injection Ph. Eur.

Sterile lyophilized powder for solution for injection

300 Units per vial

Neuromuscular Blocking Agent

Manufactured by: Ipsen Biopharm Limited
Wrexham, LL13 9UF, UK
<http://www.ipsen.com/en>

Distributed by: Galderma Canada Inc.
55 Commerce Valley Drive West
Thornhill, ON L3T 7V9

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DYSPORT AESTHETICTM

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 Units per vial	Human Serum Albumin <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

DYSPORT AESTHETICTM (abobotulinumtoxinA) is indicated:

- For the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients < 65 years of age.

Geriatrics (> 65 years of age):

The clinical data for subjects > 65 years of age are limited.

Pediatrics (< 18 years of age):

DYSPORT AESTHETICTM is not recommended for use in pediatric patients less than 18 years of age.

CONTRAINDICATIONS

DYSPORT AESTHETICTM 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 DYSPORET AESTHETIC™ activity are different from those used to describe that of other botulinum toxin preparations and the units representing DYSPORET AESTHETIC™ activity are not interchangeable with other products.
- DYSPORET AESTHETIC™ 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 DYSPORET AESTHETIC™ (See **WARNINGS AND PRECAUTIONS, General and DOSAGE AND ADMINISTRATION**).

General

Use DYSPORET AESTHETIC™ only as directed.

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

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

Caution should be exercised when administering DYSPORET AESTHETIC™ to patients with neuromuscular junction disorders or when excessive weakness or atrophy is present in the target muscle, surgical alterations to the facial anatomy, marked facial asymmetry, inflammation at the injection site(s), ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.

Muscle weakness remote to the site of injection and other serious adverse effects (e.g., dysphagia when injected into the neck region) have been very rarely reported in the administration of DYSPORET AESTHETIC™. Patients with a history of underlying neurologic disorders, dysphagia and/or aspiration are at a greater risk of these effects and should be treated with extreme caution. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. Injection intervals of DYSPORET AESTHETIC™ should be no more frequent than every three months. Indication-specific dosage and administration recommendations should be followed.

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 DYSPORE AESTHETIC™ 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 DYSPORE AESTHETIC™ for the treatment of glabellar lines, no QT/QTc prolongation was observed.

Immune

Testing for antibodies to DYSPORE AESTHETIC™ was performed. None of the patients tested positive for neutralizing antibodies (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 DYSPORE AESTHETIC™ 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.

Ophthalmologic

Risk of ptosis can be mitigated by careful examination of the upper lid for separation or weakness of the levator palpebrae muscle (true ptosis), identification of lash ptosis, and evaluation of the range of lid excursion while manually depressing the frontalis to assess compensation.

Skin

Caution should be exercised when administering DYSPORE AESTHETIC™ 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. DYSPORE

AESTHETIC™ 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 AESTHETIC™ in milk has not been studied in animals. The use of DYSPORT AESTHETIC™ during lactation is not recommended.

Pediatrics (< 18 years of age): DYSPORT AESTHETIC™ is not recommended for use in children.

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

Monitoring and Laboratory Tests

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

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. Muscle weakness remote to the site of injection and other serious adverse effects (e.g., dysphagia when injected into the neck region) have been very rarely reported in the administration of DYSPORT AESTHETIC™.

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.

Glabella Lines

Six clinical studies, including one Phase 2, three Phase 3, and two long-term safety studies were conducted with DYSPORT AESTHETIC™. The adverse reaction information from these clinical studies provides a basis for identifying the adverse reactions that appear to be related to drug use. Adverse reactions observed in these studies may not reflect those observed in clinical practice.

The adverse event data described below reflect exposure in 2,341 subjects who received 5,360 DYSPORT AESTHETIC™ or placebo treatments (4,880 DYSPORT AESTHETIC™; 480 placebo). Some subjects received up to seven treatments with DYSPORT AESTHETIC™. The population was composed of subjects 19-80 years of age, and included 263 males and 2,078 females. Most subjects were Caucasian (79.8%). Subjects received 50-80 Unit doses of DYSPORT AESTHETIC™, injected intramuscularly in the glabellar region.

Adverse events of any cause were reported for 42% of the subjects treated with DYSPORT AESTHETIC™ and 29% of the subjects treated with placebo. Treatment-emergent adverse events were generally mild to moderate in severity and the majority of events were considered unrelated or unlikely to be related to treatment. The most frequently reported adverse events were nasopharyngitis, headache, injection site pain, upper respiratory tract infection, and sinusitis. Subjects re-treated with DYSPORT AESTHETIC™ demonstrated a comparable safety profile to that of the initial treatment. Table 1 displays treatment-emergent adverse events reported in >1% of subjects, regardless of causality. Repeat dose clinical studies have demonstrated safety for up to seven administrations of DYSPORT AESTHETIC™.

Table 1: Treatment-Emergent Adverse Events with > 1% Incidence

Adverse Events by Preferred Term	DYSPORT AESTHETIC™ n=2041 (%)*	Placebo n=480 (%)*
Subjects with at least one treatment-emergent adverse event	852 (42)	141 (29)
Nasopharyngitis	123 (6)	19 (4)
Headache	110 (5)	16 (3)
Injection site pain	69 (3)	7 (1)
Upper respiratory tract infection	58 (3)	4 (<1)
Sinusitis	55 (3)	4 (<1)
Injection site bruising	34 (2)	7 (1)
Eyelid ptosis	33 (2)	1 (<1)
Influenza	31 (2)	3 (<1)

* Subjects who received treatment with placebo and DYSPORT AESTHETIC™ are counted in both treatment columns.

The frequency of any ocular adverse events in the DYSPORT AESTHETIC™ treatment group was low and decreased with subsequent treatments. The majority of eyelid ptosis events were mild to moderate in severity and resolved over several weeks. The incidence of eyelid ptosis did not increase in the long-term safety studies with multiple re-treatments at intervals \geq three months.

The frequency of any ocular TEAE in the DYSPORT AESTHETIC™ treatment group is low in Cycle 1 (3%), decreases to 2% in Cycles 2 and 3, and to 1% in Cycles 4 and 5.

Testing for antibodies to DYSPORT AESTHETIC™ was performed in 1554 subjects who had up to nine cycles of treatment. Two subjects (0.13%) tested positive for binding antibodies at baseline. Three additional subjects tested positive for binding antibodies after receiving DYSPORT AESTHETIC™ treatment. None of the patients tested positive for neutralizing

antibodies.

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: 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.

DRUG INTERACTIONS

No specific interactions have been reported.

Overview

No formal drug interaction studies have been conducted with DYSPORE AESTHETIC™.

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 DYSPORE AESTHETIC™ 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 2: 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 AESTHETIC™ 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 AESTHETIC™ 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 AESTHETIC™ 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 AESTHETIC™ should be no more frequent than**

every three months.

Recommended Dose and Dosage Adjustment

Glabellar Lines

Ten (10) Units should be injected intramuscularly at each of five injection sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 50 Units (see Figure 1).

The clinical effect of DYSPO RT AESTHETIC™ may last up to four months. Repeat dose clinical studies demonstrated continued efficacy with up to four repeated administrations; DYSPO RT AESTHETIC™ should be administered no more frequently than every three months.

Administration

Glabellar facial lines arise from the activity of the lateral corrugator and vertical procerus muscles. These can be readily identified by palpating the tensed muscle mass while having the patient frown. The corrugator depresses the skin creating a “furrowed” vertical line surrounded by tensed muscle (i.e., frown lines). The location, size, and use of the muscles vary markedly among individuals. Physicians administering DYSPO RT AESTHETIC™ must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures.

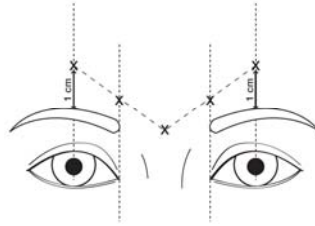
Risk of ptosis can be mitigated by careful examination of the upper lid for separation or weakness of the levator palpebrae muscle (true ptosis), identification of lash ptosis, and evaluation of the range of lid excursion while manually depressing the frontalis to assess compensation.

In order to reduce the complication of ptosis, the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Medial corrugator injections should be placed at least one centimeter above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate.
- Do not inject toxin closer than 1 centimeter above the central eyebrow.

To inject DYSPO RT AESTHETIC™, advance the needle through the skin into the underlying muscle while applying finger pressure on the superior medial orbital rim. Inject patients with the recommended dose in five equally divided aliquots using a 30 gauge needle; two in each corrugator muscle and one in the procerus muscle (see Figure 1).

Figure 1. Glabellar Lines Injection Points



**Reconstitution:
Parenteral Products:**

DYSPORE AESTHETIC™ is supplied as a single-use vial.

Each 300 Unit vial of DYSPORE AESTHETIC™ is to be reconstituted with either 1.5 or 2.5 mL of 0.9% sterile, preservative-free, saline prior to injection. The concentration of the resulting solution will be 20 Units per 0.1 mL or 12 Units per 0.1 mL, respectively (see Table 3).

Table 3: Recommended Reconstitution Volumes

Target concentration Units/0.1 mL	Diluent Volumes
12.0	2.5 mL
20.0	1.5 mL

Using a 21 gauge needle and aseptic technique, draw up sterile, preservative-free 0.9% saline. Insert the needle into the DYSPORE AESTHETIC™ 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. Gently rotate the vial (do not shake), until the white substance is fully dissolved. Reconstituted DYSPORE AESTHETIC™ should be a clear, colorless solution, free of particulate matter.

Draw DYSPORE AESTHETIC™ into a sterile syringe. Expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30 gauge needle.

Once reconstituted, DYSPORE AESTHETIC™ should be stored in a refrigerator at 2–8°C protected from light and used within 24 hours. Do not freeze reconstituted DYSPORE AESTHETIC™. 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 DYSPORE AESTHETIC™ 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.

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

DYSPORE AESTHETIC™ 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 DYSPORE AESTHETIC™ 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

DYSPORE AESTHETIC™ 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 DYSPORE AESTHETIC™ in the peripheral blood following intramuscular injection at the recommended doses.

Duration of Effect

The clinical effect of DYSPORE AESTHETIC™ may last up to 4 months. DYSPORE AESTHETIC™ should not be administered more frequently than every three months. When used

for re-treatment, DYSPORT AESTHETIC™ should be reconstituted and injected using the same techniques as the initial treatment.

STORAGE AND STABILITY

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

Administer DYSPORT AESTHETIC™ within 24 hours of reconstitution; during this period reconstituted DYSPORT AESTHETIC™ 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 AESTHETIC™ should be disposed of carefully as is done with all medical waste

DOSAGE FORMS, COMPOSITION AND PACKAGING

DYSPORT AESTHETIC™ is supplied as a single-use sterile 300 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 monohydrate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: abobotulinumtoxinA

Structural formula: AbobotulinumtoxinA (Botulinum toxin type A), the active ingredient in DYSPORE AESTHETIC™ 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 DYSPORE AESTHETIC™ corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. The method for performing the assay is specific to Ipsen's product DYSPORE AESTHETIC™. Due to differences in specific details such as vehicle, dilution scheme and laboratory protocols for various mouse LD50 assays, units of biological activity of DYSPORE AESTHETIC™ are not interchangeable with units of any other botulinum toxin or any toxin assessed with any other specific assay method.

CLINICAL TRIALS

Glabellar Lines

Two double-blind, randomized, placebo-controlled, Phase 3 clinical studies evaluated the efficacy of DYSPORE AESTHETIC™ for use in the improvement of the appearance of moderate to severe glabellar lines. Investigator/Blinded Evaluators assessed efficacy by using a validated 4-point scale (none, mild, moderate, severe). Subjects assessed efficacy by using a similar static 4-point scale. These two studies enrolled ethnically-diverse, healthy adults (ages 19–75) with glabellar lines of at least moderate severity at maximum frown. Subjects were excluded if they had marked ptosis, deep dermal scarring, or a substantial inability to lessen glabellar lines, even by physically spreading them apart. The subjects in these studies received either DYSPORE AESTHETIC™ (n=172) or placebo (n=117). The total dose was delivered in equally divided aliquots to specified injection sites (see Figure 1).

Treatment success for each of the Phase 3 studies was defined as post-treatment glabellar line severity of none or mild (from moderate or severe at baseline) at maximum frown.

After completion of the randomized studies, subjects were offered participation in a three-year, open-label re-treatment study to assess the safety of multiple treatments.

Study 719

Study 719 was a single dose, double-blind, multicenter, randomized, placebo-controlled study in which 158 previously untreated subjects received either placebo or 50 Units of DYSPORE AESTHETIC™ administered in five aliquots of 10 Units/0.05 mL (see Figure 1). Subjects were followed for 180 days. The mean age was 43 years; most of the subjects were women (85%), and predominantly Caucasian (49%) or Hispanic (47%).

In study 719, the reduction of glabellar line severity at maximum frown was greater at Day 30 in the DYSPORE AESTHETIC™ group compared to the placebo group as assessed by both Investigators and subjects (see Table 4).

A majority of DYSPORE AESTHETIC™-treated subjects (56.3%) demonstrated a 2+ grade composite (a reduction in the glabellar line severity score by a minimum of 2 grades as assessed by both the Investigator/Blinded Evaluator and subject) improvement, at maximum frown, at Day 30. Onset of effect was reported as soon as 24 hours; the median time to onset of treatment response was three days.

Table 4: Study 719: Investigators' and Subjects' Assessment of Glabellar Line Treatment Success at Maximum Frown (using 4-point scale) Following a 50 Unit Dose (% and Number of Responders/Number Assessed)

Day	Investigators		Subjects	
	DYSPO RT AESTHETIC™	Placebo	DYSPO RT AESTHETIC™	Placebo
14	94.1%* 95/101	19.6% 9/46	81.0%* 81/100	10.9% 5/46
30	89.3%* 92/103	3.9% 2/51	75.7%* 78/103	9.8% 5/51
60	66.3%* 67/101	2.0% 1/50	62.4%* 63/101	6.0% 3/50
90	46.4%* 45/97	6.4% 3/47	39.2%* 38/97	6.4% 3/47
120	24.2%† 24/99	4.1% 2/49	20.2%‡ 20/99	6.1% 3/49
150	9.5% 9/95	2.2% 1/45	8.3% 8/96	4.4% 2/45
180	6.3% 6/96	0% 0/46	7.3% 7/96	8.7% 4/46

*p<0.001; †p=0.002; ‡p=0.027

Study 085

Study 085 was a repeat dose, double-blind, multicenter, placebo-controlled, randomized study to evaluate the efficacy of repeat dosing. The study was initiated with up to two open-label treatment cycles. After open-label treatment(s), subjects were randomized to receive either placebo or 50 Units of DYSPO RT AESTHETIC™. Subjects receiving DYSPO RT AESTHETIC™ in the previous cycle, were invited to participate in the final treatment cycle, and were randomized to receive either placebo or 50 Units of DYSPO RT AESTHETIC™. Subjects could have received up to four treatments through the course of the study.

The study enrolled 311 subjects into the first treatment cycle and 142 subjects were randomized into the final treatment cycle. Subjects received either placebo or 50 Units of DYSPO RT AESTHETIC™ administered in five aliquots of 10 Units/0.05 mL (see Figure 1). Overall, the mean age was 47 years; most of the subjects were women (86%) and predominantly Caucasian (80%).

The primary efficacy endpoint was assessed in the final treatment cycle. After the final repeat treatment with DYSPO RT AESTHETIC™, the reduction of glabellar line severity at maximum frown was statistically greater at Day 30 in the DYSPO RT AESTHETIC™ group compared to the placebo group (p<0.001) as assessed by both Investigators and subjects (see Table 5).

A majority of DYSPO RT AESTHETIC™-treated subjects (52.1%) demonstrated a 2+ grade composite improvement, at maximum frown, at Day 30. Onset of effect was reported as soon as 24 hours; the median time to onset of treatment response was three days.

Table 5: Study 085: Proportion of Responders, at Day 30, Using Investigator’s and Subject’s Assessments of Glabellar Line Treatment Success at Maximum Frown (using 4-point scale) for the Final Treatment Cycle (% and Number of Responders/Number Assessed)

	DYSPORT AESTHETIC™	Placebo
Investigator	84.5%* 60/71	4.2% 3/71
Subject	78.9%* 56/71	1.4% 1/71

* p< 0.001

The proportion of responders in the final treatment cycle was comparable to the proportion of responders in all prior treatment cycles. There was no evidence of reduced response or an increase in adverse events with repeated exposure.

DETAILED PHARMACOLOGY

DYSPORT AESTHETIC™ 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 AESTHETIC™ have not been conducted.

Mutagenicity

Genotoxicity studies have not been conducted with DYSPORT AESTHETIC™.

Fertility and Reproductive Toxicity

DYSPORT AESTHETIC™ 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 AESTHETIC™ was not teratogenic when evaluated in rats and rabbits. In rats, DYSPORT AESTHETIC™ 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 AESTHETIC™ 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 AESTHETIC™ has been evaluated in both single dose and repeated dose studies in rats. In the single dose study, DYSPORT AESTHETIC™ 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 AESTHETIC™ 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

Pr**DYS**SPORT AESTHETIC™ (abobotulinumtoxinA) for injection

This leaflet is part III of a three-part “Product Monograph” published when DYSPORT AESTHETIC™ 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 AESTHETIC™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

DYSPORT AESTHETIC™ is indicated

- for the temporary improvement in the appearance of moderate to severe frown lines in adult patients < 65 years of age

What it does:

DYSPORT AESTHETIC™ is a drug that temporarily reduces movement of certain upper facial muscles that cause wrinkles. Some patients see results as soon as 24 hours with a median time to onset of three days.

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 AESTHETIC™ is supplied in a single-use, sterile 300 Unit vial.

WARNINGS AND PRECAUTIONS

BEFORE you use DYSPORT AESTHETIC™ 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 AESTHETIC™ is for intramuscular use only.

DYSPORT AESTHETIC™ should only be given by a physician with the appropriate qualifications and experience in the treatment and use of DYSPORT AESTHETIC™.

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 AESTHETIC™, 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 AESTHETIC™ 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 AESTHETIC™ 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 AESTHETIC™ 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

The most commonly reported side effects ($\geq 3\%$) were sore throat, headache, injection site pain, upper respiratory infection, or sinus infection.

The following additional side effects have been reported with DYSPORE AESTHETIC™:

- Eyelid ptosis

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

HOW TO STORE IT

Keep out of the reach and sight of children.

DYSPORE AESTHETIC™ must be stored under refrigeration at 2-8°C. Protect from light. Once reconstituted, it can be stored under refrigeration at 2-8°C 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:
<http://www.DysportCanada.ca>
or by contacting Galderma Canada Inc. at: 1-800-467-2081

This leaflet was prepared by Ipsen Biopharm Ltd.

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