

Pr BOTOX COSMETIC®

Botulinum toxin type A for injection Ph. Eur.

***Clostridium botulinum* type A neurotoxin complex (900kD)**

Sterile vacuum-dried concentrate powder for solution for injection

100 Allergan units per vial

Neuromuscular Paralytic Agent

Manufactured by: Allergan, Inc.
Irvine, CA 92715

Date of Approval:
September 26, 2008

Distributed by: Allergan, Inc.
Markham, Ontario

Submission Control No: 118532

Table of Contents

[To update, right-click anywhere in the Table of Contents and select “Update Field”, “Update entire table”, click OK.]

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	7
DOSAGE AND ADMINISTRATION	10
OVERDOSAGE	13
ACTION AND CLINICAL PHARMACOLOGY	13
STORAGE AND STABILITY	15
SPECIAL HANDLING INSTRUCTIONS	15
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	16
PART II: SCIENTIFIC INFORMATION	17
PHARMACEUTICAL INFORMATION.....	17
CLINICAL TRIALS	17
DETAILED PHARMACOLOGY	19
TOXICOLOGY	19
REFERENCES	22
PART III: CONSUMER INFORMATION	24

BOTOX COSMETIC®

Botulinum toxin type A for injection Ph. Eur
Clostridium botulinum type A neurotoxin complex (900kDt)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular	Sterile vacuum-dried concentrate; powder for solution for injection; 100 Allergan units per vial	Albumin (human) <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

BOTOX COSMETIC® (Botulinum toxin type A for injection) is indicated:

- for the treatment of upper facial rhytides, including forehead, lateral canthus, and glabellar lines.

Geriatrics (> 65 years of age):

Studies specifically designed to determine the dose in elderly patients have not been performed. Dosages for the elderly are as for other adults. Initial dosing should begin at the lowest recommended dose for the specific indication.

Pediatrics (< 18 years of age):

Use of BOTOX COSMETIC® is not recommended in children.

CONTRAINDICATIONS

BOTOX COSMETIC® is contraindicated in:

- patients who are hypersensitive to botulinum toxin type A 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.
- the presence of infection at the proposed injection site(s).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The term “Allergan unit” upon which dosing is based, is a specific measurement of toxin activity that is unique to Allergan’s formulation of botulinum toxin type A. Therefore, the “Allergan units” used to describe BOTOX COSMETIC® activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX COSMETIC® activity are not interchangeable with other products.
- BOTOX COSMETIC® should only be given 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 BOTOX COSMETIC® (See **WARNINGS AND PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**).

General

BOTOX® and **BOTOX COSMETIC®** contain the same active ingredient in the same formulation. Therefore adverse events observed with the use of **BOTOX®** also have the potential to be associated with the use of **BOTOX COSMETIC®**.

Use BOTOX COSMETIC® only as directed.

Do not use dosage recommendations and potency Units applied to other botulinum toxin products when using BOTOX COSMETIC®.

The safe and effective use of BOTOX COSMETIC® (Botulinum toxin type A for injection) depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques.

Caution should be used when BOTOX COSMETIC® is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle.

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 cosmetic application.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Patients with a history of underlying neurologic disorders, dysphagia and/or aspiration 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.

Injection intervals of BOTOX COSMETIC® should be no more frequent than every two months. Indication specific dosage and administration recommendations should be followed. If combined with non-cosmetic indications, the maximum cumulative dose should generally not exceed 6 Units/kg, up to a maximum of 360 Units, in a 3 month interval

One unit (U) of BOTOX COSMETIC® corresponds to the calculated median intraperitoneal lethal dose (LD₅₀) in mice. The method utilized for performing the assay is specific to Allergan's product, BOTOX COSMETIC®. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD₅₀ assays, Units of biological activity of BOTOX COSMETIC® cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of BOTOX COSMETIC® is approximately 20 units/nanogram of neurotoxin protein complex.

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. A 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

Studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX COSMETIC®. BOTOX COSMETIC® was not mutagenic in *in vitro* and *in vivo* mutagenicity studies. (See TOXICOLOGY Section for more information.)

Cardiovascular

There have been rare reports following administration of botulinum toxin of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including preexisting cardiovascular disease. The exact relationship of these events to BOTOX COSMETIC®/BOTOX® is unknown

Immune

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX COSMETIC® treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX® injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. When appropriate, the potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available.

Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea. Some of these reactions have been reported following the use of BOTOX COSMETIC® either alone or in conjunction with other products associated with similar reactions. If such a reaction occurs, further injection should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX COSMETIC® diluted with 5 ml of 1% lidocaine. The causal role of BOTOX COSMETIC®, lidocaine, or both cannot be reliably determined.

Neurologic

Extreme caution should be exercised when administering BOTOX COSMETIC® to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuropathy) or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular junction disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX COSMETIC®. There have been rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube. **When exposed to very high doses, patients with neurologic disorders, e.g., pediatric cerebral palsy or adult spasticity, may also be at increased risk of clinically significant systemic effects.**

Ophthalmologic

In order to reduce the complications of ptosis, avoid injection near the levator palpebrae superioris, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge. To reduce the occurrence of diplopia, injections of the lateral canthal lines should be outside the bony orbit, not medial to the vertical line through the lateral canthus. To reduce the occurrence of lip ptosis, injections should be above the insertion of the zygomaticus muscles.

Skin

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope. Care should be taken when injecting near vulnerable anatomic structures.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies of BOTOX COSMETIC® administration in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown **BOTOX COSMETIC® should not be used during pregnancy.** If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks, including abortion or fetal malformations, which have been observed in rabbits.

Nursing Women: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX COSMETIC® is administered to a nursing woman.

Pediatrics (2-18 years of age): Use of BOTOX COSMETIC® is not recommended in children.

Geriatrics (> 65 years of age): Studies specifically designed to determine the dose in elderly patients have not been performed. Dosages for the elderly are as for other adults. Initial dosing should begin at the lowest recommended dose for the specific indication

Monitoring and Laboratory Tests

There are no specific requirements for laboratory test monitoring when patients are treated with BOTOX COSMETIC®.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In general, adverse reactions occur within the first few days following injection and while generally transient may have duration of several months or, in rare cases, longer.

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 cosmetic application.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localized infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

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.

Safety was evaluated in two multicenter, double-blind, placebo-controlled, parallel group studies of identical design for the treatment of glabellar lines (N=535; 405 in the BOTOX COSMETIC®-treated group and 130 in the placebo-treated group). The most frequently reported treatment-related adverse events were headache (9.4% in the BOTOX COSMETIC®-treated group and 15.4% in the placebo-treated group) and blepharoptosis (3.2% in the BOTOX COSMETIC®-treated group and 0% in the placebo-treated group). Blepharoptosis is consistent with the pharmacologic action of BOTOX COSMETIC®, and may be technique related.

Adverse events that were reported as treatment-related and were reported in 1-3% of BOTOX COSMETIC®-treated patients are listed in decreasing order of incidence: injection site pain/burning/stinging (2.5%), face pain (2.2%), erythema (1.7%), local muscle weakness (1.7%), injection site edema (1.5%), ecchymosis (1.0%), skin tightness (1.0%), paresthesia (1.0%) and nausea (1.0%). Most adverse events reported were of mild-to-moderate severity and all were transient. In a multicenter, open-label, repeat injection study, 318 patients who had participated in one of the two double-blind studies and who had glabellar line severity of at least mild severity at maximum frown received 2 additional treatments of BOTOX COSMETIC®. In this study, adverse events were comparable in type, incidence, severity, and causality to those reported in the two placebo-controlled, double-blind studies.

In clinical studies where BOTOX COSMETIC® was administered for the treatment of forehead or periorbital wrinkles, treatment-related adverse events have been consistent with those for glabellar lines. Adverse events that were reported as treatment-related after treatment of horizontal forehead lines with 16 U of BOTOX COSMETIC® include: headache (20%), bruising (10%), eyelid swelling (15%), and aching or itching forehead (10%). Injecting well above the brow reduces the risk of ptosis.

Treatment-related adverse events associated with treatment of periorbital wrinkles include mild bruising (4-25%) and headache (5.6%); these events occurred at a similar rate on the placebo-treated side. In addition, eyelid droop or shape change, and pain have been reported. Rare cases of diplopia and an asymmetric smile due to injection of zygomaticus major have been reported. These complications can be avoided with adherence to the recommended injection location (see **WARNINGS AND PRECAUTIONS AND DOSAGE AND ADMINISTRATION SECTIONS**).

Abnormal Hematologic and Clinical Chemistry Findings

No specific trends in abnormal hematologic or clinical chemistry findings have been reported.

Post-Market Adverse Drug Reactions

BOTOX[®] and BOTOX COSMETIC[®] contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of BOTOX COSMETIC[®] also have the potential to be associated with the use of BOTOX[®].

Adverse events after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, respiratory compromise, pneumonia, and/or other significant debility. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

The following other adverse events have been reported since the drug has been marketed: abdominal pain; diarrhea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance, hypoacusis; tinnitus; vertigo; facial palsy, facial paresis; brachial plexopathy; radiculopathy; syncope; hypoaesthesia; malaise; myalgia; myasthenia gravis; paraesthesia; allergic reaction, skin rash (including erythema multiforme, urticaria and psoriasiforme eruption); pruritus; hyperhidrosis; alopecia, including madarosis.

These reactions are reported voluntarily from a population of uncertain size. The exact relationship of these events to botulinum toxin is unknown.

DRUG INTERACTIONS

Overview

No specific interactions have been reported.

Drug-Drug Interactions

Proper name of drug	Ref	Effect	Clinical comment
aminoglycoside antibiotics or spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking agents, both depolarizing (succinylcholine) and non-depolarizing (tubocurarine derivatives), lincosamides, polymyxins, quinidine, magnesium sulfate, and anticholinesterases).	T	Theoretically, the effect of botulinum toxin type A may be potentiated	The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or spectinomycin, or other drugs that interfere with neuromuscular transmission (e.g. tubocurarine-type muscle relaxants). Caution should be exercised when BOTOX COSMETIC® is used with aminoglycosides (e.g. streptomycin, tobramycin, neomycin, gentamycin, netilmicin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin 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: C = Case Study; CT = Clinical Trial; 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**
- BOTOX COSMETIC® (Botulinum toxin type A for injection) should only be given by physicians with the appropriate qualifications and experience in the treatment and the use of required equipment.
- The term “Allergan unit” upon which dosing is based, is a specific measurement of toxin activity that is unique to Allergan’s formulation of botulinum toxin type A. Therefore,

the “Allergan units” used to describe BOTOX COSMETIC® activity are different from those used to describe that of other botulinum toxin preparations and the units representing BOTOX COSMETIC® activity are not interchangeable with other products.

- The use of one vial for more than one patient is not recommended because the product and diluent do not contain a preservative.
- Treatment should be initiated at the lowest recommended dose. This dose can be gradually increased in subsequent treatments to the maximum recommended dose, if needed.
- Injection intervals of BOTOX COSMETIC® should be no more frequent than every two months. Indication specific dosage and administration recommendations should be followed. In treating adult patients, if combined with non-cosmetic indications, the maximum cumulative dose should generally not exceed 6 Units/kg, up to a maximum of 360 Units, in a 3 month interval.

Recommended Dose and Dosage Adjustment

BOTOX COSMETIC® is reconstituted only with 0.9% sterile non-preserved saline. Dilutions resulting in 4.0 U - 7.0 U per 0.1 mL are generally recommended.

Glabellar lines: 4 U should be administered intramuscularly using a 30 gauge needle in each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 U. In order to reduce the complication of ptosis, injection near the levator palpebrae superioris should be avoided, particularly in patients with larger brow-depressor complexes. Medial corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

Forehead lines: 2-6 U should be injected intramuscularly at each of 4 injection sites in the frontalis muscle, every 1-2 cm along either side of a deep forehead crease, 2-3 cm above the eyebrows, for a total dose of up to 24 U.

Lateral canthus lines: Generally, 2-6 U should be injected bilaterally at each of 1-3 injection sites at a 2-3 mm depth, lateral to the lateral orbital rim, where most lines are seen when a smile is forced. Injection should be at least 1 cm outside the bony orbit, not medial to the vertical line through the lateral canthus, and not close to the inferior margin of the zygoma.

An injection of BOTOX COSMETIC® is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin (see Dilution Table) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe may be attached to the electromyographic injection needle, preferably a 1.5 inch, 27 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX COSMETIC®.

Lack of Response:

There are several potential explanations for a lack or diminished response to an individual treatment with BOTOX COSMETIC®. These may include inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders, change in pattern of muscle involvement, patient perception of benefit compared with initial results, inappropriate storage or reconstitution, as well as neutralizing antibodies to botulinum toxin. A neutralizing antibody is defined as an antibody that inactivates the biological activity of the toxin. However, there have been patients who continued to respond to therapy and demonstrated presence of neutralizing antibodies; the proportion of patients which lose their response to botulinum toxin therapy and have demonstrable levels of neutralizing antibodies is small.

The critical factors for neutralizing antibody production are the frequency and dose of injection. To reduce the potential for neutralizing antibody formation, it is recommended that injection intervals of BOTOX COSMETIC® should be no more frequent than two months. More frequent injections should not be required, as BOTOX COSMETIC® treatment reduces the severity of the facial lines for up to 120 days.

A suggested course of action when patients do not respond to BOTOX COSMETIC® injections is:

- 1) wait the usual treatment interval;
- 2) consider reasons for lack of response listed above;
- 3) more than one treatment course should be considered before classification of a patient as a non-responder;
- 4) test patient serum for neutralizing antibody presence.

Missed Dose

Missed doses may be administered as soon as is practical.

Administration

An injection of BOTOX COSMETIC® is prepared by drawing into a sterile 1.0 mL tuberculin syringe an amount of the properly diluted toxin (see Dilution Table, below) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe may be attached to the electromyographic injection needle, preferably a 1.5 inch, 27 gauge needle. Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new sterile needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX COSMETIC® .

Reconstitution:

Parenteral Products:

To reconstitute vacuum-dried BOTOX COSMETIC®, use sterile normal saline without a preservative; 0.9% Sodium Chloride Injection is the only recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since BOTOX COSMETIC® is

denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space on the label. BOTOX COSMETIC® should be administered within twenty-four hours after reconstitution.

During this time period, reconstituted BOTOX COSMETIC® should be stored in a refrigerator (2° to 8° C). Reconstituted BOTOX COSMETIC® should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

Table 6: Dilution	
Resulting dose: Units per 0.1 mL	Quantity of Diluent Added (0.9% Sodium Chloride for Injection)
	100 U Vial
7.5 U	1.3 mL
5.0 U	2.0 mL
2.5 U	4.0 mL

OVERDOSAGE

In the event of overdosage or injection error, additional information may be obtained by contacting Allergan, Inc. at (800) 433-8871.

Overdose of BOTOX COSMETIC® is a relative term and depends upon dose, site of injection, and underlying tissue properties. Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, or overdose be suspected, the person should be medically monitored for up to several weeks for progressive signs or symptoms of muscular weakness distant from the site of injection that may include ptosis, diplopia, swallowing and speech disorders, generalized weakness or respiratory failure. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BOTOX COSMETIC® (Botulinum toxin type A for injection) is a sterile, vacuum-dried form of purified botulinum neurotoxin type A complex, produced from a culture of the Hall strain of *Clostridium botulinum* grown in a medium containing N-Z amine, glucose and yeast extract. It is purified to a crystalline complex consisting of the neurotoxin, a non-toxic protein and four major hemagglutinin proteins.

BOTOX COSMETIC® blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BOTOX COSMETIC® produces partial chemical denervation of the muscle resulting in localized muscle paralysis. When chemically denervated, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus reversing muscle weakness produced by localized injection of BOTOX COSMETIC®.

One Allergan unit of BOTOX COSMETIC® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice, performed in a mouse potency assay. This assay method is specific to Allergan's product, BOTOX COSMETIC®. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD50 assays, units of biological activity of BOTOX COSMETIC® can not be compared to or converted into units of any other botulinum toxin activity. The specific activity of BOTOX COSMETIC® is approximately 20 units/nanogram of neurotoxin protein complex .

Pharmacodynamics

When injected into neck muscles, BOTOX COSMETIC® reduces both objective signs and subjective symptoms of cervical dystonia (spasmodic torticollis). These improvements include reduced angle of head turning, reduced shoulder elevation, decreased size and strength of hypertrophic muscles, and decreased pain. Based on the results of well-controlled studies, 40-58% of patients with cervical dystonia would be expected to have a significant improvement in their symptoms.

The paralytic effect on muscles injected with BOTOX COSMETIC® reduces the excessive, abnormal contractions of blepharospasm associated with dystonia.

When used for the treatment of strabismus, it has been postulated that the administration of BOTOX COSMETIC® affects muscle pairs by inducing an atrophic lengthening of the injected muscle and a corresponding shortening of the antagonist muscle.

Following injection of BOTOX COSMETIC® some distant muscles have shown increased electrophysiologic neuromuscular jitter. This effect is not associated with other types of electrophysiologic abnormalities, or with clinical signs of weakness or symptoms regarding either safety or efficacy.

In the treatment of pediatric cerebral palsy patients with dynamic equinus foot deformity due to spasticity, BOTOX COSMETIC® injections into the gastrocnemius produce an improvement in ankle position (reduction in equinus) and an improvement in gait pattern due to increased heel-to-floor contact.

In the treatment of hyperhidrosis of the axilla (N=320), BOTOX COSMETIC®-treated patients demonstrated a responder rate based on gravimetric assessment of 95% at week 1 and 82% at week 16. The mean percentage reduction in sweat production in the BOTOX COSMETIC®-

treated patients ranged from 83% at week 1 to 69% at week 16. Treatment response has been reported to persist for 4 to 7 months (average of 5.2 months) in patients (N=12) treated with 50 U per axilla. Repeat injections should be administered when effects from previous injections subside.

When used for the treatment of focal spasticity BOTOX COSMETIC® injected into upper limb muscles reduces the objective signs and subjective symptoms of spasticity. Improvements include reduction of muscle tone, increase in range of motion, and in some patients reduction of spasticity-related disability.

Pharmacokinetics

It is believed that little systemic distribution of therapeutic doses of BOTOX COSMETIC® occurs. BOTOX COSMETIC® is not expected to be presented in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, clinical studies using single fiber electromyographic techniques have shown subtle electrophysiologic findings consistent with neuromuscular inhibition (i.e. “jitter”) in muscles distant to the injection site, but these were unaccompanied by any clinical signs or symptoms of neuromuscular inhibition from the effects of botulinum toxin.

STORAGE AND STABILITY

- Store the vacuum-dried product either in a refrigerator at 2° - 8°C, or in a freezer at or below -5° C.
- Administer BOTOX COSMETIC® within 24 hours after the vial is removed from the freezer and reconstituted.
- During these 24 hours, reconstituted BOTOX COSMETIC® should be stored in a refrigerator (2° to 8° C).
- Reconstituted BOTOX COSMETIC® should be clear, colorless and free of particulate matter.
- Do not freeze reconstituted BOTOX COSMETIC®.
- At the time of use, product acceptability should be confirmed relative to the expiration date indicated on the product vial and outer box.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

BOTOX COSMETIC® is available in 100 (U) sterile vials of *Clostridium botulinum* toxin type A in a vacuum-dried form without a preservative. One Allergan unit (U) corresponds to the calculated median lethal dose (LD₅₀) in mice using reconstituted BOTOX COSMETIC® and injected intraperitoneally.

The quantities of the ingredients in each vial are listed below:

INGREDIENTS	100 Allergan U Vial
<i>Clostridium botulinum</i> toxin type A neurotoxin complex (900kD)	100 U
Human Serum Albumin	0.5 mg
Sodium Chloride	0.9 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Botulinum toxin type A for injection

Molecular formula and molecular mass: The amino acid composition of the neurotoxin complex (based on the average of three independent assays) is as follows:

Asx₁₄₄₂Thr₄₈₅Ser₅₃₁Glx₇₁₉Pro₂₃₇Gly₃₉₅Ala₃₄₁Val₃₉₀Cys₁₀₃Met₈₄Ile₆₄₄Leu₇₁₈Tyr₄₉₉Phe₃₅₆Lys₄₈₆His₄₇Arg₂₄₁Trp₁₁₅ where Asx represents a mixture of Asn and Asp, and Glx represents a mixture of Gln and Glu.

900kD

Structural formula: The Purified Neurotoxin Complex is a 900 kD complex composed of a 150 kD neurotoxin, a 130 kD non-toxic, non-hemagglutinating protein, and various hemagglutinins ranging between 14 and 48 kD. The 150 kD neurotoxin is produced as a single-chain polypeptide. The polypeptide is activated by the proteolytic enzymes of *C. botulinum* during fermentation in a process known as nicking, which converts the single-chain polypeptide into a di-chain polypeptide comprised of a 97 kD heavy chain linked by a disulfide bond to a 53 kD light chain. The complete amino acid sequence of the neurotoxin was derived from a cloned DNA sequence. The neurotoxin, before nicking, consists of 1296 amino acids (1295 after the Met at the N-terminus is cleaved). Ten amino acid residues, from Leu₄₃₈ - Lys₄₄₇, are removed during nicking.

One Allergan unit (U) of BOTOX COSMETIC® corresponds to the calculated median intraperitoneal lethal dose (LD₅₀) in mice. The method utilized for performing the assay is specific to Allergan's product, BOTOX COSMETIC®. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD₅₀ assays, Units of biological activity of BOTOX COSMETIC® cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes precludes extrapolation of animal-dose activity relationships to human dose estimates. The specific activity of BOTOX COSMETIC® is approximately 20 units/nanogram of neurotoxin protein complex.

CLINICAL TRIALS

In a clinical study, the safety and efficacy of BOTOX COSMETIC® (Botulinum Toxin Type A For Injection) was compared with placebo for the treatment of glabellar lines. BOTOX COSMETIC® was administered to 203 subjects as a single treatment of intramuscular injections at 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle. Each injection was 0.1 mL (4 U), for a total of 0.5 mL (20 U). The following was concluded:

- >80% of subjects responded to treatment as rated by investigators and >90% by self-assessment
- For both primary efficacy variables, the investigator's rating of glabellar line severity at maximum frown and the subject's global assessment of change of appearance of glabellar lines, there was a statistically and clinically significant higher responder rate with BOTOX COSMETIC® than with placebo at all timepoints from day 7 through day 120 (p<0.001).
- For the investigator's rating of glabellar line severity at rest, there was a significantly higher responder rate with BOTOX COSMETIC® than with placebo at all timepoints.
- Subgroup analyses of the primary efficacy variables by age group (≤50 years and >51 years) and by investigator gave results similar to those for the overall study population.
- Subjects rated their impression of improvement even more highly than did the investigators, particularly later in the study. By day 120, 44.1% of subjects rated their appearance as at least moderately improved.
- BOTOX COSMETIC® was shown in this study to be well-tolerated, with no treatment-related serious adverse events.

The safety and efficacy of BOTOX COSMETIC® for the treatment of horizontal forehead lines has been described in published investigator clinical studies. BOTOX COSMETIC® was administered to 59 subjects as a single treatment of intramuscular injections at injection doses into the frontalis of 8, 16 and 24 U. The following was concluded:

- Approximately 90% of subjects responded to treatment as rated by investigators and up to 75-80% by self-assessment.
- There was a reduction in horizontal rhytide severity in all three BOTOX COSMETIC® treatment groups at both contraction and repose.
- There was a significant dose-response trend for rate of improvement at maximum brow elevation: 53% in the 24 U group versus 15% in the 8 U group at 16 weeks, by a trained observer.
- There was a significant dose-response trend for rate of relapse to baseline: 35% in the 24 U group versus 75% in the 8 U group at 16 weeks, by a trained observer.
- BOTOX COSMETIC® was shown in this study to be well-tolerated, with no treatment-related serious adverse events. The most common treatment-related adverse events were headache, local pain and swelling resulting from injection.

In another published investigator clinical study, the safety and efficacy of BOTOX COSMETIC® was compared with placebo for the treatment of lateral canthal lines (crow's feet). BOTOX COSMETIC® was administered to 60 subjects in orbicularis oculi muscle as a single injection treatment at one of 3 doses (6, 12 and 18 U total) on one side, and placebo contralaterally. In a second study of lateral canthal lines, BOTOX COSMETIC® (5-15 U) was injected on each side in 80 subjects. The following was concluded:

- BOTOX COSMETIC® was associated with significantly higher success rates than placebo at all dose levels, as determined by both trained observers and patients.
- At four weeks post-injection, 89-95% patients on the BOTOX COSMETIC®-treated side were considered by investigators as treatment responders, and 60-80% of patients felt they had treatment success, compared to approximately 5-15% and 15-45%, respectively on the placebo-treated side.

- No clear dose-response relationship was observed.
- Benefits of the second injection lasted longer than the first. The success rate of a second injection reached 100% for the 12 and 18 U groups, and approximately 80% of patients were considered treatment successes at 16 weeks, for all groups.
- Patient surveys revealed high satisfaction with BOTOX COSMETIC® treatments; 89% described themselves as satisfied or very satisfied; 93% indicated they would undergo treatment again.
- BOTOX COSMETIC® was well tolerated. No serious or severe adverse events were reported. The most common adverse event related to treatment was bruising; the incidence was similar on the placebo-treated side.

DETAILED PHARMACOLOGY

BOTOX COSMETIC® (Botulinum toxin type A for injection) blocks neuromuscular transmission by binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX COSMETIC® produces partial chemical denervation of the muscle resulting in localized reduction in muscle activity and possible muscle atrophy. When chemically denervated, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus reversing muscle denervation produced by localized injection of BOTOX COSMETIC®.

TOXICOLOGY

Mutagenicity Studies:

BOTOX COSMETIC® (Botulinum toxin type A for injection) was not mutagenic in the *in vitro* Ames microbial mutagen test with or without metabolic activation at a maximum concentration of 42.9 U/plate using tester strains of *Salmonella typhimurium* and *Escherichia coli*. No increases in the average mutant frequencies were seen in *in vitro* evaluations of BOTOX COSMETIC® at dosages as high as 43.0 U/plate (approximately 100,000 times the maximum anticipated clinical dose, based upon 360 U/60 kg person) with and without metabolic S9 activation in AS52/XPRT mammalian cells. No chromosomal aberrations were produced in *in vitro* evaluations of BOTOX COSMETIC® in Chinese hamster ovary cells at dosages as high as 43.0 U/kg with and without metabolic activation. No clastogenic effects were observed in *in vivo* micronucleus evaluations of BOTOX COSMETIC® in mice at doses as high as six to seven times the maximum anticipated human dose.

Fertility and Reproductive Toxicity:

A fertility and reproductive toxicity study with BOTOX COSMETIC® was evaluated in rats. No effects on reproduction were observed following intramuscular injection of BOTOX COSMETIC® at dosages of 4 U/kg (approximately 2/3 of the maximum recommended human dose) in male rats and at dosages of 8 U/kg in female rats. Higher dosages (8 and 16 U/kg) were associated with dose-dependent reductions in fertility in male rats, and the cohabitation period was slightly increased at dosages of 16 U/kg. Altered estrous cycling (prolonged diestrus) and interrelated reductions in fertility occurred in the female rats dosed with 16 U/kg.

Teratogenic Effects:

The teratogenic effects of BOTOX COSMETIC® were evaluated in mice, rats and rabbits. No teratogenic effects were observed when presumed pregnant mice were injected intramuscularly with doses of 4 U/kg (approximately 2/3 of the maximum recommended human dose) and 8 U/kg on days 5 and 13 of gestation; however, dosages of 16 U/kg induced a slightly lower fetal body weight. No teratogenic effects were observed in rats when injected intramuscularly with doses of 16 U/kg on days 6 and 13 of gestation, and 2 U/kg/day on days 6 through 15 of gestation. In rabbits, daily injections at dosages of 0.5 U/kg/day (days 6 through 18 of gestation) and 4 and 6 U/kg (days 6 and 13 of gestation) caused death and abortions among surviving animals. External malformations were observed in the fetus in one 0.125 U/kg/day and one 2 U/kg dosage. The rabbit appears to be a more sensitive species to BOTOX COSMETIC®.

Reproductive and Developmental Effects:

The reproductive and developmental effects of BOTOX COSMETIC® were evaluated in rats at dose levels of 4, 8 and 16 U/kg. Muscle atrophy at the injected site, reduced body weight gains and reduced absolute feed consumption were observed following intramuscular injection of BOTOX COSMETIC® at dosages of 4 U/kg and higher on days 5 and 13 of presumed gestation, and day 7 of lactation. No effects on maternal reproductive performance were observed at the highest dose tested, 16 U/kg (approximately three times the maximum recommended human dose). No adverse effects on development of the pups was observed at 4 U/kg; however, higher dosages were associated with reduced pup body weight and/or pup viability at birth.

Animal Toxicology Studies:

There were no observable toxic effects in rats that received a single intravenous or intramuscular injection of 5 U/kg of BOTOX COSMETIC®, and in monkeys that received 8 U/kg intramuscularly.

In a one year study where monkeys received seven intramuscular injections (once every two months), there were no observable toxic effects at a BOTOX COSMETIC® dosage level of 4 U/kg (approximately 2/3 of the maximum recommended human dose). Three out of six female monkeys in the 16 U/kg group were sacrificed in extremis. This probably was a treatment-related effect of high doses of BOTOX COSMETIC®. Local muscle atrophy and degeneration at the injection site (expected pharmacological effects) were observed in all BOTOX COSMETIC® treated monkeys. There was evidence of systemic toxicity in animals treated with 8 U/kg and 16 U/kg. No antibodies were detected in the sera of animals during the study. In a 20 week study where juvenile monkeys received a series of three im injection sessions (each session divided into four sites, distributed bilaterally into the heads of the gastrocnemius muscles, and given at 8 week intervals), the NOEL was at a BOTOX COSMETIC® dosage level of 8 U/kg. Local pharmacologic effects were observed in all BOTOX COSMETIC®-treated animals and included decreases in size and weights of the injected site (gastrocnemius muscles) and microscopic observations of muscle fiber atrophy with occasional involvement of the underlying soleus muscle. Systemic effects included a slight transient decrease in body weight gains in animals receiving 12 U/kg.

Antigenicity:

Antigenicity studies in rats and guinea pigs showed no effects. In an indirect hemagglutination assay, mice were immunized once per week for two weeks. Both the placebo (human serum albumin) and BOTOX COSMETIC® were antigenic when Complete Freund's Adjuvant (CFA) was used. No antigenicity was detected without the adjuvant.

Ocular or dermal irritation:

No ocular or dermal irritation was observed in rabbits at concentrations of BOTOX COSMETIC® up to 200 U/mL.

REFERENCES

1. Blitzer A, Binder W, Aviv J, Keen M, Brin M. The management of hyperfunctional facial lines with botulinum toxin- A collaborative study of 210 injection sites in 162 patients. *Arch Otolaryngol Head Neck Surg* 1997;123:389-392.
2. Carruthers A and Carruthers J. *Chapter 20: Botulinum toxin and laser resurfacing for lines around the eyes. In: Management of Facial Lines and Wrinkles.* Binder J, Boyd J B and Carruthers A, ed. Lippincott Williams and Wilkens, Philadelphia, 2000.
3. Carruthers A and Carruthers J. Botulinum toxin in the treatment of glabellar frown lines and other facial wrinkles. *In: Neurological Disease and Therapy. Therapy with Botulinum Toxin.* Jankovic J and Hallett M, ed. New York: Marcel Dekker 1994;25:577-595.
4. Carruthers A and Carruthers J. Botulinum Toxin Type A in the treatment of hyperfunctional facial lines and cosmetic disorders. *In: MF Brin, J Jankovic, M Hallett (eds.) Scientific and Therapeutic Aspects of Botulinum Toxin.* Pennsylvania: Lippincott Williams and Wilkens, 2002: Chapter 27, p. 287-93.
5. Carruthers A and Carruthers J. Clinical indications and injection technique for the cosmetic use of Botulinum A exotoxin. *J Dermatol Surg* 1998;24:1189-94.
6. Carruthers A, Carruthers J, and Cohen J. A prospective, double-blind, randomized, parallel-group, dose-ranging study of *botulinum* toxin type A in female subjects with horizontal forehead rhytides. *Dermatol Surg* 2003 May;29(5):461-7.
7. Ellis DAF and Tan AKW. Cosmetic upper-facial rejuvenation with botulinum. *J Otolaryngol* 1997;26:92-96.
8. Garcia A and Fulton JE Jr. Cosmetic denervation of the muscles of facial expression with botulinum toxin A- Dose-response study. *Dermatol Surg* 1996;22(1): 39-43.
9. Guerrissi J and Sarkissian P. Local injection into mimetic muscles of botulinum toxin A for the treatment of facial lines. *Ann Plastic Surg* 1997;39:447-53.
10. Hankins CL, Strimling R and Rogers GS. Botulinum A toxin for glabellar wrinkles: Dose and response. *Dermatol Surg* 1998;24 (11):1181-3.
11. Keen M, Blitzer A, Aviv J, Binder W, Prystowsky J, Smith H et al. Botulinum toxin A for hyperkinetic facial lines: Results of a double-blind placebo-controlled study. *Plast Reconstr Surg* 1994a;94:94-9.
12. Keen M, Kopelman JE, Aviv JE, Binder W, Brin M, and Blitzer A. Botulinum toxin A: A novel method to remove periorbital wrinkles. *Facial Plast Surg* 1994b;10:141-146.

13. Koch RJ, Troell R and Goode R. Contemporary management of the aging brow and forehead Laryngo-scope 1997; 107:710-5.
14. Lowe NJ, Maxwell A and Harper H. Botulinum A exotoxin for glabellar folds: A double-blind, placebo-controlled study with an electromyo-graphic injection technique. Am Acad Dermatol 1996;35:569-72.
15. Lowe NJ, Lask Gary, Yamauchi Paul and Moore Donna. Bilateral, double-blind, randomized comparison of 3 doses of *botulinum* toxin type A and placebo in patients with crow's feet. J Am Acad Dermatol 2002 Dec;47(6):834-40.
16. Niamtu J. 3rd Botulinum toxin A: A review of 1,085 oral and maxillofacial patient treatments. (1998-2001) J Oral Maxillofac Surg 2003;61(3):317-24.

PART III: CONSUMER INFORMATION
BOTOX COSMETIC®
(Botulinum toxin type A for injection)

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

ABOUT THIS MEDICATION

What it is used for:

BOTOX COSMETIC® is used to treat upper facial lines, including forehead, crow's feet, and frown lines.

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 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:

Botulinum toxin type A for injection is a sterile, form of purified botulinum neurotoxin type A complex

What the important nonmedicinal ingredients are:

Albumin (human) and sodium chloride.

WARNINGS AND PRECAUTIONS

BEFORE you receive **BOTOX COSMETIC®** 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 **BOTOX COSMETIC®**.
- you have an infection at a proposed injection site.
- you are scheduled to have surgery using a general anaesthetic
- you are taking or are likely to take antibiotics, especially aminoglycoside antibiotics
- you are pregnant or become pregnant while taking this drug. Repeated doses of **BOTOX COSMETIC®** given to rabbits during pregnancy have caused abortion or fetal malformations.
- you are nursing. It is not known whether this drug is excreted in human milk, but many drugs are excreted in human milk.

BOTOX COSMETIC® is for intramuscular use only.

BOTOX COSMETIC® should only be given by a physician with the appropriate qualifications and experience in the treatment and the use of required equipment

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

Tell your doctor if you experience any difficulties in swallowing food while on **BOTOX COSMETIC®**, 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 any you have bought at your pharmacy, supermarket or health food shop.

INTERACTIONS WITH THIS MEDICATION

The effect of **BOTOX COSMETIC®** 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

General

Pain, tenderness and/or bruising at the site of injection. Malaise (generally feeling unwell), lasting up to six weeks after injection with **BOTOX COSMETIC®**. Weakness and rarely, changes in the way the heart beats, chest pain, skin rash and allergic reaction (symptoms: shortness of breath, wheezing or difficulty breathing; swelling of the face, lips, tongue or other parts of the body; rash, itching or hives on the skin).

The following events have been reported rarely (<0.1%) since **BOTOX COSMETIC®** has been marketed: skin rash, itching, allergic reaction (including anaphylaxis), dysphagia, respiratory compromise, seizures, and facial paralysis. There have also been rare reports after botulinum toxin treatment of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors, including cardiovascular disease.

*This is not a complete list of side effects. For any unexpected effects while taking **BOTOX COSMETIC®**, contact your doctor or pharmacist.*

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: cadmp@hc-sc.gc.ca

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness

Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Allergan at: 1-877-255-3746

The HPFB (BGTD and TPD) website address is to be included in this section. The sponsor also has the option of including their company website address.

This leaflet was prepared by Allergan

Last revised: September 23, 2008
