

PRODUCT MONOGRAPH

PrXEOMIN[®]

incobotulinumtoxinA

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

Powder for solution for injection
50 and 100 LD₅₀ units per vial

Pharmaceutical Standard: House

Muscle relaxant, peripherally acting agent

Manufactured by: Merz Pharmaceuticals GmbH
Eckenheimer Landstraße 100
60318 Frankfurt/Main
Germany

Date of Revision:
June 19, 2013

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

Imported and distributed by:
Merz Pharma Canada Ltd.
7 Innovation Drive, Unit 115
Flamborough, ON, L9H 7H9

Control No: 165909

Date of Approval: June 28, 2013

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION.....	3
DESCRIPTION.....	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS.....	4
WARNINGS AND PRECAUTIONS	5
ADVERSE REACTIONS	8
DRUG INTERACTIONS	11
DOSAGE AND ADMINISTRATION	12
OVERDOSAGE.....	17
ACTION AND CLINICAL PHARMACOLOGY	17
STORAGE AND STABILITY	19
SPECIAL HANDLING INSTRUCTIONS.....	19
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	19
PART II: SCIENTIFIC INFORMATION	21
PHARMACEUTICAL INFORMATION.....	21
CLINICAL TRIALS	23
DETAILED PHARMACOLOGY	28
TOXICOLOGY.....	31
REFERENCES.....	35
PART III: CONSUMER INFORMATION	36

PrXEOMIN®

incobotulinumtoxinA

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

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

DESCRIPTION

XEOMIN® (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® 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 either 50 or 100 mouse LD₅₀ 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® 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[®] is indicated:

- for the treatment of hypertonicity disorders of the 7th nerve such as blepharospasm including benign essential blepharospasm and hemifacial spasm in adults.
- to reduce the subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults
- for the treatment of upper limb spasticity associated with stroke in adults.

XEOMIN[®] as a treatment for focal spasticity has been studied in association with usual standard care regimens and is not intended as a replacement for these treatment modalities. XEOMIN[®] is not likely to be effective at a joint affected by a fixed contracture.

XEOMIN[®] may only be used by physicians with suitable qualifications and experience in the application of Botulinum toxin type A.

Geriatrics (> 65 years of age):

Although clinical studies included a number of patients over the age of 65, no clinical trials specifically designed for elderly patients have been performed.

Initial dosing should begin at the lowest recommended dose for the specific indication and be cautiously titrated within the recommended range for optimal patient outcome.

Pediatrics (< 18 years of age):

XEOMIN[®] has not been studied in the paediatric population and is therefore currently not recommended in this age group.

CONTRAINDICATIONS

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

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[®]. Therefore, the "unit" or "U" used to describe XEOMIN[®] activity are different from those used to describe that of other botulinum toxin preparations and the units representing XEOMIN[®] activity are not interchangeable with other products.
- Follow the recommended dosage and frequency of administration for XEOMIN[®] (See **DOSAGE AND ADMINISTRATION**).

General

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

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

Prior to administering XEOMIN[®], the physician must familiarise himself/herself with the patient's anatomy and any alterations to the anatomy due to prior surgical procedures. Extra caution is required when injecting at sites close to sensitive structures such as the carotid artery and lung apices.

There were no clinical data available in long-term repeat dose treatment and in treatment-naïve patients for cervical dystonia and blepharospasm. However, there is information available with repeat dose treatment and in treatment-naïve patients afflicted with post-stroke spasticity of the upper limb.

XEOMIN[®] should be used with caution:

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

Clinical effects of XEOMIN[®] may increase or decrease with repeated injections. Possible reasons for change in clinical effect are different techniques of reconstitution, the chosen injection intervals, the injected muscles and marginally varying toxin activity resulting from the biological testing procedure employed or secondary non-response.

Previously akinetic or sedentary patients should be reminded to gradually resume activities following the injection of XEOMIN[®].

XEOMIN[®] as a treatment for focal spasticity has been studied in association with usual standard care regimens and is not intended as a replacement for these treatment modalities. XEOMIN[®] is not likely to be effective at a joint affected by a fixed contracture.

XEOMIN[®] 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.

Gastrointestinal

Spasmodic torticollis

Patients should be informed that injections of XEOMIN[®] for the management of spasmodic torticollis may cause mild to severe dysphagia with the risk of aspiration and dyspnoea. Medical intervention may be necessary (e.g. in the form of a gastric feeding tube) (See **ADVERSE REACTIONS**). Dysphagia can last for up to two to three weeks after injection, but a duration of up to five months has been reported in one case. Patients with smaller neck muscle mass, or patients who require bilateral injections into the sternocleidomastoid muscles are at greater risk. The occurrence of dysphagia is attributable to the spread of the pharmacological effect of Botulinum toxin as the result of the neurotoxin spread into the oesophageal musculature.

Hematologic

XEOMIN[®] 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, young age at disease onset, and higher total dosage received of Botulinum toxin. Antibody development may lead to treatment resistance (See **DOSAGE AND ADMINISTRATION**).

Ophthalmologic

Blepharospasm

Because of the anticholinergic effect of Botulinum toxin type A, XEOMIN[®] should be used with caution in patients at risk of developing angle closure glaucoma.

In order to prevent ectropion, injections into the lower lid area should be avoided, and vigorous treatment of any epithelial defect is necessary. This may require protective drops, ointments, soft bandage contact lenses, or closure of the eye by patching or similar means.

Reduced blinking following XEOMIN[®] injection into the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve disorders (facial nerve). Careful testing of corneal sensation should be performed in patients with previous eye operations.

Ecchymosis easily occurs in the soft tissues of the eyelid. Immediate gentle pressure at the injection site can limit that risk.

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[®] should not be used during pregnancy unless clearly necessary and unless the potential benefit justifies the risk.

Nursing Women:

It is not known whether Botulinum toxin type A is excreted into the breast milk. Therefore, the use of XEOMIN[®] during lactation is not recommended.

Pediatrics (< 18 years of age):

No data is available on the use of XEOMIN[®] in children and it is therefore currently not recommended in this age group.

Geriatrics (> 65 years of age):

Although clinical studies included a number of patients over the age of 65, no clinical trials specifically designed for elderly patients have been performed. Initial dosing should begin at the lowest recommended dose for the specific indication and be cautiously titrated within the recommended range for optimal patient outcome.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Undesirable effects associated with the therapeutic use of Botulinum toxin type A are mainly related to the diffusion of Botulinum neurotoxin type A from the target muscle to adjacent muscles. Such undesirable effects are rare, and most are localized in close proximity to the injection site; systemic side effects are uncommon. Intramuscular injection into neck muscles for treatment of cervical dystonia occasionally results in transient dysphagia and a general weakness in the neck muscles. Treatment of blepharospasm by periocular injection can result in ptosis and diplopia. Intramuscular injections of Botulinum toxin type A for upper limb spasticity were reported to be commonly associated with local reactions like hypertonia, ecchymosis, purpura, pain in shoulder, arm or hand, muscle weakness, bleeding and itching after administration at the injection site.

Side effects related to spread of toxin distant from the site of administration have been reported very rarely (exaggerated muscle weakness, dysphagia, and aspiration pneumonitis with fatal outcome in some cases). Dysphagia has been reported following injection to sites other than the cervical musculature. The following other adverse events have been reported following administration of conventional Botulinum toxin type A-complex: dysarthria, abdominal pain, hyperhidrosis, anorexia, hypoacusis, tinnitus, radiculopathy, and syncope.

There have been rare reports of undesirable effects related to the cardiovascular system, such as arrhythmia and myocardial infarction, some with fatal outcomes. It remains unclear whether these deaths were induced by conventional preparations containing the Botulinum toxin type A-complex or whether these were caused by pre-existing cardiovascular disease. Serious and/or immediate hypersensitivity reactions have been rarely reported, including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of conventional Botulinum toxin type A-complex either alone or in combination with other agents known to cause similar reactions.

QT interval prolongation has been reported in 2 out of 366 patients following administration of XEOMIN[®] in clinical studies with blepharospasm and cervical dystonia patients. However, these findings were not considered clinically relevant in the opinion of the treating cardiologist and the exact relationship of these events to XEOMIN[®] is unknown.

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.

In the 6 studies conducted to provide data on the safety of XEOMIN[®] 1082 subjects were treated with trial medications (XEOMIN[®], active comparator or placebo). In these studies 611 subjects received XEOMIN[®] (46 healthy male volunteers, 272 patients with cervical dystonia, 148

blepharospasm patients and 145 patients with post-stroke spasticity of the upper limb). The duration of observation was 130 days in the phase II study in cervical dystonia. For the phase III trials, patients were observed for up to 16 weeks in the focal dystonia trials and for up to 69 weeks in the spasticity trial. In the phase 1 trials volunteers were followed for up to 90 days or up to 52 weeks.

In all active-controlled trials subjects received 1 dose of either XEOMIN[®] and/or Active Comparator 1 (onabotulinumtoxinA) with doses ranging from 2- 32 units in healthy volunteers, 30-300 units in cervical dystonia patients and 15 - 100 units in blepharospasm patients. In the placebo-controlled study in post-stroke spasticity of the upper limb doses administered ranged from 80 - 435 units. In the subsequent Open-Label Extension (OLEX) Period doses administered over up to a maximum of 5 injection intervals ranged between 95 units and 500 units XEOMIN[®]. Overall the mean dose delivered was 122.4 units in the XEOMIN[®] population and 92.6 units in the active comparator population. Tables 1 to 4 summarize adverse drug reactions reported in $\geq 1\%$ in any treatment group for each indication.

Table 1: Adverse Drug Reactions Reported in $\geq 1\%$ of Cervical Dystonia Patients

System organ class Preferred term	Number of subjects (%)	
	XEOMIN [®] N=272	Active Comparator 1 (onabotulinumtoxinA) N=244
Gastrointestinal disorders	24 (8.8)	15 (6.1)
Dysphagia	24 (8.8)	15 (6.1)
Musculoskeletal & connective tissue disorders	9 (3.3)	2 (≤ 1)
Muscular weakness	4 (1.5)	1 (≤ 1)
Neck pain	5 (1.8)	1 (≤ 1)

Table 2: Adverse Drug Reactions Reported in $\geq 1\%$ of Blepharospasm Patients

System organ class Preferred term	Number of subjects (%)	
	XEOMIN [®] N=148	Active Comparator 1 (onabotulinumtoxinA) N=152
Eye disorders	12 (8.1)	12 (7.9)
Dry eye	3 (2.0)	0 (0.0)
Eyelid oedema	0 (0.0)	2 (1.3)
Eyelid ptosis	9 (6.1)	7 (4.6)
Vision blurred	0 (0.0)	3 (2.0)

Table 3 : Adverse Drug Reactions Reported in $\geq 1\%$ of Patients with Post-stroke Spasticity of the Upper Limb (Double-blind Period)

System organ class Preferred term	Number of subjects (%)	
	XEOMIN [®] N=73	Placebo N=75
Gastrointestinal disorders	0 (0.0)	1 (1.3)
Dysphagia	0 (0.0)	1 (1.3)
General disorders & administration site conditions	0 (0.0)	1 (1.3)
Injection site pain	0 (0.0)	1 (1.3)
Nervous system disorders	1 (1.4)	0 (0.0)
Headache	1 (1.4)	0 (0.0)

Table 4: Adverse Drug Reactions Reported in $\geq 1\%$ of Patients with Post-Stroke Spasticity of the Upper Limb (Open-Label Extension Period)

System organ class Preferred term	XEOMIN [®]
	Number of Subjects (%) N= 145
Gastrointestinal disorders	
Dysphagia	2 (1.4)
General disorders & administration site conditions	
Injection site pain	4 (2.8)
Musculoskeletal and connective tissue disorders	
Muscular weakness	5 (3.4)
Pain in extremity	2 (1.4)

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Cervical Dystonia: eye pain, diarrhoea, dry mouth, vomiting, colitis, asthenia, injection site inflammation, injection site tenderness, skeletal pain, myalgia, headache, tremor, dysphonia, skin rash, erythema, pruritus, sweating increased

Blepharospasm: conjunctivitis, dry mouth, inflicted injury, muscle weakness, paraesthesia, headache, skin rash

Post-stroke Spasticity of the Upper Limb:

dry mouth, peripheral oedema, myalgia, cough

Abnormal Hematologic and Clinical Chemistry Findings

In all clinical trials, there were no findings indicative of underlying pathological changes as a result of trial medication, both with regard to the incidence of abnormal hematologic and clinical chemistry values and with regard to the mean change in laboratory values for either treatment group.

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported since XEOMIN[®] has been marketed: eye swelling, eyelid oedema, madarosis, vision blurred; injection site reactions; asthenia, fatigue; dysphagia, nausea, abdominal distension; hypersensitivity reactions like swelling, oedema (also apart from injection site), erythema, pruritus, rash (local and generalized), allergic dermatitis, drug eruptions, lymphadenopathy, alopecia and breathlessness; dysphonia, cough, asthma; herpes zoster; muscular weakness, muscle spasm, myalgia, trismus; dysarthria, headache, somnolence; cardiovascular insufficiency, circulatory collapse; abnormal dreams; flu-like symptoms.

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[®] with aminoglycosides, polymyxins, tetracyclines, linomycin, 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 longer lasting effects.

4-Aminochinolines may reduce the effect of XEOMIN[®].

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 results of laboratory tests have not been established.

Drug-Lifestyle Interactions

XEOMIN[®] has minor or moderate influence on the ability to drive and use machines. Due to the nature of the disease being treated, the ability to drive and to operate machines may be reduced. This could be compounded by some of the therapeutic and/or adverse effects of XEOMIN[®], which may also modify the ability to drive and operate machinery. Consequently affected persons should consider avoiding these tasks until they have adjusted to these changes.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- **Due to unit differences in the potency assay, XEOMIN[®] units are specific to XEOMIN[®]. Therefore unit doses or “U” recommended for XEOMIN[®] are not interchangeable with those for other preparations of Botulinum toxin.**
- XEOMIN[®] may only be used by physicians with suitable qualifications and experience in the application of Botulinum toxin.
- Reconstituted XEOMIN[®] is intended for intramuscular injection. After reconstitution, XEOMIN[®] should be used for only one injection session and for only one patient.
- The minimal injection intervals and the maximum doses of XEOMIN[®] should be as recommended for the specific indication.
- The optimum dosage and number of injection sites in the treated muscle should be determined by the physician individually for each patient. A titration of the dose should be performed.
- A decrease or increase in the XEOMIN[®] dose is possible by administering a smaller or larger injection volume. Initial dosing should begin at the lowest recommended dose for the specific indication and be cautiously titrated within the recommended range for optimal patient outcome. 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.
- If no treatment effect occurs within one month after the initial injection, the following measures should be taken:

There are several potential explanations for a lack of or a diminished response to an individual

treatment with XEOMIN[®]. 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[®] 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.

- XEOMIN[®] has not been studied in the paediatric population and is therefore not recommended in the paediatric age group until further data become available.

Recommended Dose and Dosage Adjustment

Blepharospasm

The initial recommended dose is 1.25 to 2.5 units (0.05-0.1 mL volume) per injection site. The initial dose should not exceed 25 units per eye. In the management of blepharospasm, total dosing should not exceed 70 units and the period between each treatment session is recommended to be at least every 12 weeks.

The median time to first onset of effect is observed within four days after injection. The effect of each treatment generally lasts approximately 3-4 months; however, it may last significantly longer or shorter. The treatment can be repeated if required. There is limited experience in treatment naïve patients and in long-term repeat dose treatment.

At repeat treatment sessions, the dose may be increased up to two-fold (as long as the total dose of 70 units is not exceeded) if the response to the initial treatment is considered insufficient – usually defined as an effect that does not last longer than two months. However, there appears to be no additional benefit obtainable from injecting more than 5.0 units per site. Normally, no additional benefit is conferred by treating more frequently than every three months.

Spasmodic torticollis

In the management of spasmodic torticollis, XEOMIN[®] dosing must be tailored to the individual patient, based on the patient's head and neck position, location of possible pain, muscle hypertrophy, patient's body weight, and response to the injection. A suitable sterile needle (e.g. 25-30 gauge / 0.30-0.50 mm) is used for injections into superficial muscles, and an e.g. 22 gauge / 0.70 mm needle may be used for injections into deeper musculature. An injection volume of approximately 0.1 to 0.5 mL per injection site is recommended.

In practice, the usual total dose does not exceed 200 units. Doses of up to 300 units may be

given. No more than 50 units should be given at any one injection site.

The median first onset of effect is observed within seven days after injection. The effect of each treatment generally lasts approximately 3-4 months; however, it may last significantly longer or shorter. The period between each treatment session is recommended to be at least 12 weeks. There is limited experience in treatment naïve patients and in long-term repeat dose treatment.

Post-stroke Spasticity of the Upper Limb

Reconstituted XEOMIN[®] is injected using a suitable sterile needle (e.g. 26 gauge / 0.45 mm diameter / 37 mm length, for superficial muscles and a longer needle, e.g. 22 gauge / 0.7 mm diameter / 75 mm length, for deeper musculature). An injection volume of approximately 0.2 to 1 mL per injection site is recommended, but it can be exceeded to 1.5 mL in selected cases.

The doses (units) usually administered in the management of post-stroke spasticity of the upper limb are presented in Table 5.

Table 5: Dosage guide for the management of post-stroke spasticity of the upper limb

Clinical Pattern	Units
<i>Muscle</i>	
Flexed Wrist (Total)	90
<i>Flexor carpi radialis</i>	50
<i>Flexor carpi ulnaris</i>	40
Clenched Fist (Total)	80
<i>Flexor digitorum superficialis</i>	40
<i>Flexor digitorum profundus</i>	40
Flexed Elbow (Total)	130-190
<i>Brachioradialis</i>	60
<i>Biceps</i>	80
<i>Brachialis</i>	50
Pronated Forearm (Total)	25-65
<i>Pronator quadratus</i>	25
<i>Pronator teres</i>	40
Thumb-in-Palm (Total)	10-40
<i>Flexor pollicis longus</i>	20
<i>Adductor pollicis</i>	10
<i>Flexor pollicis brevis/ Opponens pollicis</i>	10

Total dosing should not exceed 400 units per treatment session involving different muscles.

Initial dosing should begin at the lowest recommended dose for the specific indication and be cautiously titrated within recommended dose range for optimal patient outcome.

The median time to first onset of effect is observed within four days after injection. The effect of

each treatment generally lasts approximately 3 months; however, it may last significantly longer or shorter. The period between each treatment session is recommended to be at least 12 weeks.

Administration

The multiple point injection technique into target muscles with disperse innervation zones can reduce undesirable effects and, at the same time, may reach more intrafusal fibres.

Blepharospasm

After reconstitution, the XEOMIN[®] solution is injected using a suitable sterile needle (e.g. 27-30 gauge / 0.30-0.40 mm). Electromyographic guidance is not necessary. An injection volume of approximately 0.05 to 0.1 mL is recommended.

XEOMIN[®] is injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. Additional sites in the brow area, the lateral orbicularis and in the upper facial area may also be injected if spasms here interfere with vision.

Injections near the levator palpebrae superioris should be avoided to reduce the occurrence of ptosis. Diplopia may develop as a result of Botulinum neurotoxin type A diffusion into the inferior oblique. Avoiding medial injections into the lower lid may reduce this adverse reaction.

Spasmodic torticollis

In the management of spasmodic torticollis, XEOMIN[®] is usually injected into the sternocleidomastoid, levator scapulae, scalenus, splenius capitis, and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may be involved and therefore require treatment. If difficulties arise isolating single muscles, injections should be performed using electromyographic guidance. The muscle mass and the degree of hypertrophy or atrophy are factors to be taken into consideration when selecting the appropriate dose.

Multiple injection sites permit XEOMIN[®] more uniform coverage of the innervated areas of the dystonic muscle and are especially useful in larger muscles. The optimum number of injection sites is dependent upon the size of the muscle to be chemically denervated.

The sternocleidomastoid should not be injected bilaterally as there is an increased risk of adverse reactions (in particular dysphagia) when bilateral injections or doses in excess of 100 units are administered into this muscle.

Post-stroke Spasticity of the Upper Limb

Localisation of the involved muscles with electromyographic guidance or nerve stimulation techniques may be necessary. Multiple injection sites may allow XEOMIN[®] to have more uniform contact with the innervation areas of the muscle and are especially useful when larger muscles are injected.

The exact dosage and number of injection sites should be tailored to the individual patient based on the size, number and location of muscles to be treated, the severity of spasticity, and the presence of local muscle weakness. Initial dosing should begin at the lowest recommended dose and be cautiously titrated within the recommended dose range for optimal patient outcome.

Reconstitution

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

XEOMIN[®] 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 6) 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[®] is a clear colourless solution free of particulate matter.

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

Table 6: Possible Dilutions of XEOMIN[®] in the Reconstituted Solution

Solvent added (sodium chloride 9 mg/mL (0.9%) solution for injection)	Resulting dose in units per 0.1 mL 50 U Vial	Resulting dose in units per 0.1 mL 100 U Vial
0.25 mL	20.0 U	--
0.5 mL	10.0 U	20.0 U
1.0mL	5.0 U	10.0 U
2.0 mL	2.5 U	5.0 U
4.0 mL	1.25 U	2.5 U
8.0 mL	--	1.25 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[®] 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.

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[®] 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. A vial with 50 units of XEOMIN[®] contains 0.3 ng Botulinum Neurotoxin A, i.e. less than 1/200 of the estimated human lethal dose following intravenous or intramuscular application.

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, or limiting the dose administered to the sternocleidomastoid muscle to prevent dysphagia in cervical dystonia). The multiple point injection technique into target muscles with disperse innervation zones (e.g., sternocleidomastoid muscle, orbicularis oculi muscle) can reduce undesirable effects in Botulinum neurotoxin type A -treated patients and, at the same time, may reach more intrafusal fibres.

Two pharmacodynamic studies were conducted with XEOMIN[®] (incobotulinumtoxinA) in healthy volunteers. 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[®] (incobotulinumtoxinA) and the

conventional Botulinum toxin type A preparation (onabotulinumtoxinA) observed in all dose groups. No local diffusion of either preparation was observed in adjacent muscles at tested doses.

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.

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[®], 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[®]

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

Each vial contains either 50 or 100 LD₅₀ units of incobotulinumtoxinA (Clostridium Botulinum neurotoxin type A (150 kD), free from complexing proteins) where one unit corresponds to the median lethal dose (LD₅₀) 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[®] is reconstituted with commercially available 0.9 % physiological saline (not supplied in the pack) to form a clear, and colorless solution.

Due to differences in the LD₅₀ assay, these units are specific to XEOMIN[®] and are not interchangeable with other Botulinum toxin preparations.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: incobotulinumtoxinA

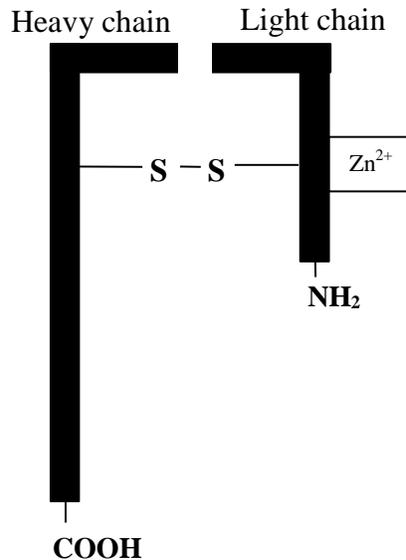
Chemical name: Botulinum Toxin Type A (*toxinum botulinicum typum A*).

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[®] (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 either 50 or 100 mouse LD₅₀ 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[®] 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[®] 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

Study demographics and trial design

The safety and efficacy of XEOMIN[®] was assessed in three randomized double-blind, parallel group, controlled multicenter trials; one per indication. Study demographics and trial design are summarized in Table 7.

Table 7: Summary of patient demographics for clinical trials on safety and efficacy of XEOMIN[®]

Study #	Trial design / Indication	Dosage and route of administration	Study subjects (n=number)	Mean age in years (Range)	No. male (%)
1-CD	Randomised double-blind active-controlled parallel group multicentre trial to test non-inferiority / Cervical dystonia	XEOMIN [®] : 70 to 300 U Active Comparator: 70 to 300 U intramuscular injection at baseline	n=463 ITT n=420 TPP	XEOMIN [®] : 50.3 (18 – 74)	87 (37.7)
				900 kD Active Comparator: 49.2 (20 – 75)	90 (38.8)
1-B	Randomised double-blind active-controlled parallel group multicentre trial to test non-inferiority / Blepharospasm	XEOMIN [®] : ≤35 U per eye Active Comparator: ≤35 U per eye intramuscular injection at baseline	n=300 ITT n=256 TPP	XEOMIN [®] : 63.9 (37 – 87)	32 (21.6)
				900 kD Active Comparator: 61.5 (25 – 81)	50 (32.9)
1-PSSUL	Randomized double-blind placebo-controlled, parallel group multicenter trial with an Open-Label Extension (OLEX) period / Post-stroke spasticity of the upper limb	Double-blind Period: XEOMIN [®] : 170 to 400 U or placebo intramuscular injection at baseline OLEX Period: XEOMIN [®] , repeated injections of up to 400 U	Double-blind Period n=148 ITT n=140 TPP OLEX Period: n = 145 ITT n = 145 TPP	Double-blind Period: XEOMIN [®] : 58.1 (34 – 78)	Double-blind Period 45 (61.6)
				Placebo: 53.3 (23 – 79)	50 (66.7)
				OLEX Period: 55.7 (23 – 79)	OLEX Period: 93 (64.1)

ITT: Intent to treat; TPP: Treated per protocol

Study results

Study 1-CD – Cervical Dystonia

The aim of this study was to show non-inferiority of XEOMIN[®] compared to Active Comparator 1 in terms of safety and efficacy in patients with cervical dystonia. Eligible patients had a Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) – severity score ≥ 10 , required injectable treatment of their cervical dystonia and had received at least two injections of Active Comparator 1 (onabotulinumtoxinA) with stable therapeutic response.

Both XEOMIN[®] and Active Comparator 1 (onabotulinumtoxinA) induced significant reductions in TWSTRS - Severity score from baseline to Week 4. This change in primary efficacy variable was statistically significant and demonstrated the efficacy of both treatments ($p < 0.0001$ in both groups, ANCOVA for mean scores at control visit vs. baseline). The least square mean difference between the groups in the primary efficacy variable was -0.33 points. The upper 95% confidence limits of this difference between the two groups in the treatment induced changes in the TWSTRS - Severity score were lower than the predefined difference of $\Delta = 1.3$ points in all ANCOVA models of adjustments for relevant covariates (TPP population: final model 0.38). Thus, non-inferiority of XEOMIN[®] compared to Active Comparator 1 (onabotulinumtoxinA) (Table 8) was demonstrated.

Table 8: Change from Baseline in TWSTRS - Severity Score – TPP Population (Study 1-CD)

	XEOMIN[®] (N=213)	Active Comparator 1 (N=207)
Mean TWSTRS - Severity score (\pmSD)		
Baseline	17.8 (\pm 3.5)	17.7 (\pm 3.7)
Control Visit (Week 4)	11.1 (\pm 4.8)	11.4 (\pm 4.8)
Least squares mean change from baseline to control visit	-6.95 $p < 0.0001$	-6.62 $p < 0.0001$
Treatment difference (XEOMIN[®] – conventional preparation with 95% CI)		-0.33 [-1.05 – 0.38]

Secondary efficacy variables confirmed the results of the primary endpoint. TWSTRS - Severity score was also significantly reduced at the final visit (up to 16 weeks) for both XEOMIN[®] and Active Comparator 1 (onabotulinumtoxinA), with no significant differences between the groups. For the TWSTRS factorial subscore, there were similar changes from baseline to control visit with XEOMIN[®] and Active Comparator 1 (onabotulinumtoxinA) for factors 1 (rotation, duration, motion + time), 2 (laterocollis + shoulder elevation/anterior displacement) and 3 (lateral shift + sensory tricks). For factor 4 (retrocollis/anterocollis and sagittal shift), a significant difference between the two groups in favour of XEOMIN[®] was observed ($p = 0.0223$, ANCOVA). Both XEOMIN[®] and Active Comparator 1 (onabotulinumtoxinA) significantly reduced TWSTRS - pain subscore and Visual Analogue Scale (VAS) score for pain from baseline to control and to final visit with no significant difference between treatment groups. Patient and investigator global assessments of efficacy were favourable for both XEOMIN[®] and

Active Comparator 1 (onabotulinumtoxinA), with no significant differences between treatments. Analyses for the ITT population were in keeping with those for the TPP population. There was no significant difference in onset of action, duration of effect or waning of effect between the two treatment groups.

Study 1-B – Blepharospasm

The aim of Study 1-B was to show non-inferiority of XEOMIN[®] compared to Active Comparator 1 (onabotulinumtoxinA) in patients with blepharospasm. Patients with a confirmed clinical diagnosis of blepharospasm who had been previously successfully treated with Active Comparator 1 (onabotulinumtoxinA) in at least 2 consecutive sessions and who had a consistent therapeutic response were enrolled.

The primary efficacy variable measured the change from baseline (day 0) in the mean Jankovic Rating Scale (JRS) sum score at the control visit (day 21±1). Both XEOMIN[®] and Active Comparator 1 (onabotulinumtoxinA) induced significant reductions in JRS from baseline by day 21 (p<0.0001, ANCOVA). XEOMIN[®] can be considered equivalent to Active Comparator 1 (onabotulinumtoxinA) with respect to efficacy since the pre-defined criteria for non-inferiority were met (Table 9). By final visit (up to 16 weeks), mean JRS scores remained significantly below baseline value in both groups, although the effect size was smaller than at control visit.

Table 9: Change from Baseline in JRS - TPP Population (Study 1-B)

	XEOMIN[®] (N=129)	Active Comparator 1 (N=127)
Mean JRS (±SD)		
At baseline	5.3 (±1.5)	5.4 (±1.5)
At control visit (3 weeks)	2.5 (±2.0)	2.8 (±2.1)
Least squares mean change from baseline to control visit	-2.9 p<0.0001	-2.7 p<0.0001
Treatment difference (XEOMIN [®] - onabotulinumtoxinA with 95% CI)		-0.23 (-0.68,+0.22)

Secondary efficacy variables confirmed the results of the primary efficacy endpoint. Significant reductions were observed from baseline in the Blepharospasm Disability Index (BSDI) to control visit and final visit for both XEOMIN[®] (-0.83; 95% CI: -0.94, -0.73 and -0.41; 95% CI: -0.54, -0.29 respectively) and Active Comparator 1 (onabotulinumtoxinA) (-0.83; 95% CI: -0.93, -0.72 and -0.26; 95% CI: -0.38, -0.13 respectively) (p<0.0001), with no significant difference between the two treatment groups. Patients evaluation of global response (on a scale -4 [‘very marked worsening’] to +4 [‘complete abolishment of all signs and symptoms’]) was significantly improved in both groups at control and final visit compared with baseline, again with no significant differences between XEOMIN[®] (2.2; SD±1.6 and 2.2; SD±1.4 respectively) and Active Comparator 1 (onabotulinumtoxinA) (1.9; SD±1.4 and 2.0; SD±1.4 respectively). Investigator rated treatment response as ‘very good’ in a higher proportion of XEOMIN[®] treated patients (35%) compared with Active Comparator 1 (onabotulinumtoxinA) (28%). Analyses for the ITT population were congruent with those for the TPP population, except for a significant

difference between the two treatment means for BSDI ($p < 0.01$) at final visit, in favour of XEOMIN[®]. There was no significant difference between XEOMIN[®] and Active Comparator 1 (onabotulinumtoxinA) in onset of action ($7.7 \pm \text{SD}12.9$ days and $9.2 \pm \text{SD}18.6$ days respectively; $p = 0.91$), duration of effect ($97.7 \pm \text{SD}25.0$ days and $97.9 \pm \text{SD}28.5$ days respectively; $p = 0.86$) or waning of effect ($10.6 \pm \text{SD}3.9$ weeks and $10.3 \pm \text{SD}4.2$ weeks respectively; $p = 0.58$).

Study 1-PSSUL – Post-stroke Spasticity of the Upper Limb

Double-Blind Period

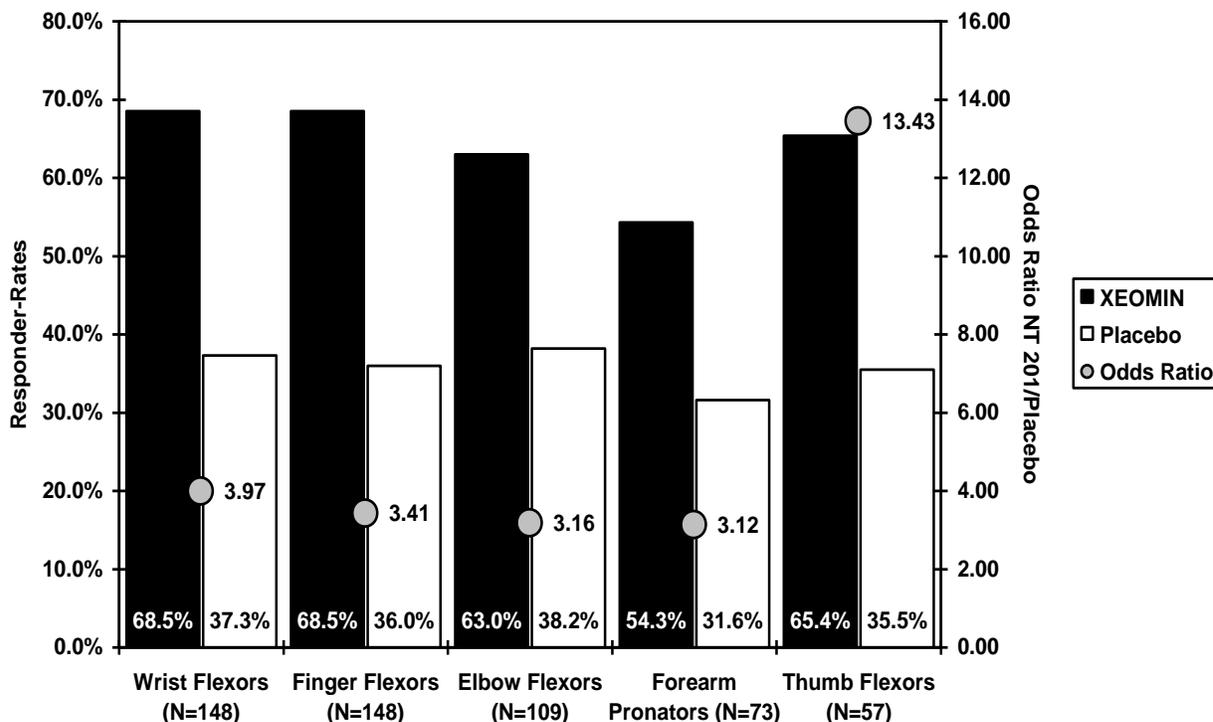
Study 1-PSSUL (double-blind period) investigated the efficacy and safety of XEOMIN[®] compared to placebo in the treatment of post-stroke spasticity of the upper limb. Naïve (73.6%) and pre-treated patients with a confirmed diagnosis of post-stroke spasticity of the upper limb were randomized to either placebo or XEOMIN[®]. All patients had clinical patterns for flexed wrist and clenched fist as well as an Ashworth score of ≥ 2 (i.e., marked increase in tone). Besides these, flexed elbow, pronated forearm, and thumb-in-palm had to be treated if the Ashworth score was ≥ 2 and could also be treated if the Ashworth score was at least 1.

Spasticity-related efficacy evaluations were based on the Ashworth Scale assessments for the treated muscle groups: flexors of elbow, wrist, fingers, thumb as well as forearm pronators. The primary outcome measure of efficacy was a responder analysis at Week 4 for patients with at least a 1-point improvement (reduction) from baseline in the Ashworth score for wrist flexors. Various additional definitions of response in flexed wrist and the other clinical patterns were assessed as secondary efficacy variables. In addition, the extent of functional impairment was measured by the Disability Assessment Scale (DAS).

In the XEOMIN[®] group, 50 patients (68.5%) were treatment responders compared to 28 patients (37.3%) in the placebo group. There was a statistically significant and clinically relevant higher chance that a patient treated with XEOMIN[®] had at least 1-point improvement in the Ashworth Scale score for wrist flexors compared with placebo (Odds Ratio XEOMIN[®]: Placebo for all covariates = 3.97; 95% CI: 1.90, 8.30, $p < 0.001$).

The results of the secondary efficacy parameters provided further evidence for a statistically significant and clinically relevant superiority of XEOMIN[®] compared to placebo. These included a 2-point improvement in the Ashworth Scale for wrist flexors at Week 4; (Odds ratio [OR] XEOMIN[®]/placebo = 6.95; 95% CI: 1.69 to 28.53; $p = 0.007$ and 1-point improvement at all post-baseline visits). Overall, higher responder rates (1-point improvement on the Ashworth Scale score from baseline) were seen in the XEOMIN[®] treatment group for all visits and for all groups of muscles, compared to the placebo group. The proportion of responders in the XEOMIN[®] treatment group was $\geq 50\%$ in all muscle groups treated for at least 8 weeks. More patients experienced improvements in Ashworth Scale in the XEOMIN[®] treatment group at all post-baseline visits compared to the placebo group. A graphic demonstration of responder rates at Week 4 in various muscle groups treated is provided in Figure 2.

Figure 2 Responder Rates (≥ 1 -point Improvement) after Four Weeks for each Muscle Group (Observed Cases for the Clinical Pattern) – ITT Population (Study 1-PSSUL)



To investigate the effect of treatment on functional impairment, assessments on the Disability Assessment Scale [DAS] were performed. Statistically significant differences were observed between treatment groups for the principal function target chosen by the investigator and patient together at screening for Weeks 2, 4, 8 and 12; $p \leq 0.005$ (Table 10).

Table 10: Secondary Efficacy Variables, Analyses of Changes from Baseline over Time in DAS Scores for the Principal Therapeutic Target - ITT Population (Study 1-PSSUL)

Treatment Group		Week 2	Week 4	Week 8	Week 12	Final Visit
XEOMIN[®] (n = 73)	Improvement (%) ¹	39.8	45.2	45.2	38.4	30.1
Placebo (n= 75)	Improvement (%) ¹	12.0	21.3	21.3	16.0	20.0
Between treatments comparisons²	p-value	< 0.001	0.002	0.005	0.005	0.214

¹ Percentage of patients with an improvement of at least 1 point on the DAS compared to baseline.

² Wilcoxon two-sample test p-values (zero change imputation) for change from baseline.

Statistically significant differences were observed between treatment groups for all therapeutic domains (ITT population) for XEOMIN[®] compared to placebo: hygiene (up to Week 8: 32.8% vs. 17.3% respectively, $p=0.036$), dressing (Week 2: 37.4% vs. 6.7%, $p=0.003$); limb position (up to Week 8: 41.1% vs. 14.6% respectively, $p=0.003$); and pain (up to Week 4: 28.8% vs. 8.0%, respectively, $p=0.042$). In the Carer Burden Scale, used to investigate the impact of treatment on carer burden, statistically significant superiority of the treatment with XEOMIN[®]

compared to placebo was observed at Week 4 for “putting the affected arm through the sleeve” ($p = 0.021$) and for “cleaning the palm of affected hand” ($p = 0.028$; ITT population). No statistically significant differences from placebo were seen for other items of the Carer Burden Scale (cutting the fingernails of the affected hand, cleaning the armpit of the affected arm, applying a splint on the affected arm) at any of the time points examined (week 4, week 12 and final visit).

A significantly shorter median time to onset of treatment effect (4 days versus 20 days; $p < 0.001$) was observed in the XEOMIN[®] group relative to placebo. The median duration of the treatment effect observed for the XEOMIN[®] group was 12.4 weeks (87 days) compared to 12 weeks (84 days) for the placebo patients.

XEOMIN[®] was effective in the treatment of post-stroke spasticity of the upper limb. As shown by the evaluation of odds ratios, XEOMIN[®] was effective in reducing muscle tone in wrist, finger, elbow, and thumb flexors as well as in forearm pronators. Treatment with XEOMIN[®] led to significant improvements in functional impairment and in some relevant tasks in caregiver burden.

Open-Label Extension (OLEX) Period

This open-label extension (OLEX) period of the completed double-blind, placebo-controlled clinical trial evaluated the long-term efficacy and safety of XEOMIN[®] treatments.

Patients who previously participated in the placebo-controlled study entered the OLEX Period and were treated with up to five injection intervals over 1 year (48 to 69 weeks). Evaluations were performed based on the Ashworth Scale, Disability Assessment Scale (DAS), global assessments, and standard safety testing.

Out of 148 patients who participated in the double-blind period of the study, 145 entered the OLEX Period and 120 patients completed the 1-year trial period. Upper limb muscle groups were treated as clinically indicated (median dose = 400 units). The majority of patients ($N = 129$) have received up to four injection intervals. Effects seen on the Ashworth Scale score were highly statistically significant ($p < 0.0001$; Wilcoxon signed rank test) during all four injection intervals and in all upper limb muscle groups treated (flexors of elbow, thumb, wrist and fingers as well as forearm pronators). XEOMIN[®] was effective in reducing functional impairment as shown on the DAS (principal therapeutic target and therapeutic domains of hygiene, dressing, limb position, and pain). Efficacy was assessed as very good or good by the majority of investigators, patients and caregivers (range: 56.3% to 85.3%).

None of the patients had positive antibody titer tested in the mouse diaphragm assay.

In conclusion, XEOMIN[®] was effective and well tolerated during 1-year repeated treatments with a median dose of 400 units in patients with post-stroke spasticity of the upper limb.

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.

Two 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.

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 LD₅₀ is approximately 50 LDU/kg corresponding to 1 LDU per animal. Based on the ratio of the intravenous to the oral approximate LD₅₀, 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 LD₅₀ is about 5 orders of magnitude higher than the intravenous and intraperitoneal LD₅₀. When compared to onabotulinumtoxinA the oral LD₅₀ 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 XEOMIN[®] (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 Embryonic 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) Consky E, Basinski A, Belle L, Ranawaya R, Lang AE. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS): Assessment of Validity and Inter-Rater Reliability. *Neurology* 1990; 40(Suppl 1): 1199P.
- 5) 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.
- 6) 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.
- 7) 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.
- 8) 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.
- 9) 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.
- 10) Roggenkämper P, Jost WH, Bihari K, Comes G, Grafe S. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. *J Neural Transm* 2006; 113(3): 303-312.
- 11) Sassin I, Raschdorf A, Comes G. Study MRZ 60201-0410/1. Prospective, double-blind, placebo-controlled, randomized, multi-center trial with an open-label extension period to investigate the efficacy and safety of NT 201 in the treatment of post-stroke spasticity of the upper limb. 2007.
- 12) 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

Pr**XEOMIN**[®]
(incobotulinumtoxinA)

This leaflet is part III of a three-part “Product Monograph” published when XEOMIN[®] 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[®]. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

XEOMIN[®] is used for the treatment of the following conditions in adults:

- eyelid spasm (blepharospasm) and spasm in one side of the face (hemifacial spasm)
- twisted neck (spasmodic torticollis)
- uncontrollable muscle stiffness and/or muscle tone in arms or hands after a stroke (post-stroke spasticity of the upper limb).

What it does:

XEOMIN[®] 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[®]
- if you suffer from generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome)
- if an infection is present at the injection site.

What the medicinal ingredient is:

incobotulinumtoxinA (purified neurotoxin free from complexing proteins)

What the important nonmedicinal ingredients are:

Human serum albumin, Sucrose (Sugar)

What dosage forms it comes in:

White powder for solution for injection, 50 or 100 LD₅₀ units per vial

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

If you develop swallowing difficulties, speech or breathing disorders, please contact medical emergency services or ask your relatives to do so.

- you suffer from any type of bleeding disorders
- 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 or have had swallowing difficulties.
- you are allergic or sensitive to XEOMIN[®]

In cases of repeated injections with XEOMIN[®], the therapeutic effect of the product may vary. The possible reasons for an increase or decrease are:

- different techniques of preparation of the product by your doctor
- different treatment intervals
- injections into another muscle
- marginally varying effectiveness of the active substance of XEOMIN[®]
- non-response/therapy failure during the course of treatment.

If you have been inactive for a long period of time, any activity should be started gradually after the XEOMIN[®] injection.

The use of XEOMIN[®] in children and adolescents has not yet been investigated and is therefore not recommended.

XEOMIN[®] should only be given by physicians with the appropriate qualifications and experience in the treatment and use of the required equipment.

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

Pregnancy and breast-feeding

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

If you are pregnant or breast-feeding, XEOMIN[®] should not be used, unless you and your doctor together discuss your particular situation and agree that there is a clear necessity, and the potential benefit justifies the risk.

XEOMIN[®] has minor or moderate influence on the ability to drive and use machines. Due to the nature of your disease being treated, the ability to drive and to operate machines may be reduced. This could be compounded by some of the therapeutic and/or side effects of XEOMIN[®], which may also modify the ability to drive and operate machinery. Consequently you should consider avoiding these tasks until you have adjusted to these changes

INTERACTIONS WITH THIS MEDICATION

BEFORE you use XEOMIN[®] talk to your doctor or pharmacist if:

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® 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® with aminoglycosides or spectinomycin requires special care. This is also relevant for medicinal products that weaken the muscle. Your doctor may reduce the starting dose of relaxant, or use an intermediate-action substance rather than substances with longer lasting effects.

Theoretically, the effect of XEOMIN® may be reduced by:

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

PROPER USE OF THIS MEDICATION

Usual dose:

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

Dissolved XEOMIN® is intended for injections into the muscle.

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® 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® 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.

Eyelid spasm (blepharospasm)

Please inform your doctor prior to any treatment, if you:

- have had an eye surgery. Your doctor will then take additional precautions.
- are at risk of developing a disease called angle closure glaucoma. This disease can cause the inner eye pressure to rise and may lead to a damaging of your optic nerve. Your doctor will know if you are at risk.

Usually, the first onset of effect is observed within four days after injection. The effect of each treatment generally lasts for about 3-4 months; however, it may last significantly longer or shorter. The treatment can be repeated if required.

Normally, no additional benefit is conferred by treating more frequently than every three months.

Twisted neck (spasmodic torticollis)

Usually, the first onset of effect is observed within seven days after injection. The effect of each treatment generally lasts for about 3-4 months; however, it may last significantly longer or shorter. The period between each treatment session is recommended to be at least 12 weeks.

Uncontrollable muscle stiffness and/or muscle tone in arms or hands after a stroke (post-stroke spasticity of the upper limb).

Usually, the first onset of effect is observed within four days after injection. The effect of each treatment generally lasts for about 3 months; however, it may last significantly longer or shorter. The period between each treatment session is recommended to be at least 12 weeks.

Overdose:

Symptoms of overdose 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

General

Like all medicines, XEOMIN® can cause side effects, although not everybody gets them.

Side effects may occur from misplaced injections of XEOMIN® temporarily paralysing nearby muscle groups. Large doses may cause paralysis in muscles distant to the injection site. Usually, side effects are observed within the first week after treatment and are temporary in nature. They may be restricted to the area around the injection site (e.g. local pain, tenderness at the injection site, and injection site haemorrhage).

If you develop swallowing difficulties, speech or breathing disorders, please contact medical emergency services immediately or ask your relatives to do so.

As with any medicine, an allergic reaction may occur with XEOMIN®. An allergic reaction can cause any of the following symptoms:

- difficulty in breathing
- swelling of the hands, feet, ankles, face, lips, mouth or throat.

Blepharospasm

During treatment, small punctuated bleedings may occur in the soft tissues of the eyelid. Your doctor can limit these by immediately applying gentle pressure at the injection site.

Common side effects reported include: drooping eyelid and dry eyes. Uncommon side effects include: muscle weakness, pins and needles, headache, inflammation of the conjunctiva (conjunctivitis), dry mouth, skin rash and inflicted injury.

After you receive a XEOMIN[®] injection into your muscle around your eye, your blinking rate may be reduced. This can lead to a prolonged exposure of the transparent front part of the eye (cornea). This exposure may lead to a damaging of the surface and an inflammation (corneal ulceration). This can occur more often if you suffer from disorders of your facial nerves

Twisted neck (spasmodic torticollis)

After the injection you may develop soreness or bruising where the injection was given. Common side effects include swallowing difficulties, muscle weakness and back pain. Uncommon side effects include: speech disorders, weakness, muscle pain, headache, shaking (tremor), eye pain, diarrhoea, dry mouth, vomiting, inflammation of the colon, skin rash, skin redness, itching, sweating increased, skeletal pain, injection site inflammation and injection site tenderness.

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

If you cannot swallow your doctor will give you special medical treatment if needed (e.g. in the form of artificial nutrition). Swallowing difficulties can last for up to two to three weeks after injection, for one patient a duration of up to five months is known.

Inform your physician immediately of any swallowing difficulties.

Uncontrollable muscle stiffness and/or muscle tone in arms or hands after a stroke (post-stroke spasticity of the upper limb)

XEOMIN[®] can be used to treat uncontrollable muscle stiffness and cramps in parts of your limb, e.g. your elbow, forearm or hands. XEOMIN[®] is effective in combination with the usual treatment methods. XEOMIN[®] should be used together with these other methods. If you suffer from a shortening of your muscles at a joint (a fixed contraction) your doctor may choose not to give you XEOMIN[®].

Common side effects include: headache, impairment of any sense, partial loss of sensation and sensation of heat, pain in extremity and injection site. Uncommon side effects include: dry mouth, swelling in extremities and face, muscle pain and cough.

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

HOW TO STORE IT

Keep out of the reach and sight of children.

XEOMIN[®], 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 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.

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.

Last revised: June 19, 2013