

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DYSPORT® safely and effectively. See full prescribing information for DYSPORT®.

DYSPORT® (abobotulinumtoxinA) for injection, for intramuscular use
Initial U.S. Approval: 2009

WARNING: DISTANT SPREAD OF TOXIN EFFECT

See full prescribing information for complete boxed warning

The effects of DYSPORT® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

RECENT MAJOR CHANGES

Indication, Upper Limb Spasticity (1.3) 07/2015
Dosage and Administration, Upper Limb Spasticity (2.1, 2.4) 07/2015

INDICATIONS AND USAGE

DYSPORT® is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:

- the treatment of adults with cervical dystonia (1.1)
- the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age (1.2)
- the treatment of upper limb spasticity in adults (1.3)

DOSAGE AND ADMINISTRATION

Instructions for Safe Use (2.1)

- Once reconstituted, store in original container in a refrigerator (2–8°C) and use within 24 hours (2.1, 16)
- Do not freeze after reconstitution (2.1), (16)
- Protect from light (16)
- Reconstitution instructions are specific for the 300 Unit and 500 Unit vials (2.1)
- Reconstituted DYSPORT® is intended for intramuscular injection only. After reconstitution, DYSPORT® should be used for only one injection session and for only one patient.

Cervical Dystonia (2.2)

- Initial dose is 500 Units given intramuscularly as a divided dose among the affected muscles
- Re-treatment every 12 to 16 weeks or longer, as necessary, based on return of clinical symptoms with doses administered between 250 and 1000 Units to optimize clinical benefit
- Re-treatment should not occur in intervals of less than 12 weeks
- Titrate in 250 Unit steps according to patient's response

Glabellar Lines (2.3)

- Administer a total dose of 50 Units, divided in five equal aliquots of 10 Units each, intramuscularly to affected muscles to achieve clinical effect
- Re-treatment should be administered no more frequently than every 3 months

Upper Limb Spasticity (2.4)

- Select dose based on muscles affected, severity of muscle spasticity, prior response and adverse reaction history following treatment with DYSPORT®.
- Re-treatment every 12 to 16 weeks or longer, as necessary, based on return of clinical symptoms with doses administered between 500 to 1000 Units.

- Re-treatment in less than 12 weeks has not been studied.

DOSAGE FORMS AND STRENGTHS

- For Injection: 300 Units or 500 Units lyophilized powder in a single-use vial for reconstitution with preservative-free 0.9% Sodium Chloride Injection, USP (3).

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin product or excipients (4, 6.1, 6.2)
- Allergy to cow's milk protein (4)
- Infection at the proposed injection site(s) (4)

WARNINGS AND PRECAUTIONS

- The potency Units of DYSPORT® are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT® cannot be compared to or converted into units of any other botulinum toxin products (5.1)
- Recommended dose and frequency of administration should not be exceeded (5.4)
- Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- DYSPORT® contains human albumin. There is a risk for transmission of Creutzfeldt-Jakob disease (CJD) however, no cases of transmission of viral diseases or CJD have ever been identified for albumin (5.6)

ADVERSE REACTIONS

Cervical Dystonia

Most commonly observed adverse reactions (> 5% of patients) are: muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, neck pain, musculoskeletal pain, dysphonia, injection site pain, and eye disorders. (6.1)
Glabellar Lines

The most frequently reported adverse reactions (≥2%) are: nasopharyngitis, headache, injection site pain, injection site reaction, upper respiratory tract infection, eyelid edema, eyelid ptosis, sinusitis, and nausea. (6.1)

Upper Limb Spasticity

The most frequently reported adverse reactions (≥2%) are: urinary tract infection, nasopharyngitis, muscular weakness, musculoskeletal pain, dizziness, fall and depression. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ipsen Biopharmaceuticals, Inc. at 877-397-7671 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Concomitant use of DYSPORT® and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of botulinum toxin may be potentiated (7)
- Anticholinergic drugs may potentiate systemic anticholinergic effects (7)
- The effect of administering different botulinum neurotoxins during the course of treatment with DYSPORT® is unknown (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Administer DYSPORT® with care in elderly patients, reflecting the greater frequency of concomitant disease and other drug therapy (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2015

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FULL PRESCRIBING INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of DYSPO[®] and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose. [see Warnings and Precautions (5.2)]

1 INDICATIONS AND USAGE

1.1 Cervical Dystonia

DYSPO[®] is indicated for the treatment of adults with cervical dystonia.

1.2 Glabellar Lines

DYSPO[®] is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients less than 65 years of age.

1.3 Upper Limb Spasticity

DYSPO[®] is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors, wrist flexors and finger flexors.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe Use

The potency Units of DYSPO[®] 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 DYSPO[®] cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method [see Description (11)].

Reconstituted DYSPO[®] is intended for intramuscular injection only.

Reconstitution instructions are specific for each of the 300 Unit vial and the 500 Unit vial. These volumes yield concentrations specific for the use for each indication (Table 1).

Table 1: Dilution Instructions for DYSPO[®] Vials (500 Units and 300 Units)

Diluent* per 500 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* per 300 Unit Vial	Resulting Dose Units per 0.1 mL
1 mL	50 Units	0.6 mL	50 Units
2.5 mL	20 Units	1.5 mL	20 Units
--	--	2.5 mL	12 Units
5 mL**	10 Units	3 mL	10 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the DYSPO[®] dose is also possible by administering a smaller or larger injection volume (i.e. 0.05 mL (50% decrease in dose), 0.08 mL (20% decrease in dose) or 0.15 mL (50% increase in dose)).

** When using 5 mL of diluent for a 500 Unit vial of DYSPO[®], complete the following steps (see also 2.4 Dosing in Upper Limb Spasticity).

1. Reconstitute a 500 Unit vial of DYSPO[®] 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[®] solution from the reconstituted vial without inverting and mix gently. The resulting concentration will be 10 units/0.1 mL.
4. Use immediately after reconstitution in the syringe. Dispose of any unused saline.

After reconstitution, DYSPORT[®] should be used for only one injection session and for only one patient. Once reconstituted, DYSPORT[®] should be stored in the original container, in a refrigerator at 2 °C to 8°C (36 °F to 46°F), protected from light for up to 24 hours. It must be discarded if not used within 24 hours. Do not freeze reconstituted DYSPORT[®]. Discard the vial and needle in accordance with local regulations.

2.2 Dosing in Cervical Dystonia

The recommended initial dose of DYSPORT[®] 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[®] dose and percentage of total dose injected into specific muscles in the pivotal clinical trials can be found in Table 8 of Section 14.1, Clinical Studies – Cervical Dystonia.) Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Clinical studies with DYSPORT[®] in cervical dystonia suggest that the peak effect occurs

between two and four weeks after injection. Simultaneous EMG-guided application of DYSPORT[®] may be helpful in locating active muscles.

Dose Modification

Where dose modification is necessary for the treatment of cervical dystonia, uncontrolled open-label studies suggest that dose adjustment can be made in 250 Unit steps according to the individual patient's response, with re-treatment every 12 weeks or longer, as necessary, based on return of clinical symptoms. Uncontrolled open-label studies also suggest that the total dose administered in a single treatment should be between 250 Units and 1000 Units. Re-treatment, if needed, should not occur in intervals of less than

12 weeks. Doses above 1000 Units have not been systematically evaluated.

Special Populations

Adults and elderly

The starting dose of 500 Units recommended for cervical dystonia is applicable to adults of all ages [*see Use in Specific Populations (8.5)*].

Pediatric Patients

The safety and effectiveness of DYSPORT[®] in the treatment in pediatric patients less than 18 years of age has not been assessed [*see Warnings and Precautions (5.2)*].

Instructions for Preparation and Administration for the Treatment of Cervical Dystonia

DYSPORT[®] is supplied as a single-use vial. Only use sterile preservative-free 0.9% Sodium Chloride Injection, USP for reconstitution of DYSPORT[®]. Each 500 Unit vial of DYSPORT[®] is to be reconstituted with 1 mL of preservative-free 0.9% Sodium Chloride Injection USP to yield a solution of 50 Units per 0.1 mL. Each 300 Unit vial of DYSPORT[®] is to be reconstituted with 0.6 mL of preservative-free 0.9% Sodium Chloride Injection USP to yield a solution equivalent to 50 Units per 0.1 mL.

Using an appropriately sized sterile syringe, needle and aseptic technique, draw up 1 mL or 0.6 mL of sterile, preservative-free 0.9% Sodium Chloride Injection USP for 500 Unit and 300 Unit vials, respectively. Insert the needle into the DYSPORT[®] 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[®] 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.

Discard the vial and needle in accordance with local regulations.

2.3 Dosing in Glabellar Lines

The dose of DYSPO[®] for the treatment of glabellar lines is a total of 50 Units given intramuscularly in five equal aliquots of 10 Units each to achieve clinical effect (*see Figure 1*).

Special Populations

Adults

A total dose of 50 Units of DYSPO[®], in five equal aliquots, should be administered to achieve clinical effect.

The clinical effect of DYSPO[®] may last up to four months. Repeat dose clinical studies demonstrated continued efficacy with up to four repeated administrations. It should be administered no more frequently than every three months. When used for re-treatment, DYSPO[®] should be reconstituted and injected using the same techniques as the initial treatment.

Pediatric Patients

DYSPO[®] for glabellar lines is not recommended for use in pediatric patients less than 18 years of age [*see Warnings and Precautions (5.2)*].

Instructions for Preparation and Administration for the Treatment of Glabellar Lines

DYSPO[®] is supplied as a single-use vial. Only use sterile preservative-free 0.9% Sodium Chloride Injection, USP for reconstitution of DYSPO[®]. Each 300 Unit vial of DYSPO[®] is to be reconstituted with 2.5 mL of preservative-free 0.9% Sodium Chloride Injection USP prior to injection. The concentration of the resulting solution will be 10 Units per 0.08 mL (12 Units per 0.1 mL) to be delivered in five equally divided aliquots of 0.08 mL each. DYSPO[®] may also be reconstituted with 1.5 mL of preservative-free 0.9% Sodium Chloride Injection USP for a solution of 10 Units per 0.05 mL (20 Units per 0.1 mL) to be delivered in five equally divided aliquots of 0.05 mL each.

Using an appropriately sized sterile syringe, needle and aseptic technique, draw up 2.5 mL or 1.5 mL of preservative-free 0.9% Sodium Chloride Injection USP. Insert the needle into the DYSPO[®] 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 DYSPO[®] should be a clear, colorless solution, free of particulate matter otherwise it should not be injected.

Draw a single patient dose of DYSPO[®] 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.

Discard the vial and needle in accordance with local regulations.

Injection Technique

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[®] must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures.

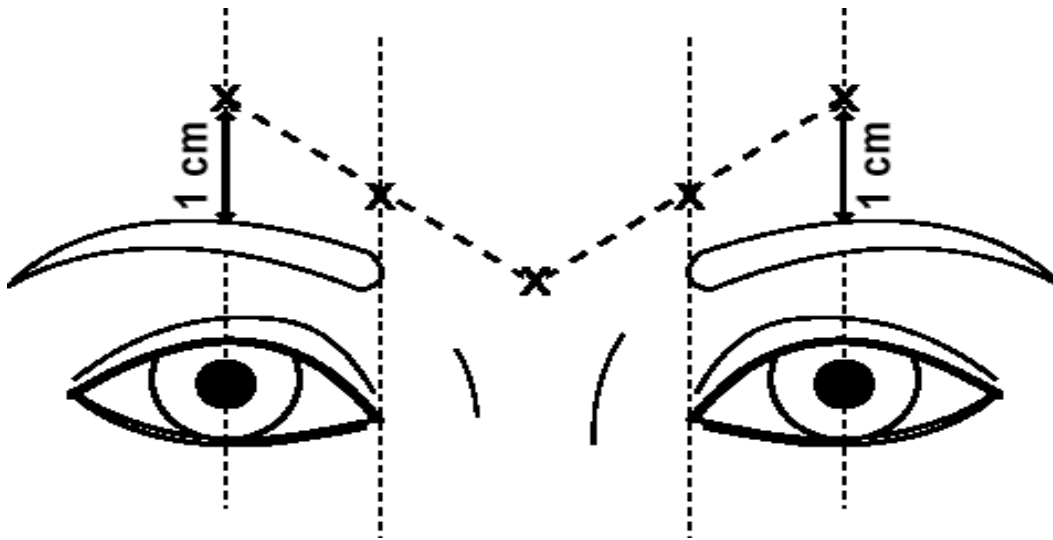
Risk of ptosis can be mitigated by careful examination of the upper lid for separation or weakness of the levator palpebrae muscle (true ptosis), identification of lash ptosis, and evaluation of the range of lid excursion while manually depressing the frontalis to assess compensation.

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 1 centimeter above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- Do not inject toxin closer than 1 centimeter above the central eyebrow.

To inject DYSPO[®], advance the needle through the skin into the underlying muscle while applying finger pressure on the superior medial orbital rim. Inject patients with a total of 50 Units in five equally divided aliquots. Using a 30 gauge needle, inject 10 Units of DYSPO[®] into each of five sites, two in each corrugator muscle, and one in the procerus muscle (*see Figure 1*).

Figure 1



2.4 Dosing in Upper Limb Spasticity

Special Populations

Adults

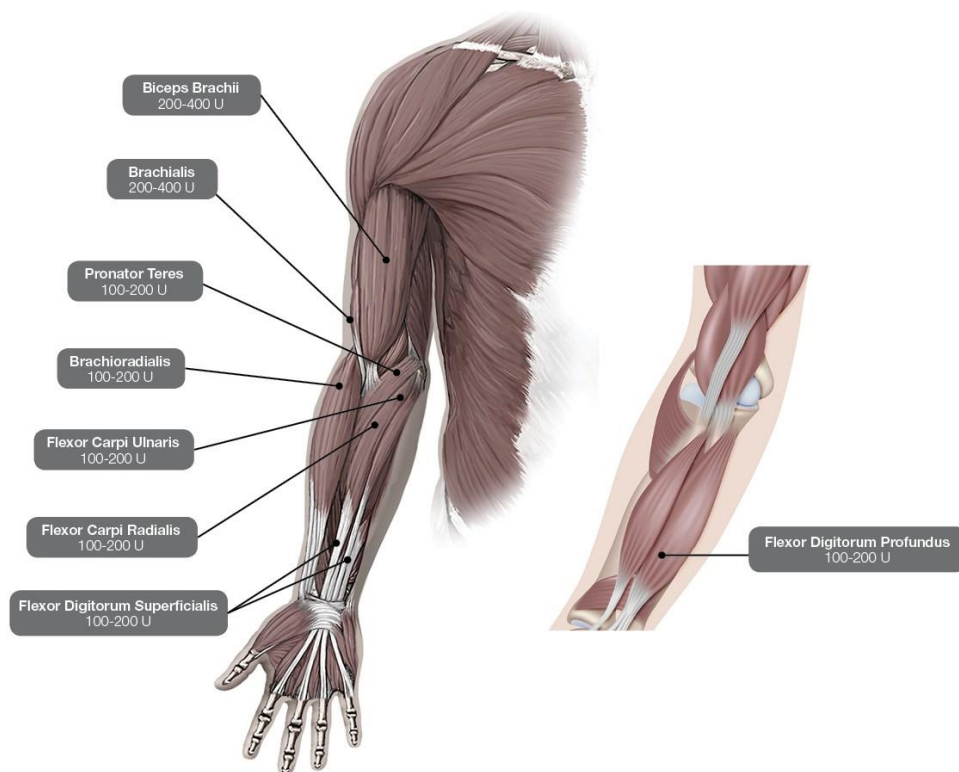
Dosing in initial and subsequent treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, and/or adverse event history with DYSPORT®. In the pivotal clinical trial, doses of 500 Units and 1000 Units were divided among selected muscles, Table 2 and Figure 2, at a given treatment session.

No more than 1 mL should generally be administered at any single injection site.

Table 2: DYSPORT® Dosing by Muscle for Upper Limb Spasticity

Muscles Injected	Recommended Dose DYSPORT®	Recommended Number of Injection(s) per Muscle
Flexor carpi radialis (FCR)	100 Units to 200 Units	1 to 2
Flexor carpi ulnaris (FCU)	100 Units to 200 Units	1 to 2
Flexor digitorum profundus (FDP)	100 Units to 200 Units	1 to 2
Flexor digitorum superficialis (FDS)	100 Units to 200 Units	1 to 2
Brachialis	200 Units to 400 Units	1 to 2
Brachioradialis	100 Units to 200 Units	1 to 2
Biceps Brachii (BB)	200 Units to 400 Units	1 to 2
Pronator Teres	100 Units to 200 Units	1

Figure 2: Muscles for Injection for Upper Limb Spasticity



Although actual location of the injection sites can be determined by palpation, the use of injection guiding technique e.g. electromyography, electrical stimulation is recommended to target the injection sites.

Repeat DYSPO[®] 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 DYSPO[®] and muscles to be injected. Clinical improvement may be expected one week after administration of DYSPO[®].

Pediatric Patients

The safety and effectiveness of DYSPO[®] in the treatment of upper limb spasticity in pediatric patients less than 18 years of age has not been demonstrated. [see Warnings and Precautions (5.2)]

Instructions for Preparation and Administration for the Treatment of Upper Limb Spasticity in Adults

DYSPO[®] is supplied as a single-use vial. Only use sterile preservative-free 0.9% Sodium Chloride Injection, USP for reconstitution of DYSPO[®]. The recommended concentration is 100 Units/mL or 200 Units/mL with preservative-free 0.9% Sodium Chloride Injection USP) (see Table 1).

Using an appropriately sized sterile syringe, needle and aseptic technique, draw up the required volume (Table 1) of preservative-free 0.9% Sodium Chloride Injection USP.

Insert the needle into the DYSPO[®] 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 (see footnote in Table 1). 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 DYSPO[®] 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.

Discard the vial and needle in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS

For injection: 300 Units or 500 Units of lyophilized powder in a single-use vial for reconstitution with preservative-free 0.9% Sodium Chloride Injection, USP.

4 CONTRAINDICATIONS

DYSPO[®] is contraindicated in patients with:

- Known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation [*see Adverse Reactions (6.1), Description (11)*]. This product may contain trace amounts of cow's milk protein. Patients known to be allergic to cow's milk protein should not be treated with DYSPO[®].
- Infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of DYSPO[®] 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 DYSPO[®] cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method [*see Description (11)*].

5.2 Spread of Toxin Effect

Post-marketing safety data from DYSPO[®] and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of the symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than the maximum recommended total dose.

5.3 Dysphagia and Breathing Difficulties

Treatment with DYSPO[®] and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved [*see Warnings and Precautions (5.2)*].

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post-marketing reports of serious breathing difficulties, including respiratory failure.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [*see Warnings and Precautions (5.2), Adverse Reactions (6.1), Clinical Pharmacology (12.2)*].

5.4 Facial Anatomy in the Treatment of Glabellar Lines

Caution should be exercised when administering DYSPO[®] to patients with surgical alterations to the facial anatomy, excessive weakness or atrophy in the target muscle(s), marked facial asymmetry, inflammation at the injection site(s), ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin [*see Dosage and Administration (2.3)*] or the inability to substantially lessen glabellar lines by physically spreading them apart [*see Clinical Studies (14.2)*].

Do not exceed the recommended dosage and frequency of administration of DYSPO[®]. In clinical trials, subjects who received a higher dose of DYSPO[®] had an increased incidence of eyelid ptosis.

5.5 Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of DYSPORT® [*see Adverse Reactions (6.1)*].

5.6 Human Albumin

This product contains 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. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

5.7 Intradermal Immune Reaction

The possibility of an immune reaction when injected intradermally is unknown. The safety of DYSPORT® for the treatment of hyperhidrosis has not been established. DYSPORT® is approved only for intramuscular injection .

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in labeling:

- Distant Spread of Toxin Effect [*see Boxed Warning*]
- Lack of Interchangeability between Botulinum Toxin Products [*see Warnings and Precautions (5.1)*]
- Spread of Effects from Toxin [*see Warnings and Precautions (5.2)*]
- Dysphagia and Breathing Difficulties [*see Warnings and Precautions (5.3)*]
- Facial Anatomy in the Treatment of Glabellar Lines [*see Warnings and Precautions (5.4)*]
- Pre-existing Neuromuscular Disorders [*see Warnings and Precautions (5.5)*]
- Human Albumin [*see Warnings and Precautions (5.6)*]
- Intradermal Immune Reaction [*see Warnings and Precautions (5.7)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Cervical Dystonia

The data described below reflect exposure to DYSPORT® in 357 cervical dystonia patients in 6 studies. Of these, two studies were randomized, double-blind, single treatment, placebo controlled studies with subsequent optional open label treatment in which dose optimization (250 to 1000 Units per treatment) over the course of 5 treatment cycles was allowed.

The population was almost entirely Caucasian (99%) with a median age of 51 years (range 18–82 years). Most patients (87%) were less than 65 years of age; 58.4% were women.

Common Adverse Reactions

The most commonly reported adverse reactions (occurring in more than 5% of patients who received 500 Units of DYSPORT® in the placebo controlled clinical trials) in cervical dystonia patients were: muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, neck pain, musculoskeletal pain, dysphonia, injection site pain, and eye disorders (consisting of blurred vision, diplopia, and reduced visual acuity and accommodation). Other than injection site reactions, most adverse reactions became noticeable about one week after treatment and lasted several weeks.

The rates of adverse reactions were higher in the combined controlled and open-label experience than in the placebo-controlled trials.

During the clinical studies, two patients (<1%) experienced adverse reactions leading to withdrawal. One patient experienced disturbance in attention, eyelid disorder, feeling abnormal and headache, and one patient experienced dysphagia.

Table 3 compares the incidence of the most frequent adverse reactions from a single treatment cycle of 500 Units of DYSPORT® compared to placebo [*see Clinical Studies (14.1)*].

Table 3: Most Common Adverse Reactions (>5%) and Greater than Placebo in the Pooled, Double-blind Phase of Clinical Trials in Patients with Cervical Dystonia

Adverse Reaction Preferred Term	DYSPORT® 500 Units (N=173)	Placebo (N=182)
	%	%
Any Adverse Reaction	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.

Dose-response relationships for common adverse reactions in a randomized multiple fixed-dose study in which the total dose was divided between two muscles (the sternocleidomastoid and splenius capitis) are shown in Table 4.

Table 4: Common Adverse Reactions by Dose in Fixed-dose Study in Patients with Cervical Dystonia

Adverse Reaction Preferred Term	DYSPORT® Dose			
	Placebo	250 Units	500 Units	1000 Units
Any Adverse Event	30%	37%	65%	83%
Dysphagia	5%	21%	29%	39%
Dry Mouth	10%	21%	18%	39%
Muscular Weakness	0%	11%	12%	56%
Injection Site Discomfort	10%	5%	18%	22%
Dysphonia	0%	0%	18%	28%
Facial Paresis	0%	5%	0%	11%
Eye Disorders ^a	0%	0%	6%	17%

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

Injection Site Reactions

Injection site discomfort and injection site pain were common adverse reactions following DYSPORT® administration.

Less Common Adverse Reactions

The following adverse reactions were reported less frequently (<5%).

Breathing Difficulty

Breathing difficulties were reported by approximately 3% of patients following DYSPO[®] administration and in 1% of placebo patients in clinical trials during the double-blind phase. These consisted mainly of dyspnea. The median time to onset from last dose of DYSPO[®] was approximately one week, and the median duration was approximately three weeks.

Other adverse reactions with incidences of less than 5% in the DYSPO[®] 500 Units group in the double-blind phase of clinical trials included dizziness in 3.5% of DYSPO[®]-treated patients and 1% of placebo-treated patients, and muscle atrophy in 1% of DYSPO[®]-treated patients and in none of the placebo-treated patients.

Laboratory Findings

Patients treated with DYSPO[®] exhibited a small increase from baseline (0.23 mol/L) in mean blood glucose relative to placebo-treated patients. This was not clinically significant among patients in the development program but could be a factor in patients whose diabetes is difficult to control.

Electrocardiographic Findings

ECG measurements were only recorded in a limited number of patients in an open-label study without a placebo or active control. This study showed a statistically significant reduction in heart rate compared to baseline, averaging about three beats per minute, observed thirty minutes after injection.

Glabellar Lines

In placebo-controlled clinical trials of DYSPO[®], the most common adverse reactions ($\geq 2\%$) following injection of DYSPO[®] were nasopharyngitis, headache, injection site pain, injection site reaction, upper respiratory tract infection, eyelid edema, eyelid ptosis, sinusitis, and nausea.

Table 5 reflects exposure to DYSPO[®] in 398 patients 19 to 75 years of age who were evaluated in the randomized, placebo-controlled clinical studies that assessed the use of DYSPO[®] for the temporary improvement in the appearance of glabellar lines [see *Clinical Studies (14)*]. Adverse reactions of any cause occurred in 48% of the DYSPO[®]-treated patients and 33% of the placebo-treated patients.

Table 5: Most Common Adverse Reactions with > 1% Incidence in Pooled, Placebo-Controlled Trials for Glabellar Lines

Adverse Reactions by Body System	DYSPO [®] n=398 (%)*	Placebo n=496 (%)*
Any Adverse Reaction	48	33
Eye Disorders		
Eyelid Edema	2	0
Eyelid Ptosis	2	<1
Gastrointestinal Disorders		
Nausea	2	1
General Disorders and Administration Site Conditions		
Injection Site Pain	3	2
Injection Site Reaction	3	<1
Infections and Infestations		
Nasopharyngitis	10	4
Upper Respiratory Tract Infection	3	2
Sinusitis	2	1
Investigations		
Blood Present in Urine	2	<1
Nervous System Disorders		
Headache	9	5

* Patients who received treatment with placebo and DYSPO[®] are counted in both treatment columns.

In the overall safety database, where some patients received up to twelve treatments with DYSPO[®], adverse reactions were reported for 57% (1425/2491) of patients. The most frequently reported of these adverse reactions were headache, nasopharyngitis, injection site pain, sinusitis, URI, injection site bruising, and injection site reaction (numbness, discomfort, erythema, tenderness, tingling, itching, stinging, warmth, irritation, tightness, swelling).

Adverse reactions that occurred after repeated injections in 2–3% of the population included bronchitis, influenza, pharyngolaryngeal pain, cough, contact dermatitis, injection site swelling, and injection site discomfort.

The incidence of eyelid ptosis did not increase in the long-term safety studies with multiple re-treatments at intervals \geq three months. The majority of the reports of eyelid ptosis were mild to moderate in severity and resolved over several weeks. [*see Dosage and Administration (2.3)*].

Upper Limb Spasticity

Table 6 lists the most frequently reported adverse reactions ($\geq 2\%$) in any DYSPO[®] dose group and more frequent than placebo in double blind studies evaluating the treatment of upper limb spasticity in adults with DYSPO[®].

Table 6: Most Common Adverse Reactions Observed in at Least 2% of Patients Treated in Pooled, Double-Blind Trials of Patients with Upper Limb Spasticity Reported More Frequently than with Placebo

Adverse Reaction Preferred Term	DYSPO [®]		Placebo (N=279) %
	500 Units (N=197) %	1000 Units (N=194) %	
Infections and infestations			
Nasopharyngitis	4	1	1
Urinary tract infection	3	1	2
Influenza	1	2	1
Infection	1	2	1
Musculoskeletal and connective tissue disorders			
Muscular weakness	2	4	1
Pain in extremity	0	2	1
Musculoskeletal pain	3	2	2
Back pain	1	2	1
Nervous system disorders			
Headache	1	2	1
Dizziness	3	1	1
Convulsion	2	2	1
Syncope	1	2	0
Hypoaesthesia	0	2	<1
Partial seizures	0	2	0
General disorders and administration site conditions			
Fatigue	2	2	0
Asthenia	2	1	<1
Injury, poisoning and procedural complications			
Fall	2	3	2
Injury	2	2	1
Contusion	1	2	<1
Gastrointestinal disorders			
Diarrhea	1	2	<1
Nausea	2	1	1
Constipation	0	2	1
Investigation			
Blood triglycerides increased	2	1	0
Respiratory, thoracic and mediastinal disorders			
Cough	1	2	1
Vascular disorders			
Hypertension	1	2	<1
Psychiatric disorders			
Depression	2	3	1

Injection Site Reactions

Injection site reactions (e.g. pain, bruising, haemorrhage, injection site erythema/haematoma etc.) have occurred following administration of DYSPO[®].

Less Common Adverse Reactions

In a pooled analysis of clinical studies, adverse reactions with an incidence of less than 2% reported in DYSPORT® treatment groups included dysphagia 0.5%, gait disturbance 0.5%, hypertension 0.5%, and sensation of heaviness 0.3%.

6.2 Postmarketing Experience

Because adverse reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been identified during post-approval use of DYSPORT®: vertigo, photophobia, influenza-like illness, amyotrophy, burning sensation, facial paresis, hypoesthesia, erythema, and excessive granulation tissue.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products in this class may be misleading.

Cervical Dystonia

About 3% of subjects developed antibodies (binding or neutralizing) over time with DYSPORT® treatment.

Glabellar Lines

Testing for antibodies to DYSPORT® was performed for 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® treatment. None of the subjects tested positive for neutralizing antibodies.

Upper Limb Spasticity

From 230 subjects treated with DYSPORT® and tested for the presence of binding antibodies, 5 subjects were positive at baseline and 17 developed antibodies after treatment. Among those 17 subjects, 10 subjects developed neutralizing antibodies. An additional 51 subjects from a separate repeat dose study were tested for the presence of neutralizing antibodies only. None of the subjects tested positive.

In total, from the 281 subjects treated in the long-term studies and tested for the presence of neutralizing antibodies, 3.6% developed neutralizing antibodies after treatment.

In the presence of binding and neutralizing antibodies to DYSPORT® some patients continue to experience clinical benefit.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with DYSPORT®.

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® 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.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of DYSPORT®.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

DYSPORT® produced embryo-fetal toxicity when given to pregnant rats at doses similar to or greater than the maximum recommended human dose (MRHD) of 1000 Units on a body weight (Units/kg) basis.

In an embryo-fetal development study in which pregnant rats received intramuscular injections daily (2.2, 6.6, or 22 Units/kg on gestation days 6 through 17) or intermittently (44 Units/kg on gestation days 6 and 12 only) during organogenesis, increased early embryonic death was observed with both dosing schedules. The no-effect dose for embryo-fetal developmental toxicity was 2.2 Units/kg (one-tenth the MRHD on a body weight basis). Maternal toxicity was seen at 22 and 44 Units/kg. In a pre- and post-natal development study in which female rats received 6 weekly intramuscular injections (4.4, 11.1, 22.2, or 44 Units/kg) beginning on day 6 of gestation and continuing through parturition to weaning, an increase in stillbirths was observed at the highest dose, which was maternally toxic. The no-effect dose for pre- and post-natal developmental toxicity was 22.2 Units/kg (approximately equal to the MRHD on a body weight basis).

There are no adequate and well-controlled studies in pregnant women. DYSPORT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether DYSPORT® is excreted in human milk.

8.4 Pediatric Use

Cervical Dystonia

Safety and effectiveness in pediatric patients have not been established [*see Warnings and Precautions (5.2)*].

Glabellar Lines

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

Upper Limb Spasticity

Safety and effectiveness in pediatric patients have not been established [*see Warnings and Precautions (5.2)*].

8.5 Geriatric Use

Cervical Dystonia

There were insufficient numbers of patients aged 65 and over in the clinical studies to determine whether they respond differently than younger patients. In general, elderly patients should be observed to evaluate their tolerability of DYSPORT®, due to the greater frequency of concomitant disease and other drug therapy [*see Dosage and Administration (2.1)*].

Glabellar Lines

Of the total number of subjects in the placebo-controlled clinical studies of DYSPORT®, 8 (1%) were 65 and over. Efficacy was not observed in subjects 65 years and over [*see Clinical Studies (14.2)*]. For the entire safety database of geriatric subjects, although there was no increase in the incidence of eyelid ptosis, geriatric subjects did have an increase in the number of ocular adverse reactions compared to younger subjects (11% vs. 5%) [*see Dosage and Administration (2.2)*].

Upper Limb Spasticity

Of the total number of subjects in placebo controlled clinical studies of DYSPORT®, 28.0 percent were 65 and over, while 8.2 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Ethnic Groups

Exploratory analyses in trials for glabellar lines in African-American subjects with Fitzpatrick skin types IV, V, or VI and in Hispanic subjects suggested that response rates at Day 30 were comparable to and no worse than the overall population.

10 OVERDOSAGE

Excessive doses of DYSPORT® 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 [*see Warnings and Precautions (5.2)*]. Symptomatic treatment may be necessary.

Symptoms of overdose are likely not 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 overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 770-488-7100. More information can be obtained at <http://www.cdc.gov/ncidod/srp/drugs/drug-service.html>.

11 DESCRIPTION

Botulinum toxin type A, the active ingredient in DYSPORT® (abobotulinumtoxinA), 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. The neurotoxin complex is composed of the neurotoxin, hemagglutinin proteins and non-toxin non-hemagglutinin protein.

DYSPORT® is supplied in a single-use, sterile vial for reconstitution intended for intramuscular injection. Each vial contains 300 Units or 500 Units of lyophilized abobotulinumtoxinA, human serum albumin (125 mcg) and lactose (2.5 mg). DYSPORT® may contain trace amounts of cow's milk proteins [*see Contraindications (4)*].

One unit of DYSPORT® corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. The method for performing the assay is specific to Ipsen's product DYSPORT®. 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® are not interchangeable with Units of any other botulinum toxin or any toxin assessed with any other specific assay method [*see Dosage Forms and Strengths (3)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

DYSPORT® 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.

12.2 Pharmacodynamics

The primary pharmacodynamic effect of DYSPORT® 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.

12.3 Pharmacokinetics

Using currently available analytical technology, it is not possible to detect DYSPORT® in the peripheral blood following intramuscular injection at the recommended doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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

Mutagenesis

Genotoxicity studies have not been conducted for DYSPORT®.

Impairment of Fertility

In a fertility and early embryonic development study in rats in which either males (2.9, 7.2, 14.5 or 29 Units/kg) or females (7.4, 19.7, 39.4 or 78.8 Units/kg) received weekly intramuscular injections prior to and after mating, dose-related increases in pre-implantation loss and reduced numbers of corpora lutea were noted in treated females. Failure to mate was observed in males that received the high dose. The no-effect dose for effects on fertility was 7.4 Units/kg in females and 14.5 Units/kg in males (approximately one-half and equal to, respectively, the maximum recommended human dose of 1000 Units on a body weight basis).

14 CLINICAL STUDIES

14.1 Cervical Dystonia

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

In both placebo controlled studies (Study 1 and Study 2), a dose of 500 Units DYSPORT[®] was given by intramuscular injection divided among two to four affected muscles. These studies were followed by long-term open label extensions that allowed titration in 250 Unit steps to doses in a range of 250 to 1000 Units, after the initial dose of 500 Units. In the extension studies, re-treatment was determined by clinical need after a minimum of 12 weeks. The median time to re-treatment was 14 weeks and 18 weeks for the 75th percentile.

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[®] group than the placebo group at Weeks 4 in both studies (*see Table 7*).

Table 7: TWSTRS Total Score Efficacy Outcome from the Phase 3 Cervical Dystonia Studies Intent to Treat Population

	Study 1		Study 2	
	DYSPORT [®] 500 Units N=55	Placebo N=61	DYSPORT [®] 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) Change from Baseline ^a	30.0 (12.7) -15.6 (2.0)	40.2 (11.8) -6.7 (2.0)	35.2 (13.8) -9.6 (2.0)	42.4 (12.2) -3.7 (1.8)
Treatment difference 95% confidence interval	-8.9* [-12.9 to -4.7]		-5.9* [-10.6 to -1.3]	
Week 8 Mean (SD) Change from Baseline ^a	29.3 (11.0) -14.7 (2.0)	39.6 (13.5) -5.9 (2.0)		
Treatment difference 95% confidence interval	-8.8* [-12.9 to -4.7]			

a. Change from baseline is expressed as adjusted least squares mean (SE)

*Significant at p -value < 0.05

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 8 indicates the average DYSPORT[®] dose, and percentage of total dose, injected into specific muscles in the pivotal clinical trials.

Table 8: DYSPORT® 500 Units starting dose (units and % of the total dose) by Unilateral Muscle Injected During Double-blind Pivotal Phase 3 studies 2 and 1 Combined

Number of patients injected per muscle ^a		DYSPORT® Dose Injected		Percentage of the total DYSPORT® Dose Injected	
		Median [DYSPORT® Units] (min, max)	75th percentile [DYSPORT® 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 2 and 1 who received initial treatment = 121.

14.2 Glabellar Lines

Three double-blind, randomized, placebo-controlled, clinical studies evaluated the efficacy of DYSPORT® for use in the temporary improvement of the appearance of moderate to severe glabellar lines. These three studies enrolled 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 DYSPORT® or placebo. The total dose was delivered in equally divided aliquots to specified injection sites (*see Figure 1*).

Investigators and subjects assessed efficacy at maximum frown by using a 4-point scale (none, mild, moderate, severe).

Overall treatment success was defined as post-treatment glabellar line severity of none or mild with at least 2 grade improvement from Baseline for the combined investigator and subject assessments (composite assessment) on Day 30 (*see Table 9*). Additional endpoints for each of the studies were post-treatment glabellar line severity of none or mild with at least a 1 grade improvement from Baseline for the separate investigator and subject assessments on Day 30.

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

Table 9: Treatment Success at Day 30 (None or Mild with at least 2 Grade Improvement from Baseline at Maximum Frown for the combined Investigator and Subject Assessments (Composite))

Study	2 Grade Improvement	
	DYSPORT® n/N (%)	Placebo n/N (%)
GL-1	58/105 (55%)	0/53 (0%)
GL-2	37/71 (52%)	0/71 (0%)
GL-3	120/200 (60%)	0/100 (0%)

Treatment with DYSPORT® reduced the severity of glabellar lines for up to four months.

Study GL-1

Study GL-1 was a single dose, double-blind, multi-center, randomized, placebo-controlled study in which 158 previously untreated subjects received either placebo or 50 Units of DYSPORT®, administered in five aliquots of 10 Units (*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%). At Day 30, 55% of DYSPORT®-treated subjects achieved treatment success: a composite 2 grade improvement of glabellar line severity at maximum frown (*Table 9*).

In study GL-1, the reduction of glabellar line severity at maximum frown was greater at Day 30 in the DYSPORT[®] group compared to the placebo group as assessed by both Investigators and subjects (*Table 10*).

Table 10: GL-1: Investigator’s and Subject’s Assessment of Glabellar Line Severity at Maximum Frown Using a 4-point Scale (% and Number of Subjects with Severity of None or Mild)

Day	Investigator’s Assessment		Subject’s Assessment	
	DYSPORT [®]	Placebo	DYSPORT [®]	Placebo
	N=105	N=53	N=105	N=53
14	90% 95	17% 9	77% 81	9% 5
30	88% 92	4% 2	74% 78	9% 5
60	64% 67	2% 1	60% 63	6% 3
90	43% 45	6% 3	36% 38	6% 3
120	23% 24	4% 2	19% 20	6% 3
150	9% 9	2% 1	8% 8	4% 2
180	6% 6	0% 0	7% 7	8% 4

Study GL-2

Study GL-2 was a repeat dose, double-blind, multi-center, placebo-controlled, randomized study. The study was initiated with two or three open-label treatment cycles of 50 Units of DYSPORT[®] administered in five aliquots of 10 Units DYSPORT[®] (*see Figure 1*). After the open-label treatments, subjects were randomized to receive either placebo or 50 Units of DYSPORT[®]. Subjects could have received up to four treatments through the course of the study. Efficacy was assessed in the final randomized treatment cycle. The study enrolled 311 subjects into the first treatment cycle and 142 subjects were randomized into the final treatment cycle. Overall, the mean age was 47 years; most of the subjects were women (86%) and predominantly Caucasian (80%).

At Day 30, 52% of DYSPORT[®]-treated subjects achieved treatment success: a composite 2 grade improvement of glabellar line severity at maximum frown (*see Table 9*).

The proportion of responders in the final treatment cycle was comparable to the proportion of responders in all prior treatment cycles.

After the final repeat treatment with DYSPORT[®], the reduction of glabellar line severity at maximum frown was greater at Day 30 in the DYSPORT[®] group compared to the placebo group as assessed by both Investigators and subjects (*Table 12*).

Table 11: GL-2: Investigator’s and Subject’s Assessments of Glabellar Line Severity at Maximum Frown Using a 4-point Scale (% and Number of Subjects with Severity of None or Mild)

Day	Investigator’s Assessment		Subject’s Assessment	
	DYSPORT [®] N=71	Placebo N=71	DYSPORT [®] N=71	Placebo N=71
30	85% 60	4% 3	79% 56	1% 1

Study GL-3

Study GL-3 was a single dose, double-blind, multi-center, randomized, placebo-controlled study in which 300 previously untreated subjects received either placebo or 50 Units of DYSPORT[®], administered in five aliquots of 10 Units (*see Figure 1*). Subjects were followed for 150 days. The mean age was 44 years; most of the subjects were women (87%), and predominantly Caucasian (75%) or Hispanic (18%).

At Day 30, 60% of DYSPORT[®]-treated subjects achieved treatment success: a composite 2 grade improvement of glabellar line severity at maximum frown (*see Table 9*).

In study GL-3, the reduction of glabellar line severity at maximum frown was greater at Day 30 in the DYSPORT[®] group compared to the placebo group as assessed by both Investigators and subjects (*see Table 12*).

Table 12. GL-3: Investigator’s and Subject’s Assessment of Glabellar Line Severity at Maximum Frown Using a 4-point Scale (% and Number of Subjects with Severity of None or Mild)

Day	Investigator’s Assessment		Subject’s Assessment	
	DYSPORT® N=200	Placebo N=100	DYSPORT® N=200	Placebo N=100
14	83% 166	5% 5	83% 165	2% 2
30	86% 171	0% 0	82% 163	2% 2
60	75% 150	1% 1	65% 130	4% 4
90	51% 102	1% 1	46% 91	2% 2
120	29% 58	1% 1	31% 61	3% 3
150	16% 32	1% 1	16% 31	3% 3

Geriatric Subjects

In GL1, GL2, and GL3, there were 8 subjects aged 65 and older who were randomized to DYSPORT® 50 Units in 5 equal aliquots of 10 Units (4) or placebo (4). None of the geriatric DYSPORT® subjects were a treatment success at maximum frown at Day 30.

14.3 Upper Limb Spasticity

The efficacy and safety of DYSPORT® 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® and 79 placebo) with upper limb spasticity (Modified Ashworth Scale (MAS) score ≥ 2 in the primary targeted muscle group for toxin naive patients or MAS score ≥ 3 in the primary targeted muscle group for toxin non-naive patients at least 4 months after the last botulinum toxin injection, of any serotype) who were at least 6 months post-stroke or post-traumatic brain injury.

DYSPORT® 500 Units (N=80), DYSPORT® 1000 Units (N=79), or placebo (N=79) was injected intramuscularly into the affected upper limb muscles. After injection of the primary targeted muscle groups (PTMG), the remainder of the dose was injected into at least two additional upper limb muscles determined by the patient’s individual presentation. Table 13 provides the mean and range of DYSPORT® doses injected and the number of injections into specific muscles of the upper limb.

Table 13 DYSPORT® Dose Injected and Number of Injections per Muscle

Muscle	DYSPORT® Treatment Group	Number of Patients	Mean DYSPORT® Units Injected (Min, Max)	Number Of Injection Sites Median, [Q1 ; Q3]
Flexor digitorum profundus (FDP)*	500 U	54	93.5 Units (50 to 100)	1, [1 ; 2]
	1000 U	65	195.5 Units (100 to 300)	2, [1 ; 2]
Flexor digitorum superficialis (FDS)*	500 U	63	95.4 Units (50 to 100)	2, [1 ; 2]
	1000 U	73	196.8 Units (100 to 300)	2, [1 ; 2]
Flexor carpi radialis (FCR)*	500 U	57	92.2 Units (25 to 100)	1, [1 ; 2]
	1000 U	57	178.1 Units (80 to 300)	1, [1 ; 2]
Flexor carpi ulnaris (FCU)*	500 U	47	89.9 Units (25 to 180)	1, [1 ; 2]
	1000 U	49	171.2 Units (80 to 200)	1, [1 ; 2]
Brachialis*	500 U	60	148.5 Units (50 to 200)	2, [1 ; 2]
	1000 U	43	321.4 Units (100 to 400)	2, [2 ; 2]
Brachioradialis*	500 U	42	88.3 Units (50 to 200)	1, [1 ; 2]
	1000 U	28	172.1 Units (50 to 200)	1, [1 ; 2]
Biceps Brachii (BB)	500 U	28	106.4 Units (50 to 200)	2, [1 ; 2]
	1000 U	19	207.4 Units (100 to 400)	2, [1 ; 2]
Pronator Teres	500 U	14	81.8 Units (45 to 200)	1, [1 ; 1]
	1000 U	30	157.3 Units (80 to 200)	1, [1 ; 1]

*PTMG

The co-primary efficacy variables were muscle tone assessed by the MAS at the primary targeted muscle group at week 4 and the Physician Global Assessment (PGA) at week 4.

Table 14 Primary Endpoints (PTMG MAS and PGA) and MAS by Muscle Group at Week 4

	Placebo (N=79)	DYSPORT®	
		(500 units) (N=80)	(1000 units) (N=79)
LS Mean Change from Baseline in PTMG Muscle Tone on the MAS	-0.3	-1.2*	-1.4*
LS Mean PGA of Response to Treatment	0.7	1.4*	1.8*
LS Mean Change from Baseline in Wrist Flexor Muscle Tone on the MAS	-0.3 (n=54)	-1.4 (n=57)	-1.6 (n=58)
LS Mean Change from Baseline in Finger Flexor Muscle Tone on the MAS	-0.3 (n=70)	-0.9 (n=66)	-1.2 (n=73)
LS Mean Change from Baseline in Elbow Flexor Muscle Tone on the MAS	-0.3 (n=56)	-1.0 (n=61)	-1.2 (n=48)
LS= Least Square; *p≤0.05			

16 HOW SUPPLIED/STORAGE AND HANDLING

DYSPORT® for Injection is supplied in a sterile, single-use, glass vial. DYSPORT® must be stored under refrigeration at 2° to 8°C (36° to 46°F). Protect from light.

Do not use after the expiration date on the vial. All vials, including expired vials, or equipment used with DYSPORT® should be disposed of carefully as is done with all medical waste.

DYSPORT® contains a unique hologram on the carton. If you do not see the hologram, do not use the product. Instead contact 877-397-7671.

Cervical Dystonia and Adult Upper Limb Spasticity

500 Unit Vial

Each vial contains 500 Units of freeze-dried abobotulinumtoxinA.

Box containing 1 vial—NDC 15054-0500-1

Box containing 2 vials—NDC 15054-0500-2

300 Unit Vial

Each vial contains 300 Units of freeze-dried abobotulinumtoxinA.

Box containing 1 vial—NDC 15054-0530-6

Glabellar Lines

Each vial contains 300 Units of freeze-dried abobotulinumtoxinA.

Box containing 1 vial—NDC 0299-5962-30

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labelling (Medication Guide).

Advise patients to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking or breathing), or if any known symptom persists or worsens.

Inform patients that if loss of strength, muscle weakness, blurred vision or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

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Biopharm Ltd. Wrexham,
LL13 9UF, UK U.S.
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and
Galderma Laboratories, L.P.
Fort Worth, TX 76177 USA

MEDICATION GUIDE
DYSPO[®] (*DIS-port*)
(abobotulinumtoxinA)
for Injection

What is the most important information I should know about DYSPO[®]?

DYSPO[®] may cause serious side effects that can be life threatening including:

- **Problems breathing or swallowing**
- **Spread of toxin effects**

These problems can happen within hours, or days to weeks after an injection of DYSPO[®]. Call your doctor or get medical help right away if you have any of these problems after treatment with DYSPO[®].

1. Problems swallowing, speaking, or breathing. These problems can happen within hours, or days to weeks after an injection of DYSPO[®] usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with DYSPO[®].

○ People with certain breathing problems may need to use muscles in their neck to help them breathe. These patients may be at greater risk for serious breathing problems with DYSPO[®].

○ Swallowing problems may last for several weeks. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving DYSPO[®] have the highest risk of getting these problems.

2. Spread of toxin effects. In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:

- loss of strength and muscle weakness all over the body
- double vision
- blurred vision and drooping eyelids
- hoarseness or change or loss of voice (dysphonia)
- trouble saying words clearly (dysarthria)
- loss of bladder control
- trouble breathing
- trouble swallowing

These symptoms can happen within hours, or days to weeks after you receive an injection of DYSPO[®]. These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving DYSPO[®]?"

What is DYSPO[®]?

DYSPO[®] is a prescription medicine that is injected into muscles and used:

- to treat cervical dystonia (CD) in adults
- to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary)
- to treat increased muscle stiffness in, elbow, wrist, and finger muscles in adults with upper limb spasticity.

CD is caused by muscle spasms in the neck. These spasms cause abnormal position of the head and often neck pain. After DYSPO[®] is injected into muscles; those muscles are weakened for up to 12 to 16 weeks or longer. This may help lessen your symptoms.

Frown lines (wrinkles) happen because the muscles that control facial expression are used often (muscle tightening over and over). After DYSPO[®] is injected into the muscles that control facial expression, the medicine stops the tightening of these muscles for up to 4 months.

- It is not known whether DYSPO[®] is safe or effective in children under 18 years of age.
- It is not known whether DYSPO[®] is safe or effective for the treatment of other types of muscle spasms.
- It is not known whether DYSPO[®] is safe or effective for the treatment of other wrinkles.

Who should not take DYSPO[®]?

Do not take DYSPO[®] if you:

- are allergic to DYSPO[®] or any of the ingredients in DYSPO[®]. See the end of this Medication Guide for a list of ingredients in DYSPO[®]
- are allergic to cow's milk protein
- had an allergic reaction to any other botulinum toxin product such as Myobloc[®] (rimabotulinumtoxinB), Botox[®] (onabotulinumtoxinA), or Xeomin[®] (incobotulinumtoxinA).
- have a skin infection at the planned injection site

What should I tell my doctor before taking DYSPO[®]?

Tell your doctor about all your medical conditions, including if you:

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about DYSPO[®]?"
- have allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- have or have had a breathing problem, such as asthma or emphysema
- have or have had swallowing problems
- have or have had bleeding problems
- have diabetes

- have or have had a slow heart beat or other problem with your heart rate or rhythm
- have plans to have surgery
- had surgery on your face
- have weakness of your forehead muscles (such as trouble raising your eyebrows)
- have drooping eyelids
- have any other change in the way your face normally looks
- are pregnant or plan to become pregnant. It is not known if DYSPORT[®] can harm your unborn baby
- are breast-feeding or planning to breast-feed. It is not known if DYSPORT[®] passes into breast milk

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products. Using DYSPORT[®] with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received DYSPORT[®] in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as Myobloc[®] (rimabotulinumtoxinB), Botox[®] (onabotulinumtoxinA) or Xeomin[®] (incobotulinumtoxinA) in the past; be sure your doctor knows exactly which product you received
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take DYSPORT[®]?

- DYSPORT[®] is an injection that your doctor will give you
- DYSPORT[®] is injected into the affected muscles
- Your doctor may give you another dose of DYSPORT[®] after 12 weeks or longer, if it is needed
- If you are being treated for CD or upper limb spasticity, your doctor may change your dose of DYSPORT[®] until you and your doctor find the best dose for you
- The dose of DYSPORT[®] is not the same as the dose of any other botulinum toxin product

What should I avoid while taking DYSPORT[®]?

DYSPORT[®] may cause loss of strength or general muscle weakness, blurred vision, or drooping eyelids within hours to weeks of taking DYSPORT[®]. **If this happens, do not drive a car, operate machinery, or do other dangerous activities. See "What is the most important information I should know about DYSPORT[®]?"**

What are the possible side effects of DYSPORT[®]?

DYSPORT[®] can cause serious side effects. See "What is the most important information I should know about DYSPORT[®]?"

The most common side effects of DYSPORT[®] in people with cervical dystonia include:

- | | | |
|------------------------|----------------------------|-------------------------|
| • muscle weakness | • neck pain or muscle pain | • difficulty swallowing |
| • dry mouth | • problems speaking | • injection site pain |
| • feeling of tiredness | • eye problems | • headache |

The most common side effects of DYSPORT[®] in people with glabellar lines include:

- | | | |
|--|---------------------------|--------------------|
| • stuffy or runny nose and sore throat | • headache | • drooping eyelids |
| • injection site pain | • injection site reaction | • sinus infection |
| • upper respiratory infection | • swelling of eyelids | • nausea |

The most common side effects of DYSPORT[®] in people with upper limb spasticity include:

- | | | |
|---------------------------|--------------|--|
| • urinary tract infection | • fall | • stuffy or runny nose and sore throat |
| • muscle weakness | • depression | • dizziness |
| • musculoskeletal pain | | |

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects DYSPORT[®]. For more information, ask your doctor pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about DYSPORT[®]:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about DYSPORT[®]. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DYSPORT[®] that is written for healthcare professionals. For more information about DYSPORT[®] call 877-397-7671 or go to www.dysport.com or www.DysportUSA.com.

What are the ingredients in DYSPORT[®]?

Active ingredient: (botulinum toxin Type A)

Inactive ingredients: human albumin and lactose. DYSPORT[®] may contain cow's milk protein.

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