

## PRODUCT MONOGRAPH

### Pr **XEOMIN COSMETIC™**

incobotulinumtoxinA

Clostridium Botulinum Neurotoxin Type A (150 kD), free from complexing proteins

Powder for solution for injection, 100 LD<sub>50</sub> units per vial

Pharmaceutical Standard: House

Muscle relaxant, peripherally acting agent

Manufactured by: Merz Pharmaceuticals GmbH  
Eckenheimer Landstraße 100  
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June 19, 2013

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# XEOMIN COSMETIC™

incobotulinumtoxinA

Clostridium Botulinum Neurotoxin Type A (150 kD), free from complexing proteins

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Intramuscular injection	Powder for solution for injection, 100 LD <sub>50</sub> units per vial	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### 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 mouse LD<sub>50</sub> 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 serum 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.

### INDICATIONS AND CLINICAL USE

XEOMIN COSMETIC™ is indicated in adults for:

- the temporary improvement in the appearance of moderate to severe glabellar lines.

**Geriatrics (>65 years of age):**

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

**Pediatrics (< 18 years of age):**

Use of XEOMIN COSMETIC™ is not recommended in children.

**CONTRAINDICATIONS**

- Hypersensitivity to Botulinum neurotoxin type A or to any of the excipients.
- Presence of infection 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 XEOMIN COSMETIC™. Therefore, the "unit" or "U" used to describe XEOMIN COSMETIC™ activity are different from those used to describe that of other botulinum toxin preparations and the units representing XEOMIN COSMETIC™ activity are not interchangeable with other products.
- Follow the recommended dosage and frequency of administration for XEOMIN COSMETIC™ (See **DOSAGE AND ADMINISTRATION**).

**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.

Caution should be used when XEOMIN 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.

Botulinum toxins are used to treat a range of disorders including spasticity and dystonia in both small and large muscles, with doses of toxin ranging from approximately 10 units to 400 units.

In very rare cases severe adverse events like muscle weakness, dysphagia or aspiration pneumonia with a suspected causal relationship to toxin spread have been reported with the use of Botulinum toxin. Also very rare cases of adverse events with a fatal outcome have been reported. Patients with a neurological underlying disease or swallowing, speech or respiratory difficulties have an increased risk for these adverse drug reactions and should be treated and supervised very carefully. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

XEOMIN COSMETIC™ should be used with caution in patients suffering from amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular dysfunction.

An anaphylactic reaction may occur rarely after injection of Botulinum neurotoxin type A. Adrenaline and other medical aids for treating anaphylaxis should be available.

Prior to administering XEOMIN COSMETIC™, the physician must familiarize himself/herself with the patient's anatomy and any alterations to the anatomy due to prior surgical procedures.

Injection intervals of XEOMIN COSMETIC™ should 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.

XEOMIN COSMETIC™ contains albumin, a derivative of human blood. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include careful selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There are no reports of viral transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.

### **Hematologic**

XEOMIN COSMETIC™ should be used with caution if bleeding disorders of any type occur. It should be used with caution in patients receiving anticoagulant therapy.

### **Immune**

The risks for development of neutralizing antibodies to Botulinum toxins are related to high dosage, too frequent injections, and higher total dosage received of Botulinum toxin. Antibody development may lead to resistance (See **DOSAGE AND ADMINISTRATION**).

### **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.

## **Skin**

As is expected for any injection procedure, localized pain, inflammation, tenderness, swelling/edema, erythema, localized infection, localized pruritus, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have also been reported. Care should be taken when injecting near vulnerable anatomic structures.

## **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 toxin type A is excreted into the breast milk. Therefore, the using of XEOMIN COSMETIC™ during lactation is not recommended.

**Pediatrics (<18 years of age):** Use of XEOMIN COSMETIC™ is not recommended in children.

### **Geriatrics (> 65 years of age):**

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

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Adverse reactions are reversible and vary in frequency depending upon the injection site, dose, physician expertise and injection technique.

The overall incidence of adverse reactions did not increase with increasing numbers of injections.

In the placebo controlled single-dose glabellar line studies, 47.1% of subjects treated with XEOMIN COSMETIC™ reported adverse events compared to 37.0% in the placebo group. One subject in the XEOMIN COSMETIC™ group was withdrawn due to an adverse event that was not considered related to treatment. Severe adverse events were reported for 6.2% and 4.1% of the XEOMIN COSMETIC™ and placebo groups, respectively. The only severe adverse drug reaction was headache occurring in 0.7% of subjects in the XEOMIN COSMETIC™ group and 0.3% in the placebo group. The adverse drug reactions reported in the XEOMIN COSMETIC™ group involved the system organ classes of nervous system disorder and musculoskeletal and connective tissue disorders. In the 3 placebo-controlled studies in glabellar lines, 5 serious

adverse events were reported. None of these were considered study treatment related.

### **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 III, 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  $\geq 1\%$  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  $\geq 1\%$  of Glabellar Line Patients (Greater than Placebo)**

<b>System Organ Class Preferred Term</b>	<b>XEOMIN COSMETIC™ (N=535) n(%)</b>	<b>Placebo (N=268) n(%)</b>
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)**

<b>System Organ Class Preferred Term</b>	<b>XEOMIN COSMETIC™* (N=535) n(%)</b>	<b>Placebo (N=268) n(%)</b>
Nervous System Disorder		
Facial Paresis	4 (0.7%)	0
General Disorders and Administration Site Conditions		
Injection Site Haematoma	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.

### **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 adverse reactions have been reported: injection site edema, myalgia, flu-like symptoms and hypersensitivity reactions such as swelling of the soft tissue (oedema), redness, itching, rash (local and generalized) and breathlessness.

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**

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 aminoglycosides, polymyxins, tetracyclines, lincomycin, spectinomycin 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 lasting effects.

4-Aminochinolines may reduce the effect of XEOMIN COSMETIC™.

### **Drug-Food Interactions**

Interactions with food are not relevant.

### **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 drooping eyelids that interfere with vision, blurred vision or muscle weakness 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 treatment and the use of required equipment.

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.

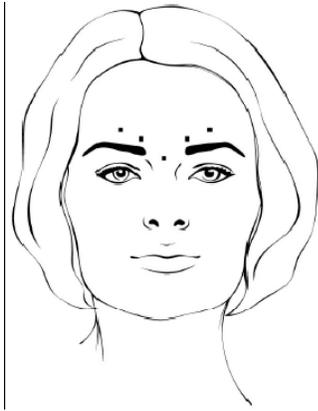
The smaller the injection volume the less pressure sensation and the less spread of Botulinum neurotoxin type A in the injected muscle occurs. This is of benefit in reducing effects on nearby muscles when small muscle groups are being injected.

Injection intervals of XEOMIN COSMETIC™ should be no more frequent than every three months. Indication specific dosage and administration recommendations should be followed. When treating patients with XEOMIN COSMETIC™ previous treatment with all Botulinum toxin products for all other indications should be taken into consideration.

### **Recommended Dose and Dosage Adjustment**

XEOMIN COSMETIC™ is reconstituted 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 should be avoided in order to avoid ptosis. 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.



### **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, 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 gauge needle). See dilution table below for volume of properly diluted toxin.

### **Reconstitution:**

#### **Parenteral Products:**

This medicinal product must not be mixed with other medicinal products except those mentioned below.

XEOMIN COSMETIC™ is reconstituted prior to use with sterile unpreserved sodium chloride 9 mg/ml (0.9%) solution for injection. 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 3) is drawn up into a

syringe. The exposed portion of the rubber stopper of the vial is cleaned with alcohol (70%) prior to insertion of the needle. Reconstitution should be performed gently to avoid foam formation. The vial must be discarded, if the vacuum does not pull the solvent into the vial. Record the date and time of reconstitution on the vial.

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 3: Possible Dilutions of XEOMIN COSMETIC™ in the Reconstituted Solution**

<b>Solvent added</b> (sodium chloride 9 mg/mL (0.9%) solution for injection)	<b>Resulting dose in units per 0.1 mL</b>
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**

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

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

### **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**

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

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

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 LD<sub>50</sub> units of incobotulinumtoxinA (Clostridium Botulinum neurotoxin type A (150 kD), free from complexing proteins) where one unit corresponds to the median lethal dose (LD<sub>50</sub>) when the reconstituted product is injected intraperitoneally into mice under defined conditions, 4.7 mg of sucrose and 1.0 mg of human serum 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

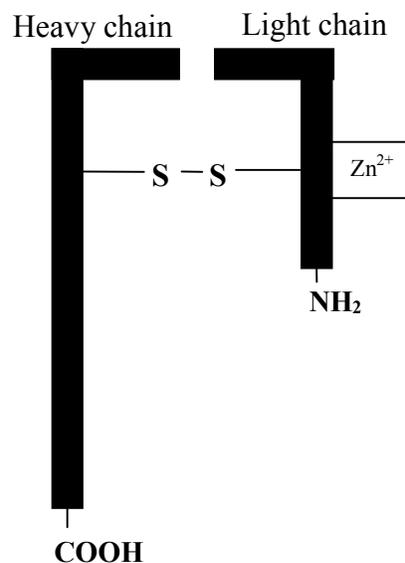
**Chemical name:** Botulinum Toxin Type A  
(*toxinum botulinicum typum A*).

#### 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 mouse LD<sub>50</sub> 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 serum 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 (Mr = 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 4 and 5 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 4: CETS: Responder analysis at Day 30 - imputation of missing data – FAS (Study 1)**

CETS	Response: Yes [n (%)]	1
	Response rate (RR)*	
	Difference RR (NT 201-Placebo)	0
	95% CI for difference RR	
	p-value (Fisher's exact test)	
2-point response investigator assessment	Response: Yes [n (%)]	1
2-point response patient assessment	Response: Yes [n (%)]	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 with response on N.

\*Missing data were imputed with last observation carried forward (LOCF)  
Note: Visit 3 = Day 30.

**Table 5: CETS: Responder analysis at Day 30 - imputation of missing data – FAS (Study 2)**

CETS	Response: Yes [n (%)]	8
	Response rate (RR)*	
	Difference RR (NT 201-Placebo)	0
	95% CI for difference RR	
	p-value (Fisher's exact test)	
2-point response investigator assessment	Response: Yes [n (%)]	1
2-point response patient assessment	Response: Yes [n (%)]	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 with response on N.

\*Missing data were imputed with last observation carried forward (LOCF)  
Note: Visit 3 = Day 30.

In an open-label study 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 III study. 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.

## 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<sup>2</sup>, respectively). The maximal area of anhidrosis over 6 weeks was significantly larger with Active Comparator 2 (459.1 [±151.81] mm<sup>2</sup>) than with XEOMIN COSMETIC™ (Table 6). 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 6: Maximal Area of Anhidrosis within 6 Weeks\***

		<b>XEOMIN COSMETIC™ M N=13</b>	<b>Active Comparato r 1 N=16</b>	<b>Active Comparato r 2 N=17</b>
Mean	mm <sub>2</sub>	364.3	343.1	459.1
Standard Deviation	mm <sub>2</sub>	138.13	110.72	151.81
Median	mm <sub>2</sub>	298	345	436
Coefficien t 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 muscle recovery 26 weeks after the last injection, although histological recovery of muscle atrophy was advanced but 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 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<sub>50</sub> is about 5 orders of magnitude higher than the intravenous and intraperitoneal LD<sub>50</sub>. When compared to onabotulinumtoxinA, the oral LD<sub>50</sub> 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 to 32 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. 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 *gastrocnemius* muscle seemed to be more rapidly affected than the *biceps*. 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 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 reproductive 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 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. 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/dose 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. Reproductive performance was impaired at 30 LDU/kg/dose. There were no indications of systemic toxicity other than growth retardation at a dose of 10 LDU/kg/dose 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).

### **Haemolytic Activity**

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

## REFERENCES

1. Arnon SS, Schechter R, Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, et al. Botulinum toxin as a biological weapon: Medical and public health management. *JAMA* 2001; 285(8): 1059-1070.
2. Benecke R, Jost W, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. *Neurology* 2005; 64: 1949-1951.
3. Blümel J, Frevert J, Schwaier A. Comparative Antigenicity of Three Preparations of Botulinum Neurotoxin Type A in the Rabbit. *Neurotox Res* 2005; 60: 64.
4. De Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO. Functional repair of motor endplates after botulinum neurotoxin type A poisoning: Biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci U S A* 1999; 96(6): 3200-3205.
5. Dolly JO, Black J, Williams RS, Melling J. Acceptors for botulinum neurotoxin reside on motor nerve terminals and mediate its internalization. *Nature* 1984; 307(5950), 457-460.
6. Göschel H, Wohlfarth K, Frevert J, Dengler R, Bigalke H. Botulinum A toxin therapy: Neutralizing and nonneutralizing antibodies - therapeutic consequences. *Exp Neurol* 1997; 147(1): 96-102.
7. Jost WH, Kohl A, Brinkmann S, Comes G. Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT201) compared with commercially available botulinum toxin type A (BOTOX®) in healthy volunteers. *J Neural Transm* 2005; 112(7): 905-913.
8. Pearce LB, Borodic GE, Johnson EA, First ER, MacCallum R. The median paralysis unit: A more pharmacologically relevant unit of biologic activity for botulinum Neurotoxin. *Toxicon* 1995; 33(2): 217-227.
9. Wohlfarth K, Müller C, Sassin I, Comes G, Grafe S. Neurophysiological double-blind trial of a botulinum neurotoxin type A free of complexing proteins. *Clin Neuropharmacol* 2007; 30(2): 86-94.

**PART III: CONSUMER INFORMATION****XEOMIN 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 moderate to severe 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 is present at the injection site
- If you suffer from generalized disorders of muscle activity (e.g., myasthenia gravis, Eaton Lambert-Syndrome)

What the medicinal ingredient is:

incobotulinumtoxinA (purified neurotoxin free from complexing proteins)

What the important nonmedicinal ingredients are:

Albumin (human) and sucrose (sugar).

What dosage forms it comes in:

White powder for solution for injection, 100 LD<sub>50</sub> units per vial

**WARNINGS AND PRECAUTIONS**

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 (anticoagulant therapy)
- 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. This disease leads to a wasting of muscle tissue.
- you suffer from any disease that disturbs the interaction between nerves and skeletal muscles (peripheral neuromuscular dysfunction)

- you have swallowing difficulties.
- if you have problems with injections of Botulinum toxin type A in the past.
- if you are due to have surgery.

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

Tell your doctor if you experience any difficulties in swallowing food while on XEOMIN 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.

Ask your doctor or pharmacist for advice before taking any medicine.

If you are pregnant or breast-feeding, XEOMIN COSMETIC™ should not be used.

If you experience drooping eyelids that interfere with vision, blurred vision or muscle weakness you should avoid engaging in potentially hazardous activities such as driving until you have adjusted to the changes or the issues have resolved.

**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.

Theoretically, the effect of XEOMIN COSMETIC™ may be increased by:

- aminoglycoside antibiotics.
- medicinal products that interfere with the transfer of an impulse from a nerve to a muscle, e.g. tubocurarine-type muscle relaxants that weaken the muscles.

Therefore, the concomitant use of XEOMIN COSMETIC™ with aminoglycosides or spectinomycin requires special care.

Theoretically, the effect of XEOMIN COSMETIC™ may be reduced by:

- certain anti-malaria/ anti-rheumatic medicines (4-Aminochinolines)

**PROPER USE OF THIS MEDICATION**Usual dose:

XEOMIN COSMETIC™ may only be used by health care professionals experienced in the application of Botulinum toxin.

The optimum dosage and number of injection sites in the treated muscle will be chosen by your doctor 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.

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.

Your body may develop antibodies after you received Botulinum toxin type A preparations. Antibodies may reduce the therapeutic effectiveness of the product.

#### Overdose:

Overdose with XEOMIN COSMETIC™ is a relative term that can reflect undesired aesthetic effect. Symptoms of overdose for this product, as for all botulinum toxins, are related to the dose, the condition being treated and susceptibility of the patient. Symptoms are not apparent immediately after the injection and may include general weakness, drooping eyelid, double vision, swallowing and speech difficulties, and pneumonia.

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

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

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

### **SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Side effects following treatment with XEOMIN COSMETIC™ are rare and are generally not serious.

The most commonly reported side effects include headache, swelling around the eye, changes in the shape of the eyebrow, drooping of the eyelid and pain and bruising near the injection site.

*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™, unconstituted, 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](http://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 0701D  
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](http://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.

This leaflet was prepared by Merz Pharmaceuticals GmbH

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