[Pr]BOTOX COSMETIC®

onabotulinumtoxinA for injection Ph. Eur.

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

Sterile vacuum-dried concentrate powder for solution for injection

50, 100 and 200 Allergan units per vial

Neuromuscular Paralytic Agent

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION 3
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 3
WARNINGS AND PRECAUTIONS 4
ADVERSE REACTIONS 8
DOSAGE AND ADMINISTRATION 11
OVERDOSAGE 14
ACTION AND CLINICAL PHARMACOLOGY 15
STORAGE AND STABILITY 16
SPECIAL HANDLING INSTRUCTIONS 16
DOSAGE FORMS, COMPOSITION AND PACKAGING 16

PART II: SCIENTIFIC INFORMATION 18
PHARMACEUTICAL INFORMATION 18
CLINICAL TRIALS 18
DETAILED PHARMACOLOGY 20
TOXICOLOGY 20
REFERENCES 23

PART III: CONSUMER INFORMATION 25

BOTOX COSMETIC®

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

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; 50, 100 and 200 Allergan units per vial	Albumin (human) *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

BOTOX COSMETIC® **(**onabotulinumtoxinA 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 any 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**).
- DISTANT SPREAD OF TOXIN EFFECT: The effects of BOTOX COSMETIC® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

General

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® (onabotulinumtoxinA for injection) depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques.

Physicians administering BOTOX COSMETIC® should be familiar with the relevant anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received **BOTOX®** injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of **BOTOX®** near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

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.

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.

Progressive signs or symptoms of muscular weakness remote to the site of injection may include ptosis and diplopia, as well as other serious adverse effects including swallowing and speech disorders, generalized weakness or respiratory failure. In addition, certain adverse effects (e.g., dysphagia, aspiration pneumonia) have been rarely reported in both pediatric and adult patients, some of which have been associated with a fatal outcome.

When exposed to very high doses, patients with neurologic disorders, e.g. pediatric cerebral palsy or adult spasticity, may be at increased risk of clinically significant systemic effects.

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 three months. Indication specific dosage and administration recommendations should be followed. If combined with non-cosmetic indications, the maximum cumulative dose in a 3 month interval should generally not exceed 6 Units/kg or 360 Units, whichever is lower.

The primary release procedure for BOTOX COSMETIC® uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's product BOTOX COSMETIC®. One Allergan Unit (U) of BOTOX COSMETIC ® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols, 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. 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 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 pre-existing 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, hypoe sthesia, 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.

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 of BOTOX COSMETIC® specifically designed to determine the dose in elderly patients have not been performed. Dosages for the elderly are as for other adults. In addition, aggregate review of BOTOX® post-marketing and clinical trial safety reports showed that, in general, the risk of adverse events is comparable between the elderly and younger population. In general, dose selection for an elderly patient should be cautious, usually starting 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, hypoesthesia, 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, regardless of indication, include rare spontaneous reports of death, sometimes associated with dysphagia, respiratory compromise, pneumonia, and/or other significant debility. There have also been 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. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The reports in children were predominantly from cerebral palsy patients treated for spasticity. The exact relationship of these events to the botulinum toxin injection has not been established.

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® either alone or in conjunction with other products associated with similar reactions. One fatal case of anaphylaxis has been reported in which the patient died after being injected with BOTOX® inappropriately diluted with 5 ml of 1% lidocaine. The causal role of BOTOX®, lidocaine, or both cannot be reliably determined.

The following list of adverse drug reactions or other medically relevant adverse events have been reported since the drug has been marketed, regardless of indication, and may be in addition to those cited in the WARNING AND PRECAUTIONS, and Clinical Trials Adverse Drug Reactions sections: denervation/muscle atrophy; respiratory depression and/or respiratory failure; dyspnea; aspiration pneumonia; dysarthria; dysphonia; dry mouth; strabismus; peripheral neuropathy; abdominal pain; diarrhea; nausea; vomiting; pyrexia; anorexia; vision blurred; visual disturbance; hypoacusis; tinnitus; vertigo; facial palsy; facial paresis; brachial plexopathy; radiculopathy; syncope; hypoesthesia; malaise; myalgia; myasthenia gravis; paresthesia; allergic reaction; skin rash (including erythema multiforme, urticarial, dermatitis psoriasiform, and psoriasiforme eruption); pruritus; hyperhidrosis; alopecia, including madarosis; worsening of migraine.

Angle closure glaucoma has been reported very rarely following BOTOX® treatment for blepharospasm.

Lagophthalmos has been reported following BOTOX COSMETIC® injection into the glabellar lines or crow's feet lines.

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

Table 1: Established or Potential 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. tubocuraine-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® **(**onabotulinumtoxinA 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. The exact dosage and number of injection sites should be tailored to the patient's needs based on the size, number and location of muscles involved, presence of local muscle weakness, response to previous treatment, and the patient's medical condition.

- Injection intervals of BOTOX COSMETIC® should be no more frequent than every three months. Indication specific dosage and administration recommendations should be followed. In treating adult patients, if combined with non-cosmetic indications, the maximum cumulative dose in a 3 month interval should generally not exceed 6 Units/kg, or 360 Units, whichever is lower.

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 (2º to 8º 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 2: Dilution

Resulting dose: Units per 0.1 mL	**Quantity of Diluent Added (0.9% Sodium Chloride for Injection)**		
	50 U Vial	**100 U Vial**	**200 U Vial**
7.5 U	0.7 mL	1.3 mL	2.6 mL
5.0 U	1.0 mL	2.0 mL	4.0 mL
2.5 U	2.0 mL	4.0 mL	8.0 mL

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

OVERDOSAGE

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

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. Excessive doses may produce local, or distant, generalized and profound neuromuscular paralysis. 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.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

BOTOX COSMETIC® (onabotulinumtoxinA 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®.

The primary release procedure for BOTOX COSMETIC® uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's product BOTOX COSMETIC®. One Allergan Unit (U) of BOTOX COSMETIC® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols, Units of biological activity of BOTOX COSMETIC® cannot 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

No formal pharmacodynamic studies have been conducted with BOTOX COSMETIC® (onabotulinumtoxinA) for injection.

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 2º - 8ºC, or in a freezer at or below -5º 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 (2º to 8º 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 in direct contact with the drug should be disposed of as medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of dilute hypochlorite solution (0.5% or 1%) for five minutes is recommended prior to disposal as medical waste.

DOSAGE FORMS, COMPOSITION AND PACKAGING

BOTOX COSMETIC® is available in 50, 100 and 200 unit (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 (LD_{50}) in mice using reconstituted BOTOX COSMETIC® and injected intraperitoneally.

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

INGREDIENTS	**50 Allergan U Vial**	**100 Allergan U Vial**	**200 Allergan U Vial**
Clostridium botulinum toxin type A neurotoxin complex (900kD)	50 U	100 U	200 U
Human Serum Albumin	0.25 mg	0.5 mg	1.0 mg
Sodium Chloride	0.45 mg	0.9 mg	1.8 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: OnabotulinumtoxinA for injection

Molecular formula: The amino acid composition of the neurotoxin complex (based on the average of three independent assays) is as follows: $Asx_{1442}Thr_{485}Ser_{531}Glx_{719}Pro_{237}Gly_{395}Ala_{341}Val_{390}Cys_{103}Met_{84}Ile_{644}Leu_{718}Tyr_{499}Phe_{356}Lys_{486}His_{47}Arg_{241}Trp_{115}$ where Asx represents a mixture of Asn and Asp, and Glx represents a mixture of Gln and Glu.

Molecular mass: 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 Leu_{438} - Lys_{447}, are removed during nicking.

The primary release procedure for BOTOX COSMETIC® uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's product BOTOX COSMETIC®. One Allergan unit (U) of BOTOX COSMETIC® corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay such as the vehicle, dilution scheme and laboratory protocols, 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. 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® (onabotulinumtoxinA 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® (onabotulinumtoxinA 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 aceylcholine receptors may develop. There is evidence that reinneration of the muscle may occur, thus reversing muscle denervation produced by localized injection of BOTOX COSMETIC®.

TOXICOLOGY

Mutagenicity Studies:
BOTOX COSMETIC® (onabotulinumtoxinA 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 were 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.

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PART III: CONSUMER INFORMATION
BOTOX COSMETIC®
(onabotulinumtoxinA 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:
OnabotulinumtoxinA 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.

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

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.

PROPER USE OF THIS MEDICATION

Overdose:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9

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

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Allergan Inc. at: 1-800-668-6424.

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