PRODUCT MONOGRAPH

PrXEOMIN COSMETIC®

incobotulinumtoxinA for injection

Clostridium Botulinum Neurotoxin Type A (150 kD), free from complexing proteins
100 units per vial

Pharmaceutical Standard: House

Muscle relaxant, peripherally acting agent

Manufactured by: Merz Pharmaceuticals GmbH
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60318 Frankfurt/Main
Germany

Date of Initial Approval:
April 12, 2012

http://www.merz.com/company/merz_pharmaceuticals/

Imported and distributed by:
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	incobotulinumtoxinA for injection 100 units per vial	None *For a complete listing see* ***Dosage Forms, Composition and Packaging*** *section.*

DESCRIPTION

Xeomin Cosmetic® (incobotulinumtoxinA) is produced by the anaerobic bacterial fermentation process from the Hall strain of *Clostridium botulinum*. It consists of the purified neurotoxin which has been separated from complexing proteins (hemagglutinins and a non-toxic non-hemagglutinating protein) during production. It is a polypeptide comprised of a heavy chain, with a molecular weight of approximately 100 kD, and a light chain, with a molecular weight of approximately 50 kD. These separated chains are covalently linked via a disulphide bond. The light chain is associated with a zinc ion and functions as a zinc-dependent endopeptidase. The heavy chain comprises two functional domains: the N-terminal section is the translocation domain and the C-terminal section is the binding domain.

Xeomin Cosmetic® is supplied as a sterile, white, preservative free powder for solution for injection (lyophilisate) packed under nitrogen in glass vials. The vials are closed with rubber stoppers and aluminum caps. Each vial contains 100 units of incobotulinumtoxinA (*Clostridium Botulinum* Neurotoxin Type A (150 kD), free from complexing proteins), 4.7 mg of sucrose and 1.0 mg of human albumin. One unit corresponds to the median lethal dose (LD_{50}) in mice or the equivalent cell-based potency units. Prior to use Xeomin Cosmetic® is reconstituted with commercially available 0.9 % physiological saline (not supplied in the pack) to form a clear, and colorless solution. The size of the vials allows different concentrations (i.e. doses) to be prepared.

INDICATIONS AND CLINICAL USE

XEOMIN COSMETIC® is indicated in adults for:

- the temporary improvement in the appearance of moderate to severe horizontal forehead lines, lateral canthal lines, and glabellar lines.

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

Pediatrics (< 18 years of age):
XEOMIN COSMETIC® has not been studied in the pediatric population and is therefore not recommended in this age group.

CONTRAINDICATIONS

- Hypersensitivity to Botulinum neurotoxin type A or to any of the excipients.
- Infection or inflammation at the proposed injection site(s).
- Generalized disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The term "unit" or "U" upon which dosing is based, is a specific measurement of toxin activity that is unique to MERZ Pharmaceuticals GMBH's formulation of Xeomin Cosmetic®. Therefore, the "unit" or "U" used to describe Xeomin Cosmetic's® activity are different from those used to describe that of other botulinum toxin preparations and the units representing Xeomin Cosmetic's® activity are not interchangeable with other products.
- Xeomin 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 Xeomin Cosmetic® (see **DOSAGE AND ADMINISTRATION**).
- DISTANT SPREAD OF TOXIN EFFECT: The effects of Xeomin 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 hour 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

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

Use Xeomin Cosmetic® only as directed.

The safe and effective use of Xeomin Cosmetic® depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques.

Prior to administering Xeomin Cosmetic®, the physician must familiarize himself/herself with the patient's anatomy and any alterations to the anatomy. Care should be taken to ensure that Xeomin Cosmetic® is not injected into a blood vessel. Failure to correctly target the desired musculature through misplaced applications may result in apparent lack of efficacy.

If proposed injection sites are marked with a pen, Xeomin Cosmetic® must not be injected through the pen marks; otherwise a permanent tattooing effect may occur.

Injection intervals of Xeomin Cosmetic® should generally be no more frequent than every three

months although injection intervals need to be tailored to patient needs. Indication specific dosage and administration recommendations should be followed.

This product contains human albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. The theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for human albumin.

Hematologic

Xeomin Cosmetic® is administered by intramuscular injection. Care should be taken to minimize injection site related trauma. Xeomin Cosmetic® should be used with caution

- if bleeding disorders of any type exist
- in patients receiving anticoagulant therapy or taking other substances in anticoagulant doses.

Hypersensitivity Reactions

Hypersensitivity reactions have been reported with Botulinum neurotoxin products. If serious (e.g. anaphylactic reactions) and/or immediate hypersensitivity reactions occur, appropriate medical therapy should be instituted.

Immune

The risks for development of neutralizing antibodies to Botulinum toxins have been reported to be related to high dosage, too frequent injections, and higher total dosage received of Botulinum toxin. Antibody development may lead to treatment failure (see **DOSAGE AND ADMINISTRATION**).

Local and Distant Spread of Toxin Effect

Symptoms of local spread of toxin effects such as eyelid ptosis and facial paresis were reported in clinical studies for treatment of a single type of upper facial line or combined upper facial lines (horizontal forehead lines, lateral canthal lines, and glabellar lines). The combined treatment of three upper facial lines may increase the risk of toxin spread to distal areas, such as the oral pharyngolaryngeal region (see **Clinical Trial Adverse Drug Reactions**). Patients should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

Ophthalmologic

In order to reduce the complications of blepharoptosis, avoid injection near the levator palpebrae superioris and into the cranial portions of the orbicularis oculi, particularly in patients with larger brow depressor complexes. Medial corrugator injections should be placed in the central portion of the muscle belly at least 1 cm above the bony supraorbital ridge.

Pre-existing Neuromuscular Disorders

The injection of Xeomin Cosmetic® is not recommended for patients with a history of dysphagia and aspiration.

Xeomin Cosmetic® should be used with caution:

- In patients suffering from amyotrophic lateral sclerosis (ALS)
- In patients with other diseases which result in peripheral neuromuscular dysfunction
- In targeted muscles which display pronounced weakness or atrophy.

Monitoring and Laboratory Tests

There are no specific requirements for laboratory test monitoring when patients are treated with Xeomin Cosmetic®.

Special Populations

Pregnant Women: There have been no studies in pregnant women. Studies in animals have shown reproductive toxicity (see **TOXICOLOGY**). The potential risk for humans is unknown.

Xeomin Cosmetic® should not be used during pregnancy.

Nursing Women: It is not known whether Botulinum neurotoxin type A is excreted into the breast milk. Therefore, the using of Xeomin Cosmetic® during lactation is not recommended.

Pediatrics (<18 years of age): Xeomin Cosmetic® has not been studied in the pediatric population and is therefore not recommended in this age group.

Geriatrics (> 65 years of age):

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In general, adverse drug reactions to Xeomin Cosmetic® occur within the first few days following injection and are generally transient, however, in some cases may last for several months.

In Studies 6 and 7, the overall incidence of adverse reactions did not increase with increasing numbers of treatment sessions when there was a 120-day interval between two treatment sessions.

Local muscle weakness represents the expected pharmacological action of botulinum toxin. Symptoms of local spread of toxin effects such as eyelid ptosis and facial paresis were reported in clinical studies for treatment of a single type of upper facial line or combined upper facial lines (horizontal forehead lines, lateral canthal lines, and glabellar lines). The combined

treatment of three upper facial lines may increase the risk of toxin spread to distal areas, such as the oral pharyngolaryngeal region (see **Clinical Trial Adverse Drug Reactions**).

Serious and/or immediate hypersensitivity reactions including anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea have been rarely reported.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Glabellar Lines

There were three Phase 3, placebo-controlled trials conducted in 803 subjects with glabellar line treatment in which 535 subjects received a single dose of 20 units Xeomin Cosmetic® and 268 subjects received placebo.

A summary of subjects with adverse reactions ≥ 1 % in glabellar line studies is presented in Table 1. Table 2 shows a summary of adverse reactions in < 1% of patients.

Table 1: Adverse Reactions Reported in ≥ 1% of Glabellar Line Patients (Greater than Placebo)

System Organ Class **Preferred term**	**Xeomin Cosmetic®** **(20 units)** **(N=535)** **n (%)**	**Placebo** **(N=268)** **n (%)**
Patients with Adverse Reactions	46 (8.6%)	10 (3.7%)
Nervous System Disorder Headache	27 (5%)	5 (1.9%)

Table 2: Adverse Reactions Reported in < 1% of Glabellar Line Patients (Greater than Placebo)

System Organ Class Preferred term	Xeomin Cosmetic®* (20 units) (N=535) n (%)	Placebo (N=268) n (%)
Nervous System Disorder Facial paresis	4 (0.7%)	0
General Disorders and Administration Site Conditions Injection site hematoma	4 (0.7%)	1 (0.4%)

*The cut-off for the table of ADRs reported in < 1% of glabellar line patients has been set to at least 2 Xeomin Cosmetic® subjects (0.4%) (greater than placebo).

In a prospective, open-label, multicenter, repeat-dose trial, 796 patients who had completed one of 4 prospective, randomized, double-blind, placebo-controlled, multicenter trials and who had at least moderate glabellar line severity received up to 8 additional treatments. The most common adverse drug reactions were headache (3.5%), injection site hematoma (0.5%), injection site pain (0.5%), eyelid edema (0.3%), and eyelid ptosis (0.3%). In this study the adverse events remained fairly constant in each subsequent cycle, indicating a stable safety pattern after repeated dosing.

Additional adverse reactions from pooled placebo-controlled, single-dose studies were: facial (brow) asymmetry, discomfort (heavy feeling of the eyelid/eyebrow), local tenderness, fatigue, muscle disorders (elevation of eyebrow), muscle spasms (above eyebrows), vision blurred, and nasopharyngitis.

Lateral Canthal Lines

In the placebo-controlled, single-dose study (Study 5, see **CLINICAL TRIALS**), adverse reactions were reported for 6 of 83 patients (7.2%) in the Xeomin Cosmetic® group (a single dose of 12 units per lateral eye area), compared to 0 of 28 patients in the placebo group. A summary of patients with adverse reactions ≥ 1% in the lateral canthus lines study is presented in Table 3.

Table 3: Adverse Reactions Reported in ≥ 1% of Lateral Canthus Line Patients (Greater than Placebo)

System Organ Class Preferred term	Xeomin Cosmetic ® (24 units) (N=83) n (%)	Placebo (N=28) n (%)
Patients with Adverse Reactions	6 (7.2%)	0
Eye Disorders		
Eye lid edema	3 (3.6%)	0
Dry eye	1 (1.2%)	0
Eye pain	1 (1.2%)	0
General Disorders and Administration Site Conditions		
Injection site hematoma	2 (2.4%)	0
Skin and Subcutaneous Tissue Disorders		
Vitiligo	1 (1.2%)	0

Upper Facial Lines (UFL)

Two clinical studies were conducted to investigate the efficacy and safety of combined treatment of upper facial lines (horizontal forehead lines, lateral canthal lines, and glabellar lines) with Xeomin Cosmetic®. One study (Study 6, see **CLINICAL TRIALS**) was a randomized, double-blind, placebo-controlled, multicenter trial with an open-label extension phase (OLEX). The other study (Study 7) was a prospective, open-label, multicenter, repeat-dose study to investigate the safety of Xeomin Cosmetic® in the combined treatment of upper facial lines. A total dose of between 54 and 64 units of Xeomin Cosmetic® was administered at a treatment session with a 120-day interval between two treatment sessions (up to four treatment sessions in total). A greater proportion of patients in the Xeomin Cosmetic® group in Study 6 received a higher dose (60 to 64 units) than that in Study 7.

Table 4 lists the adverse reactions reported in ≥ 1% of patients (N=105) in the single-dose analysis in Study 6.

Table 4: Adverse Reactions Reported in ≥ 1% of Upper Facial Line Patients (Greater than Placebo) in the Single-dose Analysis

System Organ Class Preferred term	Xeomin Cosmetic ® (54 to 64 units: 10 to 20 units for horizontal forehead lines, 24 units for lateral canthal lines, and 20 units for glabellar lines) (N=105) n (%)	Placebo (N=51) n (%)
Patients with Adverse Reactions	24 (22.9%)	6 (11.8%)
Nervous System Disorders		
Headache	12 (11.4%)	0
Dyskinesia	1 (1.0%)	0
Hypoesthesia	1 (1.0%)	0
General Disorders and Administration Site Conditions		
Application site bruise	1 (1.0%)	0
Application site pain	1 (1.0%)	0
Discomfort (heavy feeling of frontal area)	1 (1.0%)	0
Eye Disorders		
Eyelid ptosis	2 (1.9%)	0
Abnormal sensation in eye	1 (1.0%)	0
Blepharochalasis	1 (1.0%)	0
Dry eye	1 (1.0%)	0
Musculoskeletal and Connective Tissue Disorders		
Facial asymmetry*	3 (2.9%)	0
Gastrointestinal Disorders		
Hypoesthesia oral	1 (1.0%)	0
Nausea	1 (1.0%)	0
Skin and Subcutaneous Tissue Disorders		
Skin burning sensation	1 (1.0%)	0

* The symptoms reported as eye brow asymmetry and facial asymmetry.

The rate of headache and facial paralytic dysfunctions (facial asymmetry, eyelid/eyebrow ptosis and others) in the combined treatment of upper facial lines with Xeomin Cosmetic® (54 to 64 units per treatment) in Studies 6 and 7, was higher than that in treatment of glabellar lines alone (Table 1 and Table 2) or lateral canthal lines alone (Table 3) with a dose up to 24 units per treatment. In the majority of cases, the severity of headache and facial paralytic dysfunctions was mild.

Neither the overall incidence nor the incidence of the individual adverse reactions increased with increasing numbers of treatment sessions when there was a 120-day interval between two treatment sessions.

Overall, in Study 6 (Main Period + OLEX), 40 of 150 patients (26.7%) experienced adverse reactions (N=150 received one treatment session; N=94 received two treatment sessions). The most frequently reported adverse reactions were headache (17 patients, 11.3%), followed by

injection site hematoma (13 patients, 8.7%), and injection site erythema, eyelid ptosis, and facial asymmetry (3 patients each 2.0%]). Brow ptosis occurred in 1 patient (0.7%).

In addition, one patient in Study 6 experienced prolonged headache (for 42 days) and numbness of the palate (for 14 days), and also experienced eyelid ptosis following injection of 64 units of Xeomin Cosmetic®. One patient in Study 7 developed mild accommodation disorder in the eye for 2 days and speech disorder for 5 days following injection of 54 units of Xeomin Cosmetic®.

Abnormal Hematologic and Clinical Chemistry Findings

No clinically meaningful shifts or changes from baseline in hematological or clinical chemistry findings were reported in the clinical studies.

Post-Market Adverse Drug Reactions

During post-approval use of Xeomin Cosmetic®, the following unexpected adverse reactions have been reported: flu-like symptoms, and hypersensitivity reactions like swelling, edema (also apart from injection site), erythema, pruritus, rash (local and generalized), muscle atrophy, dyspnea and sialolithiasis.

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

DRUG INTERACTIONS

Drug-Drug Interactions

No interaction studies have been performed.

Theoretically, the effects of Botulinum toxin may be potentiated by aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission, e.g. tubocurarine-type muscle relaxants.

Therefore, the concomitant use of Xeomin Cosmetic® with spectinomycin or aminoglycoside antibiotics or any other drugs that interfere with neuromuscular transmission requires special care. Peripheral muscle relaxants should be used with caution, if necessary reducing the starting dose of relaxant, or using an intermediate-acting substance such as vecuronium or atracurium rather than substances with longer lasting effects.

4-Aminochinolines may reduce the effect of Xeomin Cosmetic®.

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.

Drug-Lifestyle Interactions
Patients should be counselled that if asthenia, muscle weakness, vision disorders, dizziness or drooping eyelids occur they should avoid engaging in potentially hazardous activities such as driving until they have adjusted to the changes or the issues have resolved.

DOSAGE AND ADMINISTRATION

Dosing Considerations

For Intramuscular Use Only.

Xeomin Cosmetic® should only be given by physicians with the appropriate qualifications and experience in the application of Botulinum toxin.

The use of one vial for more than one injection session or patient is not recommended because the product and diluent do not contain a preservative.

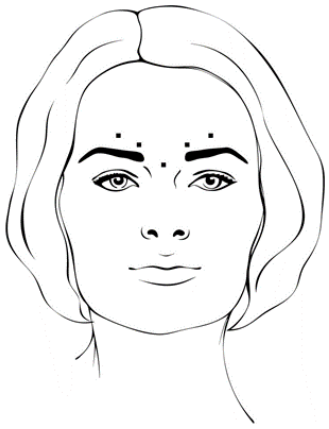
The smaller the injection volume the less pressure sensation and the less spread of Botulinum neurotoxin type A in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

Undesirable effects may occur from misplaced injections of Botulinum neurotoxin type A that temporarily paralyse nearby muscle groups.

Recommended Dose and Dosage Adjustment

Xeomin Cosmetic® is reconstituted prior to use with sterile preservative free 0.9% sodium chloride solution.

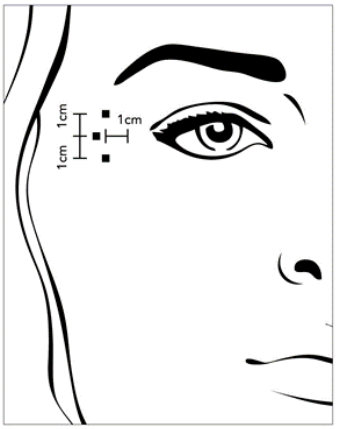
Glabellar Lines: The recommended dose is 20 units per treatment session. In a dose finding study of 191 subjects evaluating doses up to 30 units, 48 subjects received the highest doses of 30 units. Four (4) units should be injected into each of 5 injection sites, two injections in each corrugator muscle and one injection in the procerus muscle (see diagram below). Injections near the levator palpebrae superioris muscle and into the cranial portion of the orbicularis oculi should be avoided in order to avoid blepharoptosis. Injections into the corrugator muscle should be done in the medial portion of the muscle, and in the central portion of the muscle belly at least 1 cm above the bony edge of the orbital rim.



Lateral Canthal Lines: The total recommended standard dose per treatment is 12 units per side (overall total dose: 24 units).

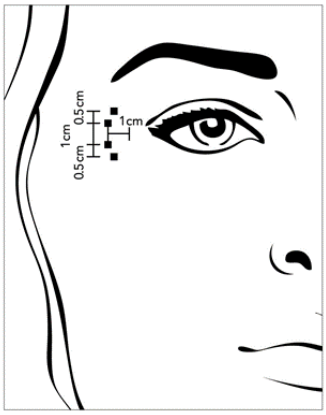
3-point injection scheme

Four (4) units are to be injected bilaterally into each of the 3 injection sites per eye area. One injection of 4 units is placed approximately 1 cm lateral from the bony orbital rim into the orbicularis oculi muscle. The other two injections of 4 units each should be placed approximately 1 cm above and below the area of the first injection. Injections too close to the zygomaticus major muscle should be avoided to prevent lip ptosis.

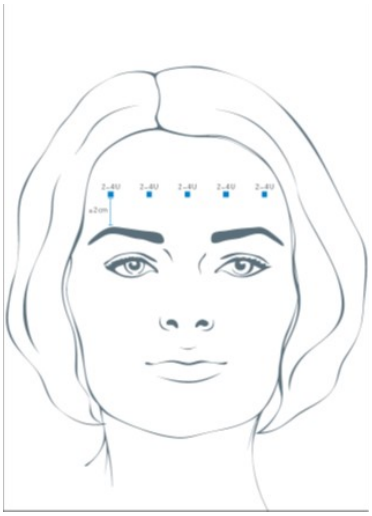


4-point injection scheme

Three (3) units are to be injected bilaterally into each of the 4 injection sites per eye area. Mark the 1 cm lateral from the bony orbital rim. The first two injections of 3 units is placed approximately 0.5 cm above and below this point. The other two injections of 3 units each should be placed approximately 1 cm above and below the first marked point. Injections too close to the zygomaticus major muscle should be avoided to prevent lip ptosis.



Horizontal Forehead Lines: The recommended total dose range is 10 to 20 units according to the individual needs of the patients. Ten (10) to 20 units are injected into the frontalis muscle in five horizontally aligned injection sites at least 2 cm above the orbital rim. Two (2), 3 or 4 units are applied per injection point, respectively. Injections too close to the orbital rim should be avoided to reduce the risk of brow ptosis.



The optimum dosage, frequency, and number of injection sites in the treated muscle should be determined by the physician individually for each patient at each treatment. Retreatment with Xeomin Cosmetic® should be administered no more frequently than every three months. When treating patients with Xeomin Cosmetic® previous treatment with all Botulinum toxin products for all other indications should be taken into consideration.

Lack of Response:

There are several potential explanations for a lack of or a diminished response to an individual treatment with Xeomin Cosmetic®. These may include inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, failure to correctly target the desired muscle through misplaced injections, 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 suggested course of action when patients do not respond to Xeomin Cosmetic® injections is:

1) wait the usual treatment interval;
2) consider reasons for lack of response listed above;
3) test patient using an acceptable method (i.e., test for anhydrotic rings with a starch iodine test or test for serum antibodies).

More than one treatment course should be considered before classification of a patient as a non-responder.

Administration

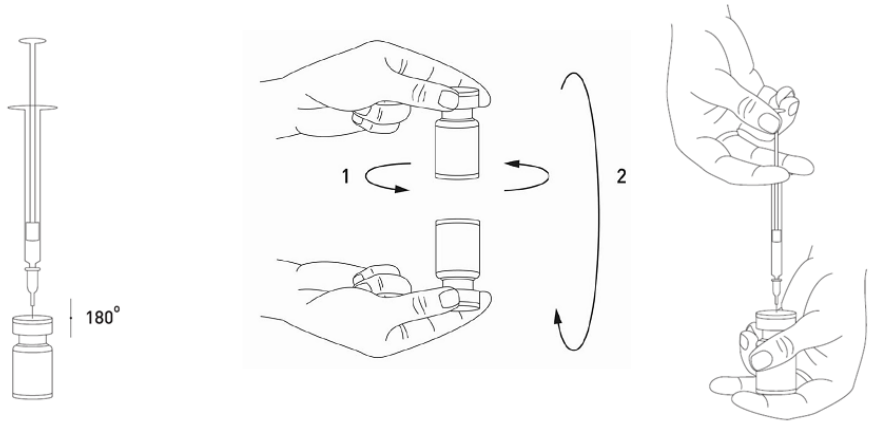
Reconstituted Xeomin Cosmetic® is injected using a thin sterile needle (e.g., 30-33 gauge needle). See dilution table below for volume of properly diluted toxin.

Reconstitution:
Parenteral Products:

Xeomin Cosmetic® is reconstituted prior to use with sterile preservative free sodium chloride 9 mg/mL (0.9%) solution for injection. Xeomin Cosmetic® should not be mixed with any medicinal products other than sterile preservative free sodium chloride (0.9%). Reconstitution and dilution should be performed in accordance with good clinical practice guidelines, particularly with respect to asepsis.

It is good practice to perform vial reconstitution and syringe preparation over plastic-lined paper towels to catch any spillage. An appropriate amount of solvent (Table 5) is drawn up into a syringe. A 20-27 gauge short bevel needle is recommended for reconstitution. The exposed portion of the rubber stopper of the vial is cleaned with alcohol (70%) prior to insertion of the needle. After vertical insertion of the needle through the rubber stopper the solvent is injected gently into the vial in order to avoid foam formation. The vial must be discarded if the vacuum does not pull the solvent into the vial. Remove the syringe from the vial and mix Xeomin Cosmetic® with the solvent by carefully swirling and inverting the vial – do not shake vigorously. Record the date and time of reconstitution on the vial.

If needed, the needle used for reconstitution should remain in the vial and the required amount of solution should be drawn up with a new sterile syringe suitable for injection.



Reconstituted Xeomin Cosmetic® is a clear colourless solution free of particulate matter.

Xeomin Cosmetic® should not be used if the reconstituted solution (prepared as above) has a cloudy appearance or contains floccular or particulate matter.

Table 5: Possible Dilutions of Xeomin Cosmetic ® in the Reconstituted Solution

Solvent added (sodium chloride 9 mg/mL (0.9%) solution for injection)	**Resulting dose in units per 0.1 mL 100 U Vial**
1.0 mL	10.0 U
1.25 mL	8.0 U
2.0 mL	5.0 U
2.5 mL	4.0 U
4.0 mL	2.5 U

Any solution for injection that has been stored for more than 24 hours as well as any unused solution for injection should be discarded. For safe disposal of the reconstituted solution, see **SPECIAL HANDLING INSTRUCTIONS**.

OVERDOSAGE

The lethal amount of crystalline Botulinum toxin type A for a 70 kg human is calculated to be approximately 0.09 to 0.15 µg applied intravenously or intramuscularly, and 70 µg applied orally. A vial with 100 units Xeomin Cosmetic® contains 0.6 ng Botulinum neurotoxin type A, i.e. less than 1/100 of the estimated human lethal dose following intravenous or intramuscular application.

Symptoms of Overdose

Overdose of Xeomin Cosmetic® depends upon dose, site of injection and underlying tissue properties. Signs and symptoms of overdose are not apparent immediately post-injection. Increased doses may result in pronounced neuromuscular paralysis distant from the site of injection with a variety of symptoms. Symptoms may include general weakness, ptosis, diplopia, breathing difficulties, speech difficulties, paralysis of the respiratory muscles or swallowing difficulties which may result in aspiration pneumonia.

Measures in Cases of Overdose

Should accidental injection or oral ingestion occur, or overdose be suspected, the person should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary. Respiratory support may be required if paralysis of the respiratory muscles occurs.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of Botulinum neurotoxin type A is well characterized. It involves a 4 step process resulting in a reduction in muscular contractions. The 4 steps include binding, uptake within a vesicle, translocation into cytosol and proteolytic cleavage of SNAP 25.

The C-terminal end of the heavy chain of Botulinum neurotoxin type A binds to binding sites (ganglioside GT1b and the synaptic vesicle membrane protein SV2C) on presynaptic cholinergic axon terminals with very high specificity and affinity (picomolar range). The actual protein binding site of Botulinum neurotoxin type A has not yet been fully characterized.

After binding, the complete Botulinum neurotoxin type A molecule is taken up by endocytosis so that it resides in an endocytic vesicle in the cytosol of the nerve terminal. Translocation of the Botulinum neurotoxin type A light chain from the vesicle into the cytosol is then mediated by a 50 kD N-terminal domain of the heavy chain which undergoes a configuration change to form a transmembrane hydrophilic pore in the vesicle, through which the light chain, a zinc-dependent endopeptidase, protrudes into the cytosol. Translocation is detectable *in vitro* within 20 minutes of binding, and reaches a peak after 90 minutes.

After translocation into the nerve terminal cytosol, the light chain of the neurotoxin becomes proteolytically active and specifically cleaves a component (SNAP 25) of the vesicle fusion machinery, which is essential for the release of acetylcholine. By inhibiting acetylcholine release Botulinum neurotoxin type A reduces muscular contractions. The blockade of transmission at the neuromuscular junction leads to retraction of the endplate nerve terminals and subsequent loss of endplate organization.

Extensive compensatory sprouting by the affected terminal nerve membrane begins within 4 days, leading to the formation of temporary functional synapses and partial recovery of muscle function within approximately 28 days of treatment. Within approximately 2 months, the affected nerve terminals begin to recover their ability to release acetylcholine and the original endplate connections are progressively restored. Sprouting stops and the temporary synapses begin to lose their functionality. Within approximately 3 months, the original nerve endings recover full functionality, leading to the normalization of the original motor endplates. This induces retraction and regression of the sprouts and a complete functional repair of the original terminals.

In addition, cholinergic, autonomic, parasympathetic, and postganglionic sympathetic nerve synapses are also potential targets of therapeutic intervention, e.g. the intradermal application of Botulinum neurotoxin type A leads to denervation of eccrine glands. It is therefore conceivable that systematic autonomic side effects of local Botulinum neurotoxin type A injections may include dryness of the mouth and eyes and ocular accommodation difficulties.

Pharmacodynamics

The pharmacodynamics of locally injected Botulinum neurotoxin type A are well established, with dose-related muscle weakness resulting from the irreversible blockade of acetylcholine release from presynaptic vesicles.

The desired pharmacological effect of Botulinum neurotoxin type A relates to reduced muscle contraction in the target muscle, whereas undesirable effects appear to relate to the diffusion of toxin from the target muscle to adjacent muscles and/or nerves. Muscle relaxation generally occurs within 2 to 5 days after intramuscular injection, with an expected maximum effect after 2 weeks and a duration of effect for an average of 9 to 16 weeks.

The diffusion of Botulinum neurotoxin type A from intramuscular injection sites into surrounding tissue is dose-dependent. Limiting the dose of Botulinum neurotoxin type A in critical anatomical areas is therefore helpful in preventing complications (e.g. limiting dose administered to the orbicularis oculi muscle to prevent ptosis).

Three pharmacodynamic studies were conducted with Xeomin Cosmetic® (incobotulinumtoxinA) in healthy volunteers. Two of the studies were active-control (onabotulinumtoxinA) studies conducted in a small foot muscle [extensor digitorum brevis (EDB)] model. Active control studies showed a reduction in compound muscle action potential (CMAP) in all subjects with similar effects between treatments. No significant difference was seen between preparations with respect to degree of paralysis, onset of paralysis, and duration of effect. In a dose-response study overall, a dose-response relationship was observed when the highest dose (32 unit) and the lowest dose (2 unit) groups were compared with similar effects for Xeomin Cosmetic® (incobotulinumtoxinA) and the conventional Botulinum toxin type A preparation containing onabotulinumtoxinA observed in all dose groups. No local diffusion of either preparation was observed in adjacent muscles at tested doses. The third active-controlled study examined the diffusion characteristics of Xeomin Cosmetic® in comparison with onabotulinumtoxinA and abobotulinumtoxinA products in an anhydrosis model. All subjects responded to the 3 botulinum toxin type A treatments. The maximal area of anhidrosis observed with Xeomin Cosmetic® over 6 weeks did not differ significantly from that of the onabotulinumtoxinA comparator but was significantly smaller than the abobotulinumtoxinA comparator.

Pharmacokinetics

Classic kinetic and distribution studies cannot be conducted with Botulinum neurotoxin type A because the active substance is applied in very small quantities (picograms per injection), and because it binds so rapidly and irreversibly to cholinergic nerve terminals.

It is believed that little systemic distribution of therapeutic doses of Xeomin Cosmetic® occurs. Xeomin Cosmetic® is not expected to be presented in the peripheral blood at measurable levels following intramuscular 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.

Like many other proteins of its size, Botulinum neurotoxin type A has been shown to undergo retrograde axonal transport after intramuscular injection. Retrograde transsynaptic passage of active Botulinum neurotoxin type A into the central nervous system however has not been found. Proteolyzed Botulinum neurotoxin type A yields amino acids which will enter the normal physiological metabolic pathways, being recycled or catabolized, according to the needs of the cell.

Duration of Effect
See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**.

STORAGE AND STABILITY

Xeomin Cosmetic®, unreconstituted, is stored at room temperature (up to 25°C) and should not be used after the expiry date stated on the outer package.

Reconstituted solution: This product does not contain any antimicrobial preservatives and should ideally be used immediately after reconstitution. Reconstituted solution is stable for up to 24 hours at 2 to 8°C.

Do not freeze reconstituted Xeomin Cosmetic®.

SPECIAL HANDLING INSTRUCTIONS

Procedure to follow for a safe disposal of vials, syringes and materials used:
Any unused vials or remaining Xeomin Cosmetic® solution in the vial and/or syringe should be inactivated by adding one of the following solutions: 70% ethanol, 50% isopropanol, 0.1% sodium dodecyl sulfate (SDS) (anionic detergent), sodium hydroxide solution (0.1 N NaOH), or diluted sodium hypochlorite solution (at least 0.1% NaOCl).

After inactivation used vials, syringes, and materials should not be emptied and should be discarded into appropriate containers and disposed of in accordance with local requirements.

Recommendations should any incident occur during the handling of Botulinum neurotoxin type A:
Any spills of the product must be wiped up: either using absorbent material impregnated with any of the above listed solutions in case of the powder, or with dry, absorbent material in case of reconstituted product.

The contaminated surfaces should be cleaned using absorbent material impregnated with any of the above listed solutions, then dried.

If a vial is broken, proceed as mentioned above by carefully collecting the pieces of broken glass and wiping up the product, avoiding any cuts to the skin.

If the product comes into contact with skin, rinse the affected area abundantly with water.

If product gets into the eyes, rinse thoroughly with plenty of water or with an ophthalmic eyewash solution.

If product comes into contact with a wound, cut or broken skin, rinse thoroughly with plenty of water and take the appropriate medical steps according to the dose injected.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Xeomin Cosmetic® is supplied as a sterile, white, preservative free powder for solution for injection (lyophilisate) packed in a vial of type 1 glass with a latex-free stopper (bromobutyl rubber) and tamper-proof seal (aluminum).

Xeomin Cosmetic® is available in pack sizes of 1 (single unit pack), 2, 3 or 6 vials (multi-packs).

Each vial contains 100 units of incobotulinumtoxinA (*Clostridium Botulinum* Neurotoxin Type A (150 kD), free from complexing proteins) where one unit corresponds to the median lethal dose (LD_{50}) in mice or the equivalent cell-based potency units, 4.7 mg of sucrose and 1.0 mg of human albumin. Prior to use Xeomin Cosmetic® is reconstituted with commercially available 0.9 % physiological saline (not supplied in the pack) to form a clear, and colorless solution.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: incobotulinumtoxinA

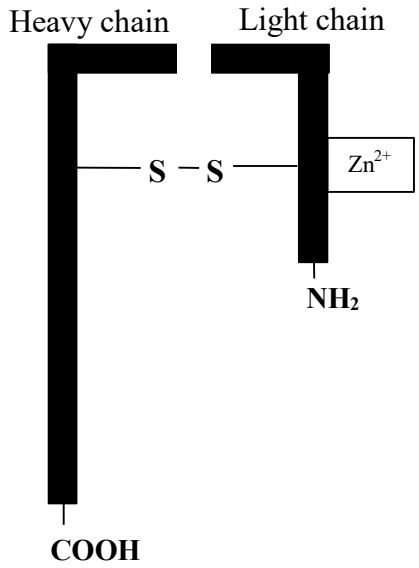
Chemical name: Botulinum Toxin Type A (*toxinum botulinicum typum A*).

Molecular formula and molecular mass:

IncobotulinumtoxinA is synthesised by the anaerobic bacterium *Clostridium botulinum* as a single chain polypeptide (1,296 amino acid residues, molecular weight ~150 kD), which is subsequently split between residues 438 and 439 as well as between residues 448 and 449 by an endogenous protease during post-translational modification. A decapeptide (residue 439 to residue 448) is cleaved from the protein, resulting in a heavy chain, with a molecular weight of ~100 kD, and a light chain, with a molecular weight of ~50 kD. These separate chains are covalently linked via a disulphide bond. The light chain is associated with one zinc ion and functions as a zinc-dependent endopeptidase. The heavy chain comprises two functional domains: the N-terminal section is the translocation domain and the C-terminal section is the binding domain (Figure 1).

Structural formula:

Figure 1: Structure of the 150 kD purified neurotoxin free from complexing proteins (incobotulinumtoxinA)



Physicochemical properties:

Xeomin Cosmetic® (incobotulinumtoxinA) is supplied as a sterile, white, preservative free powder for solution for injection (lyophilisate) packed under nitrogen in single-use glass vials. Each vial contains 100 units of incobotulinumtoxinA (*Clostridium Botulinum* Neurotoxin Type A (150 kD), free from complexing proteins), 4.7 mg of sucrose and 1.0 mg of human albumin. Prior to use Xeomin Cosmetic® is reconstituted with commercially available 0.9 % physiological saline (not supplied in the pack) to form a clear, and colorless solution. The size of the vials allows different concentrations (i.e. doses) to be prepared.

Product characteristics:

Xeomin Cosmetic® is a formulation of incobotulinumtoxinA. It is produced by the anaerobic bacterial fermentation process from the Hall strain of *Clostridium botulinum* as a single chain polypeptide with a molecular weight of approximately 150 kD. The neurotoxin is a part of a high molecular weight complex (MW = 900 kD) consisting of at least five additional proteins (= complexing proteins). During the unique manufacturing process of the drug substance the neurotoxin is taken through a number of purification steps, which separate the complexing proteins from the neurotoxin. It consists of the purified neurotoxin which has been separated from complexing proteins (hemagglutinins and a non-toxic non-hemagglutinating protein) during production.

CLINICAL TRIALS

Glabellar Lines

Two identical randomized, double-blind, multi-center, placebo-controlled Phase 3 clinical trials (Study 1 and Study 2) were conducted to evaluate Xeomin Cosmetic® for the use in the temporary improvement of moderate to severe glabellar lines. The studies included a total of 547 subjects of which 193 subjects were > 50 years of age and 55 subjects were male. The study patients received either 20 units Xeomin Cosmetic® or an equal amount of placebo. The total dose was delivered in 5 equally divided aliquots of 4 units each to specific injection sites.

Overall, treatment success was defined as a 2-point improvement at maximum frown on Day 30 on a 4-point scale (Facial Wrinkle Scale, FWS, 0=none, 1=mild, 2=moderate, 3=severe) compared to baseline for both the investigator's and patient's assessments (composite endpoint).

At Day 30, Xeomin Cosmetic® improved wrinkles significantly better than placebo (2-point simultaneous improvement on investigator and patient assessment). There was a statistically significant ($p < 0.0001$) response rate between Xeomin Cosmetic® and placebo for the composite endpoint (see Tables 6 and 7 below).

Xeomin Cosmetic® also consistently showed better efficacy than placebo at maximum frown based on both the investigator's and patient's rating on the 4-point scale. Secondary efficacy endpoints support the results of the primary endpoint.

The highest response rates were observed on Day 30 (subjects were evaluated on the efficacy assessment at baseline and Days 7, 30, 60, 90 and 120) and then decreased until nearly all subjects had lost response by Day 120.

Table 6: CETS: Responder analysis at Day 30 - imputation of missing data – FAS (Study 1)

	NT 201 (N=184)	Placebo (N=92)
CETS		
Response: Yes [n (%)]	111 (60.3)	0 (0.0)
Response rate (RR)*	0.60	0.00
Difference RR (NT 201-Placebo)	0.60	
95% CI for difference RR	0.52, 0.68	
p-value (Fisher's exact test)	<0.0001	
2-point response investigator assessment		
Response: Yes [n (%)]	141(76.6)	0 (0.0)
2-point response patient assessment		
Response: Yes [n (%)]	120 (60.4)	0 (0.0)

CETS = Composite endpoint treatment success; CI = Confidence interval; FAS = Full Analysis Set; FWS = Facial wrinkle scale; N= Number of subjects in specific group; n= Number of subjects; Calculation of percentages based on N.
*Missing data were imputed with last observation carried forward (LOCF)
Note: Visit 3 = Day 30.

Table 7: CETS: Responder analysis at Day 30 - imputation of missing data – FAS (Study 2)

	NT 201 (N=182)	Placebo (N=89)
CETS		
Response: Yes [n (%)]	87 (47.8)	0 (0.0)
Response rate (RR)*	0.48	0.00
Difference RR (NT 201-Placebo)	0.48	
95% CI for difference RR	0.40, 0.56	
p-value (Fisher's exact test)	<0.0001	
2-point response investigator assessment		
Response: Yes [n (%)]	129 (70.9)	0 (0.0)
2-point response patient assessment		
Response: Yes [n (%)]	101 (55.5)	1 (1.1)

CETS = Composite endpoint treatment success; CI = Confidence interval; FAS = Full Analysis Set; FWS = Facial wrinkle scale; N= Number of subjects in specific group; n= Number of subjects; Calculation of percentages based on N.
*Missing data were imputed with last observation carried forward (LOCF)
Note: Visit 3 = Day 30.

In an open-label study (Study 3) evaluating the long-term safety of Xeomin Cosmetic® patients who had previously participated in placebo-controlled studies in glabellar lines were treated with up to another 8 repeat dose cycles. A total of 694, 322, 309, 291, 261, 191 and 48 subjects entered Cycles 2, 3, 4, 5, 6, 7 and 8, respectively.

There was no increase in the incidence of adverse events indicating a stable safety pattern after repeated dosing. No new unexpected events occurred and the safety profile was consistent with that observed in other studies.

Non-inferiority of Xeomin Cosmetic® efficacy as compared to a comparator product containing the conventional Botulinum toxin type A complex (onabotulinumtoxinA) was shown in one comparative single-dosing Phase 3 study (Study 4). In this study, 381 females between 18 and 50 years of age with glabellar lines of at least moderate severity at maximum frown were treated either with 24 units Xeomin Cosmetic® or 24 units onabotulinumtoxinA, randomized in a 2:1 ratio (Xeomin Cosmetic®: onabotulinumtoxinA). The patients assessed efficacy at maximum frown on Day 28 of treatment using the FWS. Treatment success was defined as a 1-point improvement on this scale compared to baseline.

Lateral Canthal Lines

Two clinical studies (Study 5 and Study 6) were conducted to investigate the treatment effects of Xeomin Cosmetic® for lateral canthal lines.

Study 5 was a Phase 3, double-blind, intraindividually randomized for eye side and application schemes, independent rater-blind, multicenter placebo-controlled trial with parallel group design conducted to investigate the efficacy and safety of Xeomin Cosmetic® in comparison to placebo in the treatment of moderate to severe lateral canthal lines at maximum smile, and to assess and compare two different application schemes of Xeomin Cosmetic®. Of the 111 patients (22 to 62 years of age; mean age 47.1 years), 83 were randomized to receive 12 units Xeomin Cosmetic® per side (right/left eye area) and 28 patients were randomized to receive the respective volume of placebo in a single dose divided among 3 or 4 injections.

The primary efficacy variable was treatment response rate where treatment response was defined as an improvement of at least 1 point on the 4-point scale for lateral periorbital wrinkles (lateral canthal lines) assessed by an independent rater using standardized digital photographs taken at maximum smile at Week 4 for either eye area compared to baseline. Based on study inclusion criteria, subjects should have moderate (grade 2) or severe (grade 3) symmetrical lateral periorbital wrinkles assessed by the investigator according to the 4-point scale at maximum smile at both the screening and baseline visits. However, a notable number of subjects were rated as having mild wrinkles at baseline by the independent rater.

Both the 3-injection and 4-injection schemes demonstrated superiority over placebo at Week 4 ($p<0.0001$).

The efficacy of Xeomin Cosmetic® was also demonstrated for lateral canthal lines in Study 6 described below in which the combined treatment of horizontal forehead lines, lateral canthal lines and glabellar lines with 54 to 64 units of Xeomin Cosmetic® was investigated (see Table 8).

Upper Facial Lines

Study 6 was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study in the combined treatment of upper facial lines with a 120-day Main Period and a 120-day Open-label Extension (OLEX) Period. Patients with glabellar lines, horizontal forehead lines, and symmetrical lateral canthal lines of moderate to severe intensity at maximum contraction as assessed by the investigator according to a validated 5-point aesthetics scale, were randomly assigned to 1 of 2 treatment groups, Xeomin Cosmetic® treatment group and placebo group. A total dose of between 54 and 64 units of Xeomin Cosmetic®, or an equivalent volume of placebo, was administered as a single treatment session, consisting of 4 divided doses, forehead (10 to 20 U), glabellar area (20 U), lateral left eye (12 U) and lateral right eye (12 U). The OLEX Period also consisted of one treatment in which all patients received Xeomin Cosmetic® treatment in the same areas of the face and same total dose range as during the Main Period. The full analysis set (FAS) included 105 patients in the Xeomin Cosmetic® group and 51 placebo patients. At the end of the study, 87 Xeomin Cosmetic®-treated (Main Period) patients and 45 placebo (Main Period) patients had completed the OLEX Period.

The majority of subjects were female (86.5%) and White (97.4%). The mean age was 47.5 years. In both treatment groups the baseline severity across all three areas was assessed as mostly severe.

Primary efficacy variables were: (a) Response at maximum contraction at Day 30 individually for each of the three treated areas, as assessed by the investigator according to the aesthetics scale, i.e. a score of none (0) or mild (1), and (b) Response at maximum contraction at Day 30 simultaneously for all three treatment areas, as assessed by the investigator according to the aesthetics scale, i.e. a sum score of 3 or lower. A 4-step hierarchical test procedure (logistic regression model) was used. A statistically significant difference between Xeomin Cosmetic® and the placebo group was observed for all three areas ($p<0.0001$) and for all three treatment areas combined ($p=0.0001$).

Table 8: Responder Rates at Day 30 in Upper Facial Lines Study (Main Period)

Treatment Area	Xeomin Cosmetic ® (n=105)	Placebo (n=51)	P-value
Glabellar lines	82.9%	0.0%	<.0001
Horizontal Forehead lines	71.4%	2.0%	<.0001
Lateral Canthal lines	63.8%	2.0%	<.0001
All areas combined	54.3%	0.0%	0.0001

The primary efficacy analysis demonstrated statistically significant treatment differences and high responder rates under Xeomin Cosmetic® in the treatment of glabellar lines, horizontal forehead lines, and lateral canthal lines alone as well as for all areas combined.

DETAILED PHARMACOLOGY

Mechanism of Action

See **ACTION AND CLINICAL PHARMACOLOGY**.

Human Pharmacodynamics

The desired pharmacological effect of Botulinum neurotoxin type A relates to reduced muscle contraction in the target muscle, whereas undesirable effects appear to relate to the diffusion of toxin from the target muscle to adjacent muscles and/or nerves. Muscle relaxation generally occurs within 2 to 5 days after intramuscular injection, with an expected maximum effect after 2 weeks and a duration of effect for an average of 9 to 16 weeks.

Three pharmacodynamic studies were conducted with incobotulinumtoxinA in healthy volunteers.

An active controlled study was conducted in 14 healthy male volunteers to compare the effect of incobotulinumtoxinA versus onabotulinumtoxinA on compound muscle action potential (CMAP) in a small foot muscle. Volunteers received intramuscular injections of 4 units of each preparation into the extensor digitorum brevis (EDB) of opposite feet. Measurements of CMAP were obtained by surface electromyography (EMG) after supramaximal electrical stimulation of the peroneal nerve at regular intervals up to 90 days after treatment. The primary efficacy variable was the change from baseline in maximal CMAP.

Both incobotulinumtoxinA and onabotulinumtoxinA induced a reduction in CMAP in all subjects with no significant differences seen between the preparations with respect to degree of paralysis, onset of paralysis and duration of effect. Both were well tolerated, with no adverse events reported. The study confirmed that locally injected incobotulinumtoxinA is at least as effective as onabotulinumtoxinA at tested equal doses.

Another study was conducted in 32 healthy male volunteers to investigate the dose-response relationship, diffusion into the adjacent muscles, and duration of paralytic effect caused by incobotulinumtoxinA in the EDB model.

Volunteers were injected with a dose of 2, 4, 16, or 32 units of incobotulinumtoxinA in the EDB muscle of one foot, as randomly assigned. The same dose of onabotulinumtoxinA was injected in the contralateral EDB muscle. The primary efficacy endpoint was CMAP M-wave amplitude reduction (CAmR (%)) relative to baseline obtained in the EDB muscle at Week 4 for

incobotulinumtoxinA. All dose groups showed a statistically significant EDB CAmR (%) at Week 4 compared to baseline. In the 32-unit dose group, the effect in the EDB CAmR (%) was higher compared to the other dose groups.

The systemic diffusion effects of the two products were compared by calculating within-subject differences of the ADQ CAmRs (%) and AH CAmRs (%) at Week 4. An effect was defined as a CAmR (%) decrease to < 80% of the baseline value and diffusion into adjacent ADQ and AH muscles, as indicated by the mean values of the CAmR (%) in these muscles observed over all dose groups. No systemic diffusion of incobotulinumtoxinA and onabotulinumtoxinA was observed in adjacent muscles at tested equal doses.

Another active-controlled study was conducted in 29 healthy female volunteers to investigate and compare the diffusion characteristics of incobotulinumtoxinA versus two other formulations of Botulinum toxin type A-complex (onabotulinumtoxinA and abobotulinumtoxinA). In this double-blind, randomized, single-dose, single center study, subjects received an intramuscular injection into the forehead. The number of injections of each of the three products was equal (1:1:1 randomization). Each subject received two of the three treatments (5 units incobotulinumtoxinA, 5 units onabotulinumtoxinA Comparator 1 and 12.5 units abobotulinumtoxinA Comparator 2, one on the right side and one on the left side of the forehead. Eligible subjects had a healthy skin test area at baseline and displayed uniform sweating activity under standardized sweating conditions.

The primary efficacy variable was the maximal area of anhidrosis within 6 weeks. This was compared between the products. The area of anhidrosis was determined by a standardized sweating test recorded by standardized photo documentation and assessed by a dermatologist blinded to the subject's treatment assignment.

All subjects responded to the 3 botulinum toxin A treatments, and showed an anhidrotic halo on both sides of the forehead. The maximal area of anhidrosis with Xeomin Cosmetic® over 6 weeks did not differ significantly from that of comparator 1 (mean [±SD]: 364.3 [±138.13] and 343.1 [±110.72] mm^2, respectively). The maximal area of anhidrosis over 6 weeks was significantly larger with Active Comparator 2 (459.1 [±151.81] mm^2) than with Xeomin Cosmetic® (Table 9). Moreover, the results of the sensitivity analysis for maximal area of anhidrosis over 6 months were consistent with those of the primary analysis for the area of anhidrosis over 6 weeks.

Table 9: Maximal Area of Anhidrosis within 6 Weeks*

		Xeomin Cosmetic® N=13	Active Comparator 1 N=16	Active Comparator 2 N=17
Mean	mm^2	364.3	343.1	459.1
Standard Deviation	mm^2	138.13	110.72	151.81
Median	mm^2	298	345	436
Coefficient of Variation	%	37.9	32.3	33.1

* Per protocol set

Secondary efficacy variables revealed that the area under the effect (area of anhidrosis) curve (AUEC) over 6 months were comparable between Xeomin Cosmetic® and Active Comparator 1 (mean [±SD]: 43142 [±17401.5] and 40611 [±17798.7], respectively). The AUEC over 6 months with Active Comparator 2 (51586 [±22657.9]) was greater than that with Xeomin Cosmetic®.

After 6 months, anhidrosis was observable in all subjects.

Human Pharmacokinetics

No specific pharmacokinetic studies have been performed with incobotulinumtoxinA. As Botulinum neurotoxin type A is administered in very small quantities (picograms per injection) and binds so avidly and irreversibly to cholinergic terminals, classic kinetic and distribution studies are not feasible in humans (see **ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics**).

Animal Pharmacodynamics

The paralytic activity of incobotulinumtoxinA and Botulinum Neurotoxin Type A-complex (Active Comparators 1 (onabotulinumtoxinA) and 2 (abobotulinumtoxinA) was assessed in the mouse regional paralysis test after 3 repeated injections at 6 and 13 week intervals. Doses administered were approximately 32 LDU/kg for Active Comparator 1 and incobotulinumtoxinA and 72 LDU/kg for Active Comparator 2. Active Comparator 1 and incobotulinumtoxinA were equipotent in terms of mean paralysis score and animal days with severe paralysis. Degree and duration of paralysis were dose-dependent and were more marked after the second and third injections. The maximal paralytic effect was reached within days after the injections with all three preparations.

In another study, time course of paralysis and paralytic activity were almost comparable between Active Comparator 1 and incobotulinumtoxinA with maximum EMG activity inhibition one or two weeks after treatment in the Cynomolgus monkey. Recovery of the muscle activity began on average 9 weeks after treatment with full recovery achieved at study week 37.

Effects of incobotulinumtoxinA, onabotulinumtoxinA and abobotulinumtoxinA on motility were assessed in an acute intravenous toxicity study in mice at doses up to 68 LDU/kg. A significant dose dependent reduction in motility parameters was observed starting at 20 LDU/kg showing no differences between forms of Botulinum toxin type A. The NOAEL for motility parameters in mice after a single intravenous injection was 9 LDU/kg.

The *in vitro* inhibition of rapidly-activating delayed rectifier potassium currents (I_{Kr}) by incobotulinumtoxinA was tested in Chinese Hamster Ovary cells stably expressing ether-à-go-go-related gene (hERG) product. At a concentration of 10,000 LDU/mL, there was no effect on tail currents at -20 mV. The tested concentration exceeds the maximum achievable concentration in human blood by a factor of at least 10,000 indicating that negative interactions with hERG channels in humans is extremely unlikely.

ECG parameters were studied in Cynomolgus monkeys after a single intramuscular administration of 16 LDU/kg incobotulinumtoxinA. There appeared to be no potential deleterious effect on the atrioventricular and intraventricular conduction velocity and ventricular repolarization.

A study of denervated muscle recovery in rats injected intramuscularly with incobotulinumtoxinA at doses up to 16 LDU/kg at weekly intervals showed full functional muscle recovery 26 weeks after the last injection, although histological recovery of muscle atrophy was not completed.

Intramuscular repeat dose studies of 13-39 weeks in Cynomolgus monkeys examined effects of doses up to 12 and 16 LDU/kg on cardiovascular function. The absence of cardiovascular effects was confirmed in all studies at all doses.

A study in the conscious rat after administration of up to 32 LDU/kg of incobotulinumtoxinA demonstrated no effect on intestinal transit 4 days after injection.

Animal Pharmacokinetics

The direct pharmacokinetic measurement of the absorption and bioavailability of incobotulinumtoxinA is not feasible because of its very low and thus undetectable effective tissue concentrations. However, the oral bioavailability can be estimated indirectly by comparing the potency of the drug substance after oral administration and the potency of the drug product after intravenous injection.

Single oral doses of incobotulinumtoxinA of up to 10,000 LDU did not produce mortality or clinical signs in male mice; a dose of 100,000 LDU produced 40% mortality. The intravenous LD_{50} is approximately 50 LDU/kg corresponding to 1 LDU per animal. Based on the ratio of the intravenous to the oral approximative LD_{50}, the oral bioavailability of incobotulinumtoxinA in mice is therefore 1:100,000 or 0.001%.

In the literature, animal studies of tissue distribution using radiolabeled neurotoxin have shown that Botulinum toxin type A-complex remains concentrated at the intramuscular site for some time, with diffusion into tissues over distances of up to 5 cm depending on the volume injected. Furthermore, retrograde transport of Botulinum toxin type A-complex was observed in animals. However, no intact neurotoxin has been detected in the spinal cord, nor has biological activity of neurotoxin been found within the central nervous system after ventral root or intramuscular injection. Due to its molecular weight, there is no passage of the actual neurotoxin molecule into the CNS via the blood-brain barrier. After systemic absorption, Botulinum toxin type A-complex, like all protein fragments, is rapidly metabolized by proteases and the molecular components are recycled through normal metabolic pathways.

TOXICOLOGY

Single-Dose Toxicity

Single dose toxicity studies have been conducted with incobotulinumtoxinA) in mice and rats by the intravenous, intraperitoneal, intramuscular and/or oral routes. A key finding of the acute toxicity studies is that incobotulinumtoxinA is practically non-toxic by oral administration. The oral LD_{50} is about 5 orders of magnitude higher than the intravenous and intraperitoneal LD_{50}. When compared to Botulinum Neurotoxin Type A-complex, the oral LD_{50} values for incobotulinumtoxinA in rats were about 60 times higher (55,300 LDU/kg versus approximately 3,200,000 LDU/kg, respectively).

A dose of 5 LDU/kg is considered the NOAEL for a single intramuscular administration of incobotulinumtoxinA in mice.

Repeat-Dose Toxicity

Repeat dose toxicity studies were conducted in mice, rabbits and monkeys by the intended clinical intramuscular route of administration.

A 28-week repeat-dose study was conducted in mice with intramuscular injection three times at 6 and 13 week intervals at doses of up to32 LDU/kg/administration for incobotulinumtoxinA and Active Comparator 1, and doses up to 78 LDU/kg/administration for Active Comparator 2. Active Comparator 1 and incobotulinumtoxinA were comparable in paralytic effect and in toxicity (in terms of weight loss per LDU). The NOAEL for incobotulinumtoxinA in this study was <13 LDU/kg.

A repeat-dose study (3 intramuscular injections at 14 day intervals) was conducted in rabbits involving 3 biweekly doses of incobotulinumtoxinA from 2.5 to 40 LDU/kg. Mortality was seen at 5 LDU/kg and higher. No marked local reactions and no treatment-related lesions were noted in any of the dose groups during necropsy examinations. The dose level of 3.5 LDU/kg can be considered as the Maximum Tolerated Dose (MTD).

Repeat dose studies of 13 and 39 weeks were conducted in the Cynomolgus monkey where incobotulinumtoxinA was administered intramuscularly in 4-12 week intervals (dose levels of up to 16 LDU/kg). Study results revealed local effects related to the pharmacological properties of the drug. The only systemic effects were transient dose-dependent reductions in mean body weight or body weight gain.

In the 39-week toxicity study where Cynomolgus monkeys received repeated intramuscular injections of incobotulinumtoxinA in the left *gastrocnemius* and *biceps brachialis* muscles (dose of 16 LDU/kg with varying dosing intervals of up to 12 weeks for a total of 4 administrations) the occurrence of atrophy seemed to be time-related, and not specifically related to the number of administrations. Pronounced atrophy was observed following 4 intramuscular administrations of 16 U/kg/administration. The NOAEL for this study was 16 LDU/kg for a dosing interval of at least 8 weeks.

Most effects seen in repeated dose toxicity studies were related to the pharmacological action of local muscle paralysis (i.e., reduced motility and muscular tonus, ataxia) or to generalized low-grade blockade of autonomic neurotransmission (piloerection, ptosis, lacrimation or mydriasis). No severe systemic effects or apparent organ toxicity were detected.

Mutagenicity / Carcinogenicity

Studies have not been performed to evaluate the carcinogenic and mutagenic potential of incobotulinumtoxinA. Based on the chemical structure and mode of action there is no reason to suspect mutagenic or carcinogenic potential. Studies conducted with Active Comparator 1 have indicated no mutagenic potential.

Reproductive and Developmental Toxicity

Fertility and Early Embryotic Development

The effects of incobotulinumtoxinA on gonadal function, mating behaviour and reproductive performance were assessed after repeated intramuscular administration in rabbits at doses of 1.25, 2.5 and 3.5 LDU/kg. There were no effects of these parameters at any dose level given therefore 3.5 LDU/kg was considered the NOAEL under the defined experimental conditions.

Embryo-foetal Development

The effects of incobotulinumtoxinA on embryonic and foetal development of the rat were evaluated following intramuscular injections of total doses up to 98 LDU/kg during the period of organogenesis. A total dose of 30 LDU/kg (weekly 10 or biweekly 6 LDU/kg) was considered the maternal NOAEL. There were no indications of embryo-toxicity in any treated group except for a slight reduction in foetal weights in the groups where maternal toxicity resulted in reduced terminal maternal body weights. The total dose level of 98 or 90 LDU/kg (weekly 30, twice weekly 18 or daily 7 LDU/kg) was considered the NOAEL for embryo-toxicity.

Effects on embryo-foetal development were also evaluated in rabbits following multiple dose intramuscular administration of incobotulinumtoxinA at single dose levels of up to 5 LDU/kg. Maternal toxicity was observed at 2.5 and 5 LDU/kg. The maternal NOAEL was determined to be 1.25 LDU/kg after intramuscular administration during gestation. Abortions between GD 23 and 29 occurred in females at 5 LDU/kg; these were most likely associated with the observed maternal toxicity, as indicated by severe body weight loss in the affected females and the absence of embryo-fetal effects in the surviving dams. No indications of embryotoxicity or teratogenicity were seen at any of the dose levels tested, and therefore the single dose level of 5 LDU/kg was considered as the foetal NOAEL under the defined experimental conditions.

Peri- and Post-natal Development

The embryo-foetal, peri and post-natal development of the rat and the subsequent reproductive performance of the offspring was evaluated following repeated intramuscular doses of incobotulinumtoxinA from day 6 of gestation to weaning. There was no adverse effect of maternal treatment on pre- or post-natal development or reproductive performance of the offspring in any group. The NOAEL for the embryo-foetal and peri- and post-natal development of the rat and subsequent reproductive performance of the offspring was therefore weekly 20 (total of 120 LDU/kg) or daily 3 LDU/kg (total of 114 LDU/kg).

Post-weaning Development in Juvenile Animals

The effects of incobotulinumtoxinA on post-weaning development in juvenile rats were assessed after repeated intramuscular injections of up to 30 LDU/kg/administration at 2 week intervals up to 11 weeks of age. Dose-dependent decreases in size and weight of injected muscle, mean body weight gain, and food consumption were observed however there were no relevant effects on sexual maturation and post-weaning development. At 30 LDU/kg, some males failed to mate, i.e., reproductive performance was impaired, while some others had atrophy of the testicular germinal epithelium, however, not all animals were affected. There were no adverse effects on mating performance or on the testicular germinal epithelium at lower dose levels. There were no indications of systemic toxicity other than growth retardation at a dose of 10 LDU/kg and below.

Local Tolerance

Local tolerance of incobotulinumtoxinA was assessed in mice, rabbits, and monkeys. Studies indicate that incobotulinumtoxinA does not induce clinically relevant local intolerance reactions after repeated intramuscular injection up to 40 LDU/kg or repeated intradermal administration up to 8.34 LDU/kg.

IncobotulinumtoxinA was also found to be non-irritating when administered via the ocular route in rabbits (100 LDU/animal).

Hemolytic Activity

In an *in vitro* study with pelleted human erythrocytes, incobotulinumtoxinA was not hemolytic at concentrations up to 400 LDU/mL (concentrations at least 400 times the maximal achievable concentration in human blood). Therefore, a hemolytic potential in human blood appears extremely unlikely.

Antigenicity

The antigenicity of incobotulinumtoxinA was examined in two repeated-dose studies in rabbits.

In the initial study the-formation of neutralizing antibodies against the active neurotoxin was measured before, during and after five intradermal biweekly applications of a high dose (25 LDU per administration, approximately 8.34 LDU/kg) of incobotulinumtoxinA or Active Comparator 1. In study week 12, Botulinum neurotoxin type A-neutralizing antibodies were found in 4 of 8 surviving rabbits treated with Active Comparator 1 versus 0 of 10 surviving rabbits treated with incobotulinumtoxinA.

Results were confirmed with another study at lower doses where rabbits were administered incobotulinumtoxinA or Active Comparator 1 at 16 LDU per administration for 8 administrations, with a 25 LDU final booster administration over 33 weeks. An Active Comparator 2 treatment group was dosed at 40 LDU per administration for 5 administrations with a reduced dose of 20 LDU for the sixth (final) administration (due to an observed toxicity in terms of reduced body weight). After 6 injections 15 of 20 Active Comparator 2 sera were able to neutralize the paralytic activity of the neurotoxin. In test week 36, four of 20 animals treated with Active Comparator 1 had detectable neutralizing antibodies versus 0 of 20 animals administered incobotulinumtoxinA.

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PART III: CONSUMER INFORMATION

PrXEOMIN COSMETIC®
(incobotulinumtoxinA)

This leaflet is part III of a three-part "Product Monograph" published when Xeomin 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 Xeomin Cosmetic®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Xeomin Cosmetic® is used in adults for the temporary improvement in the appearance of upper facial lines including forehead, crow's feet and frown lines.

What it does:
Xeomin Cosmetic® is a medicine that relaxes the muscles.

When it should not be used:

- if you are allergic (hypersensitive) to Botulinum neurotoxin type A or any of the other ingredients of Xeomin Cosmetic®
- if an infection or inflammation is present at the proposed injection site
- If you suffer from generalized disorders of muscle activity (e.g., myasthenia gravis, Lambert- Eaton Syndrome).

What the medicinal ingredient is:
incobotulinumtoxinA (purified Botulinum neurotoxin type A, free from complexing proteins)

What the important nonmedicinal ingredients are:
Albumin (human) and sucrose (sugar)

What dosage forms it comes in:
incobotulinumtoxinA for injection, 100 units per vial

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- The term "unit" upon which dosing is based is a specific measurement of toxin activity that is unique to MERZ Pharmaceuticals GMBH's formulation of Xeomin Cosmetic. Therefore, the "units" used to describe Xeomin Cosmetic's activity are different from those used to describe that of other botulinum toxin preparations and the units representing Xeomin Cosmetic's activity are not interchangeable with other products.

BEFORE you use Xeomin Cosmetic® talk to your doctor or pharmacist if:

- you suffer from any type of bleeding disorder
- you receive substances that prevent the blood from clotting (e.g. coumarin, heparin, acetylsalicylic acid, clopidogrel)
- you suffer from pronounced weakness or decreased muscle volume in the muscle where you will receive the injection.
- you suffer from a disease called amyotrophic lateral sclerosis (ALS) which can lead to generalized muscle decrease.
- you suffer from any disease that disturbs the interaction between nerves and skeletal muscles (peripheral neuromuscular dysfunction).
- you have or have had swallowing difficulties.
- you have had problems with injections of Botulinum toxin type A in the past.
- you are due to have surgery.

Side effects may occur after injections of Xeomin Cosmetic® temporarily paralysing affected muscle groups. Patients who receive the recommended doses may rarely experience excessive muscle weakness.

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

Immediately tell your doctor if you experience any difficulties in swallowing, speech and/or breathing while on Xeomin Cosmetic®. These symptoms, ranging from very mild to severe, can persist for 1-3 weeks or longer after injection.

Tell your doctor if you are taking other medicines, including any you have bought at your pharmacy, supermarket or health food shop.

If you are pregnant or breast-feeding, Xeomin Cosmetic® should not be used.

The risks for development of neutralizing antibodies to Botulinum toxins have been reported to be related to high dosage and too frequent injections. Antibodies may reduce the therapeutic effectiveness of the product.

Driving and using machines You should not drive or engage in other potentially hazardous activities if drooping eyelids, weakness (asthenia), muscle weakness, dizziness, or vision disorder occur. If in doubt ask your doctor for advice.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

The effect of Xeomin 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

Usual dose:
Xeomin Cosmetic® may only be used by health care professionals experienced in the application of Botulinum toxin.

Dissolved Xeomin Cosmetic® is intended for injections into the muscle.

The optimum dosage, frequency and number of injection sites in the treated muscle will be chosen by your doctor individually for you. The results of initial treatment with Xeomin Cosmetic® should be evaluated and may lead to dose adjustment until the desired therapeutic effect is achieved. Treatments should generally be more than 3 months apart.

If you have the impression that the effect of Xeomin Cosmetic® is too strong or too weak, let your doctor know. In cases where no therapeutic effect is apparent, alternative therapies should be taken into consideration.

Overdose:
Overdose with Xeomin Cosmetic® is a relative term that can reflect undesired esthetic effect. Symptoms of overdose for this product, as for all botulinum toxins, are related to the dose, the condition being treated and susceptibility of the patient. Symptoms are not apparent immediately after the injection and may include general weakness, drooping eyelid, double vision, breathing and speech difficulties, and paralysis of the respiratory muscles or swallowing difficulties which may result in pneumonia.

In case you feel symptoms of overdose please seek medical emergency services immediately or ask your relatives to do so, and have yourself admitted to hospital. Medical supervision for up to several days and assisted ventilation may be necessary.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Xeomin Cosmetic® can cause side effects, although few people get them.

Side effects may be restricted to the area around the injection site (e.g. localised muscle weakness, local pain, inflammation, pins and needles, reduced sense of touch, tenderness, swelling (general), swelling of the soft tissue, skin redness, itching, localised infection, bleeding and/or bruising). Flu-like symptoms have been reported.

The most commonly reported side effects include headache, swelling around the eye/eyelid, changes in the shape of the eyebrow, including raised eyebrow, drooping of the eyelid, pain, bleeding and/or bruising, and redness near the injection site, dry eye, heavy feeling of frontal area, reduced sense of touch, facial asymmetry, and nausea. Uncommon side effects include heavy feeling of the eyelid/eyebrow, fatigue, muscle twitching, blurred vision, and inflammation of the nose and throat (nasopharyngitis).

Rare side effects may include excessive muscle weakness distant from the injection site which may result in swallowing, speech or breathing problems. Serious immediate allergic reactions including hives, swelling including swelling of the face, lips, mouth or throat, swelling of the hands, feet or ankles, wheezing, feeling faint and shortness of breath have been rarely reported. **Seek immediate medical attention if you experience anaphylaxis, serum sickness, or any of the above side effects.**

In rare cases swallowing difficulties may lead to problems with breathing and you may have a higher risk of inhaling foreign substances or fluids resulting in lung inflammation or infection (pneumonia).

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

HOW TO STORE IT

Keep out of the reach and sight of children.

Xeomin Cosmetic®, unreconstituted, is stored at room temperature (up to 25°C). Once reconstituted with physiological saline, it may be stored for up to 24 hours at 2 to 8°C.

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 Merz Pharma Canada at: 1-866-815-8715.

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