Distant Spread of Toxin Effect
Post marketing reports indicate that the effects of XEOMIN and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

1. NAME OF THE MEDICINAL PRODUCT

XEOMIN 50
XEOMIN 100

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 50 LD_{50} units of botulinum toxin type A, free from complexing proteins.*

One vial contains 100 LD_{50} units of botulinum toxin type A, free from complexing proteins.*
** Botulinum neurotoxin type A, purified from cultures of Clostridium botulinum (Hall strain)*
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection
White to off white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XEOMIN is indicated for the symptomatic treatment of blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis) and of post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist in adults.
XEOMIN is indicated for the temporary improvement in the appearance of moderate to severe vertical lines between eyebrows seen at frown (glabellar frown lines) in adults below 65 years when the severity of these lines has an important psychological impact for the patient.

4.2 Posology and method of administration

Due to unit differences in the potency assay, unit doses for XEOMIN are not interchangeable with those for other preparations of botulinum toxin type A.

For detailed information regarding clinical studies with XEOMIN in comparison to conventional botulinum toxin type A complex (900 kD), see section 5.1.

General
XEOMIN may only be administered by physicians with suitable qualifications and the requisite experience in the application of botulinum toxin type A.

For blepharospasm, spasmodic torticollis and post-stroke spasticity of the upper limb, the optimum dose, frequency 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.

The recommended single doses of XEOMIN should not be exceeded.

Posology

Blepharospasm
The initial recommended dose is 1.25 to 2.5 units per injection site. The initial dose should not exceed 25 units per eye. Total dosing should not exceed 100 units every 12 weeks. Treatment intervals should be determined based on the actual clinical need of the individual patient.

The median time to first onset of effect is observed within four days after injection. The effect of a XEOMIN treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter. The treatment can be repeated if required.

At repeat treatment sessions, the dose may be increased up to two-fold if the response to the initial treatment is considered insufficient. However, there appears to be no additional benefit obtainable from injecting more than 5.0 units per site.

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.

No more than 200 units should be injected for the first course of therapy, with adjustments made in the subsequent courses depending on the response. A total dose of 300 units at any one session should not be exceeded. No more than 50 units should be administered at any one injection site.
The median first onset of effect is observed within seven days after injection. The effect of a XEOMIN treatment generally lasts approximately 3-4 months, however, it may last significantly longer or shorter. Treatment intervals of less than 10 weeks are not recommended. Treatment intervals should be determined based on the actual clinical need of the individual patient.

Post-stroke Spasticity of the upper limb presenting with flexed wrist and clenched fist in adults The exact dose and number of injection sites should be tailored to the individual patient based on the size, number and location of muscles involved, the severity of spasticity, and the presence of local muscle weakness.

Recommended initial doses:

Clinical Pattern *Muscle*	**Units**
Flexed Wrist	
Flexor carpi radialis	50
Flexor carpi ulnaris	40
Clenched Fist	
Flexor digitorum superficialis	40
Flexor digitorum profundus	40
Flexed Elbow	
Brachioradialis	60
Biceps	80
Brachialis	50

Pronated Forearm	
Pronator quadratus	25
Pronator teres	40
Thumb-in-Palm	
Flexor pollicis longus	20
Adductor pollicis	10
Flexor pollicis brevis/ Opponens pollicis	10

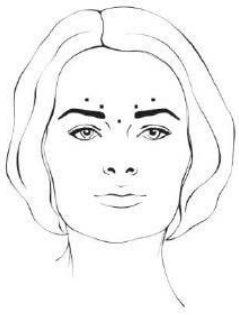
Recommended treatment doses for repeated treatment per muscle:

Clinical Pattern *Muscle*	**Units (Range)**	**Number of injection sites per muscle**
Flexed Wrist		
Flexor carpi radialis	25-100	1-2
Flexor carpi ulnaris	20-100	1-2
Clenched Fist		
Flexor digitorum superficialis	40-100	2
Flexor digitorum profundus	40-100	2
Flexed Elbow		
Brachioradialis	25-100	1-3
Biceps	75-200	1-4
Brachialis	25-100	1-2
Pronated Forearm		
Pronator quadratus	10-50	1
Pronator teres	25-75	1-2
Thumb-in-Palm		
Flexor pollicis longus	10-50	1
Adductor pollicis	5-30	1
Flexor pollicis brevis/ Opponens pollicis	5-30	1

The maximum total dose for the treatment of upper limb spasticity should not exceed 400 units per treatment session.
Patients reported the onset of action 4 days after treatment. The maximum effect as an improvement of muscle tone was perceived within 4 weeks. In general, the treatment effect lasted 12 weeks, however, it may last significantly longer or shorter. Repeated treatment should generally be no more frequent than every 12 weeks. Treatment intervals should be determined based on the actual clinical need of the individual patient.

Moderate to Severe Vertical Lines between the Eyebrows seen at frown (Glabellar Frown Lines) in Adults below 65 Years When the Severity of These Lines Has an Important Psychological Impact For The Patient

After reconstitution of XEOMIN a dose of 4 units is injected into each of the 5 injection sites: two injections in each corrugator muscle and one injection in the procerus muscle, which corresponds to a standard dose of 20 units. The dose may be increased by the physician to up to 30 units if required by the individual needs of the patients, with at least ‘3-months’ interval between treatments.



An improvement in the vertical lines between the eyebrows seen at frown (glabellar frown lines) generally takes place within 2 to 3 days with the maximum effect observed on day 30. The effect lasts up to 4 months after the injection.

If no treatment effect occurs within one month after the initial injection, the following measures should be taken:

- ***Glabellar Frown Lines indication***
  - Analysis of the reasons for non-response, e.g. too low dose, poor injection technique, possible development of neurotoxin-neutralising antibodies
  - Dose adjustment with regard to the analysis of the most recent therapy failure
  - Review of botulinum neurotoxin type A treatment as an adequate therapy
  - If no adverse reactions have occurred during the initial treatment, an additional course of treatment can be performed in compliance with the minimum interval of 3 months between the initial and repeat treatment

- ***All other indications***
  - Clinical verification of the neurotoxin effect on the injected muscle: e.g. an electromyographic investigation in a specialised facility
  - Analysis of the reasons for non-response, e.g. poor isolation of the muscles intended to be injected, too low dose, poor injection technique, fixed contracture, too weak antagonist, possible development of antibodies
  - Review of botulinum neurotoxin type A treatment as an adequate therapy
  - If no adverse reactions have occurred during the initial treatment, an additional course of treatment can be performed under the following conditions: 1) dose adjustment with regard to analysis of the most recent therapy failure, 2) localisation of the involved muscles with techniques such as electromyographic guidance, 3) the recommended minimum interval between the initial and repeat treatment is followed

Special populations
There are limited clinical data from phase 3 studies of XEOMIN in patients over 65 years of age for the treatment of Glabellar Frown Lines. Until further data are available in this age group, XEOMIN is not recommended for use in patients over 65 years of age for the treatment of Glabellar Frown Lines.

Paediatric population
The safety and efficacy of XEOMIN in children and adolescents younger than 18 years has not yet been established. XEOMIN is thus not recommended in the paediatric population.

Method of administration

All indications
For instructions on reconstitution of the medicinal product before administration and for instructions on disposal of the vials, see section 6.6. After reconstitution, XEOMIN should be used immediately (see section 6.3), for only one injection session and for only one patient.

Reconstituted XEOMIN is intended for intramuscular injection.

Blepharospasm
After reconstitution, the XEOMIN solution is injected using a suitable sterile needle (e.g. 27-30 gauge/0.30-0.40 mm diameter/12.5 mm length). 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 muscle of the upper lid and the lateral orbicularis oculi muscle of the lower lid. Additional sites in the brow area, the lateral orbicularis oculi muscle and in the upper facial area may also be injected if spasms here interfere with vision.

Spasmodic torticollis
A suitable sterile needle (e.g. 25-30 gauge/0.30-0.50 mm diameter/37 mm length) is used for injections into superficial muscles, and an e.g. 22 gauge/0.70 mm diameter/75 mm length 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 the management of spasmodic torticollis, XEOMIN is 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 techniques such as electromyographic guidance or ultrasound. 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 depends on 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 U are administered into this muscle.

Post Stroke Spasticity of the upper limb presenting with flexed wrist and clenched fist in adult
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).

Localisation of the involved muscles with techniques such as electromyographic guidance or ultrasound is recommended in case of any difficulty in isolating the individual muscles. 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.

Glabellar frown lines
Reconstituted XEOMIN is injected using a thin sterile needle (e.g. 30-33 gauge/0.20-0.30 mm diameter/13 mm length needle). An injection volume of approximately 0.04 to 0.1 ml per injection site is recommended. The intervals between treatments should not be shorter than 3 months. If the treatment fails, or the effect lessens with repeated injections, alternative treatment methods should be used.

Before and during the injection, the thumb or index finger should be used to apply firm pressure below the edge of the eye socket in order to prevent diffusion of the solution in this region. Superior and medial alignment of the needle should be maintained during the injection. To reduce the risk of blepharoptosis, injections near the levator palpebrae superioris and into the cranial portion of the orbicularis oculi should be avoided. Injections into the corrugator muscle should be done in the medial portion of the muscle, and in the central portion of the muscle belly at least 1 cm above the bony edge of the eye socket.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome).
- Infection or inflammation at the proposed injection site.

4.4 Special warnings and precautions for use

Traceability:
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded

General
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.

Care should be taken to ensure that XEOMIN is not injected into a blood vessel.

It should be taken into consideration that horizontal forehead lines may not only be dynamic, but may also result from the loss of dermal elasticity (e.g. associated with aging or photodamage). In this case, patients may not respond to Botulinum toxin products.

XEOMIN should be used with caution:
- if bleeding disorders of any type exist
- in patients receiving anticoagulant therapy or other substances that could have an anticoagulant effect.

The clinical effects of botulinum neurotoxin type A may increase or decrease by repeated injections. The possible reasons for changes in clinical effects are different techniques of reconstitution, the chosen injection intervals, the injection sites and marginally varying toxin activity resulting from the biological testing procedure employed or secondary non-response.

Local and distant spread of toxin effect
Undesirable effects may occur from misplaced injections of botulinum neurotoxin type A that temporarily paralyse nearby muscle groups. Large doses may cause paralysis in muscles distant from the injection site.

There have been reports of undesirable effects that might be related to the spread of botulinum toxin type A to sites distant from the injection site (see section 4.8). Some of these can be life threatening and there have been reports of death, which in some cases was associated with dysphagia, pneumonia and/or significant debility.

Patients treated with therapeutic doses may experience excessive muscle weakness.
Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

Dysphagia has also been reported following injection to sites other than the cervical musculature.

Pre-existing neuromuscular disorders
Patients with neuromuscular disorders may be at increased risk of excessive muscle weakness particular when treated intramuscularly. The botulinum toxin type A product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk.
Generally, patients with a history of aspiration or dysphagia should be treated with caution. Extreme caution should be exercised when treating these patients for cervical dystonia.

XEOMIN should be used with caution:
- in patients suffering from amyotrophic lateral sclerosis
- in patients with other diseases which result in peripheral neuromuscular dysfunction

- in targeted muscles which display pronounced weakness or atrophy

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

Antibody formation
Too frequent doses may increase the risk of antibody formation, which can result in treatment failure (see section 4.2).
The potential for antibody formation may be minimised by injecting with the lowest effective dose at the longest intervals between injections as clinically indicated.

Paediatric population
Spontaneous reports of possible distant spread of toxin have been very rarely reported for other preparations of Botulinum toxin type A in paediatric patients with comorbidities, predominantly with cerebral palsy. In general the dose used in these cases was in excess of that recommended for these products.
There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin products, including following off label use (e.g. neck area). The risk is considered particularly high in paediatric patients with a poor underlying health status or in patients who have significant neurologic debility, dysphagia, or in patients who have a recent history of aspiration pneumonia or lung disease.
Indication-specific warnings

Blepharospasm
Injections near the levator palpebrae superioris muscle 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 muscle. Avoiding medial injections into the lower lid may reduce this adverse reaction.

Because of the anticholinergic effect of botulinum neurotoxin type A, XEOMIN should be used with caution in patients at risk of developing a narrow angle 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.

Spasmodic torticollis
XEOMIN should be injected carefully when injecting at sites close to sensitive structures such as the carotid artery, lung apices and oesophagus.

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

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 also section 4.8). Limiting the dose injected into the sternocleidomastoid muscle to less than 100 units may decrease the occurrence of dysphagia. 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 XEOMIN as the result of the neurotoxin spread into the oesophageal musculature.

Post-stroke Spasticity of the upper limb
XEOMIN should be injected carefully when injecting at sites close to sensitive structures such as the carotid artery lung apices and oesophagus.

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 in improving range of motion at a joint affected by a fixed contracture.

New onset or recurrent seizures have been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to botulinum toxin injection has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Theoretically, the effect of botulinum neurotoxin 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 or spectinomycin 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-Aminoquinolines may reduce the effect of XEOMIN.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of botulinum neurotoxin type A in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore, XEOMIN should not be used during pregnancy unless clearly necessary and unless the potential benefit justifies the risk.

Breast-feeding
It is unknown whether botulinum neurotoxin type A is excreted into breast milk. Therefore, XEOMIN should not be used during breast-feeding.

Fertility
There are no clinical data from the use of botulinum neurotoxin type A. No adverse effects on male or female fertility were detected in rabbits (see section 5.3).

4.7 Effects on ability to drive and use machines

XEOMIN has a minor or moderate influence on the ability to drive and use machines. Patients should be counselled that if asthenia, muscle weakness, dizziness, vision disorders or drooping eyelids occur, they should avoid driving or engaging in other potentially hazardous activities.

4.8 Undesirable effects

Usually, undesirable effects are observed within the first week after treatment and are temporary in nature. Undesirable effects may be related to the active substance, the injection procedure, or both.

Undesirable effects independent from indication

Application related undesirable effects
Localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling, oedema, erythema, itching, localised infection, haematoma, bleeding and/or bruising may be associated with the injection. Needle related pain and/or anxiety may result in vasovagal responses, including transient symptomatic hypotension, nausea, tinnitus, and syncope.

Undesirable effects of the substance class botulinum toxin type A
Localised muscle weakness is one expected pharmacological effect of botulinum toxin type A. Blepharoptosis, which can be caused by injection technique, is associated with the pharmacological effect of XEOMIN.

Toxin spread
When treating other indication with botulinum toxins, undesirable effects related to spread of toxin distant from the site of administration have been reported very rarely to produce symptoms consistent with botulinum toxin type A effects (excessive muscle weakness, dysphagia, and aspiration pneumonia with a fatal outcome in some cases) (see section 4.4). Undesirable effects such as these cannot be completely ruled out with the use of XEOMIN.

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

Undesirable effects from clinical experience

The following adverse reactions have been reported with XEOMIN. he frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Blepharospasm

System Organ Class	Adverse Reaction	Frequency
Nervous system disorders	Headache, facial paresis	Uncommon
Eye disorders	Eyelid ptosis	Very common
	Dry eyes, vision blurred, visual impairment	Common
	Diplopia, lacrimation increased	Uncommon
Gastrointestinal disorders	Dry mouth	Common
	Dysphagia	Uncommon
Skin and subcutaneous tissue disorders	Rash	Uncommon
Musculoskeletal and connective tissue disorders	Muscular weakness	Uncommon
General disorders and administration site conditions	Injection site pain	Common
	Fatigue	Uncommon

Spasmodic torticollis

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Upper respiratory tract infection	Common
Nervous system disorders	Headache, presyncope, dizziness	Common
	Speech disorder	Uncommon
Respiratory, thoracic and mediastinal disorders	Dysphonia, dyspnoea	Uncommon
Gastrointestinal disorders	Dysphagia	Very common
	Dry mouth, nausea	Common
Skin and subcutaneous tissue disorders	Hyperhidrosis	Common
	Rash	Uncommon
Musculoskeletal and connective tissue disorders	Neck pain, muscular weakness, myalgia, muscle spasms, musculoskeletal stiffness	Common
General disorders and administration site conditions	Injection site pain, asthenia	Common

The management of spasmodic torticollis may cause dysphagia with varying degrees of severity with the potential for aspiration which may require medical intervention. Dysphagia may persist for two to three weeks after injection, but has been reported in one case to last five months.

Post-stroke Spasticity of the upper limb

System Organ Class	Adverse Reaction	Frequency
Nervous system disorders	Headache, hypoaesthesia	Uncommon
Gastrointestinal disorders	Dry mouth	Common
	Dysphagia, nausea	Uncommon
Musculoskeletal and connective tissue disorders	Muscular weakness, pain in extremity, myalgia	Uncommon
General disorders and administration site conditions	Asthenia	Uncommon
	Injection site pain	Not known

Moderate to severe *Vertical Lines between the Eyebrows seen at frown (Glabellar Frown Lines)*
The following adverse reactions were reported with XEOMIN:

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Bronchitis, Nasopharyngitis, Influenza like illness	Uncommon
Psychiatric disorders	Insomnia	Uncommon
Nervous system disorders	Headache	Common
Eye disorders	Eyelid oedema, eyelid ptosis, blurred vision	Uncommon
Skin and subcutaneous tissue disorders	Pruritus, Skin nodule, Brow ptosis	Uncommon
Musculoskeletal and connective tissue disorders	Mephisto sign (lateral elevation of eyebrows)	Common
	Muscle twitching, Muscle spasm, Facialasymmetry (brow asymmetry)	Uncommon
General disorders and administration site conditions	Injection site haematoma, injection site pain, (local) Tenderness, Fatigue, Discomfort (heavy feeling of eyelid/ eyebrow)	Uncommon
Vascular disorders	Haematoma	Uncommon

Post-Marketing Experience
The following adverse reactions were reported with unknown frequency for the use of XEOMIN since market launch independent from indication:

System Organ Class	Adverse Reaction
Immune system disorders	Hypersensitivity reactions like swelling, oedema (also distant from injection site), erythema, pruritus, rash (localised and generalised) and breathlessness
Musculoskeletal and connective tissue disorders	Muscle atrophy
General disorders and administration site conditions	Flu-like symptoms

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation via either a link of "Side Effects Reporting form" located at the Ministry of Health internet site home page, (**http://www.health.gov.il**) which refer the user to an online adverse reaction reporting form, or by entering the following link: https://sideeffects.health.gov.il.

4.9 Overdose

Please see information on risks associated with local and distant spread of toxin effect in section 4.4.

Symptoms of overdose
Increased doses of botulinum neurotoxin type A may result in pronounced neuromuscular paralysis distant from the injection site with a variety of symptoms. Symptoms may include general weakness, ptosis, diplopia, breathing difficulties, speech difficulties, paralysis of the respiratory muscles or swallowing difficulties which may result in aspiration pneumonia.

Measures in cases of overdose
In the event of overdose the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary. Respiratory support may be required if paralysis of the respiratory muscles occurs.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other muscle relaxants, peripherally acting agents,
ATC code: M03AX01

Botulinum neurotoxin type A blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine. The nerve terminals of the neuromuscular junction no longer respond to nerve impulses, and secretion of the neurotransmitter at the motor endplates is prevented (chemical denervation). Recovery of impulse transmission is re-established by the formation of new nerve terminals and reconnection with the motor endplates.

Mechanism of action
The mechanism of action by which botulinum neurotoxin type A exerts its effects on cholinergic nerve terminals can be described by a four-step sequential process which includes the following steps:

- Binding: The heavy chain of botulinum neurotoxin type A binds with exceptionally high selectivity and affinity to receptors only found on cholinergic terminals.
- Internalisation: Constriction of the nerve terminal's membrane and absorption of the toxin into the nerve terminal (endocytosis).
- Translocation: The amino-terminal segment of the neurotoxin's heavy chain forms a pore in the vesicle membrane, the disulphide bond is cleaved and the neurotoxin's light chain passes through the pore into the cytosol.
- Effect: After the light chain is released, it very specifically cleaves the target protein (SNAP 25) that is essential for the release of acetylcholine.

Complete recovery of endplate function/impulse transmission after intramuscular injection normally occurs within 3-4 months as nerve terminals sprout and reconnect with the motor endplate.

Results of the clinical studies

Therapeutic equivalence of XEOMIN as compared to the comparator product Botox containing the botulinum toxin type A complex (onabotulinumtoxinA, 900 kD) was shown in two comparative single-dosing Phase III studies, one in patients with blepharospasm (study MRZ 60201-0003, n=300) and one in patients with cervical dystonia (study MRZ 60201-0013, n=463). Study results also suggest that XEOMIN and this comparator product have a similar efficacy and safety profile in patients with blepharospasm or cervical dystonia when used with a dosing conversion ratio of 1:1 (see section 4.2).

Blepharospasm

XEOMIN has been investigated in a Phase III, randomised, double-blind, placebo-controlled, multi-center trial in a total of 109 patients with blepharospasm. Patients had a clinical diagnosis of benign essential blepharospasm, with baseline Jankovic Rating Scale (JRS) severity subscore ≥ 2, and a stable satisfactory therapeutic response to previous administrations of the comparator product (onabotulinumtoxinA).

Patients were randomised (2:1) to receive a single administration of XEOMIN (n=75) or placebo (n=34) at a dose that was similar (+/- 10 %) to the 2 most recent Botox injection sessions prior to study entry. The highest dose permitted in this study was 50 units per eye; the mean XEOMIN dose was 32 units per eye.

The primary efficacy endpoint was the change in the JRS severity subscore from baseline to Week 6 post-injection, in the intent-to-treat (ITT) population, with missing values replaced by the patient's most recent value (last observation carried forward). In the ITT population, the difference between the XEOMIN group and the placebo group in the change of the JRS severity subscore from baseline to Week 6 was -1.0 (95% CI -1.4; -0.5) points and statistically significant (p <0.001).

Patients could continue with the Extension Period if a new injection was required. The patients received up to five injections of XEOMIN with a minimum interval between two injections of at least six weeks (48-69 weeks total study duration and a maximum dose of 50 units per eye.

Over the entire study, the median injection interval in subjects treated with XEOMIN ranged between 10.14 (1^{st} interval) and 12.00 weeks (2^{nd} to 5^{th} interval).

Another double-blind, placebo-controlled Phase III clinical trial with an open-label extension period investigated efficacy of XEOMIN in a total of 61 patients, with a clinical diagnosis of benign essential blepharospasm and baseline Jankovic Rating Scale (JRS) severity subscore ≥ 2, who were botulinum toxin treatment-naïve, i.e., who had not received any botulinum toxin treatment of blepharospasm for at least 12 months prior to administration of XEOMIN. In the main period (6-20 weeks), the patients were randomised to receive a single administration of XEOMIN at the doses of 12.5 units per eye (n=22), 25 units per eye (n=19) or placebo (n=20), respectively. The patients requiring a new injection could continue with the extension period and received one further injection of XEOMIN.

In the main period, the median duration of the treatment interval was 6 weeks in the placebo group, 11 weeks in the group treated with 12.5 units per eye, and 20 weeks in the group treated with 25 units per eye. The ANCOVA LS mean difference vs. placebo (95% CI) in the change of the JRS severity subscore from baseline to week 6 was -1.2 (-1.9, -0.6) in the group administered 25 units XEOMIN per eye and found statistically significant, whereas the respective difference vs. placebo in the group given XEOMIN 12.5 units was -0.5 (-1.1, 0.2) which was not statistically significant.

During the extension period the patients received an injection of XEOMIN (n=39) at a mean dose close to 25 units (range: 15-30 units) per eye, and the median duration of the treatment interval was 19.9 weeks.

Spasmodic torticollis

XEOMIN has been investigated in a Phase III, randomised, double-blind, placebo-controlled, multi-center trial in a total of 233 patients with cervical dystonia. Patients had a clinical diagnosis of predominantly rotational cervical dystonia, with baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score ≥ 20.

Patients were randomised (1:1:1) to receive a single administration of XEOMIN 240 units (n=81), XEOMIN 120 units (n=78), or placebo (n=74). The number and sites of the injections were to be determined by the Investigator.

The primary efficacy variable was the LS mean change from Baseline to Week 4 following injection in the TWSTRS-Total score, in the Intent-to-Treat (ITT) Population with missing values replaced by the patient's baseline value (full statistical model). The change in TWSTRS-Total score from Baseline to Week 4 was significantly greater in the XEOMIN groups, compared with the change in the placebo group ($p < 0.001$ across all statistical models). These differences were also clinically meaningful: e.g. -9.0 points for 240 units vs. placebo, and -7.5 points for 120 units vs. placebo in the full statistical model. Patients could continue with the Extension Period if a new injection was required. The patients received up to five injections of 120 units or 240 units of XEOMIN with a minimum interval between two injections of at least six weeks (48-69 weeks total study duration). Over the entire study, the median injection interval in subjects treated with XEOMIN ranged between 10.00 (1st interval) and 13.14 weeks (3rd and 6th interval). Based on the patient's request for retreatment, the median duration of response following XEOMIN treatment in this study (both double-blind and the open-label extension period) was 12 weeks (Interquartile ranges: 9 to 15 weeks). In the majority of injection cycles (96.3%) the time to retreatment was between 6 and 22 weeks and in individual cases up to 28 weeks.

Post-stroke Spasticity of the upper limb
In the pivotal study (double-blind, placebo-controlled, multicentre) conducted in patients with post-stroke spasticity of the upper limb, 148 patients were randomised to receive XEOMIN (n=73) or Placebo (n=75). The cumulative dose after up to 6 repeated treatments in a clinical trial was in average 1333 units (maximum 2395 units) over a period of up to 89 weeks.

As determined for the primary efficacy parameter (response rates for the wrist flexors Ashworth Scale score at Week 4, response defined as improvement of at least 1-point in the 5-point Ashworth Scale score), patients treated with XEOMIN (response rate: 68.5%) had a 3.97 fold higher chance of being responders relative to patients treated with placebo (response rate: 37.3%; 95% CI: 1.90 to 8.30; $p < 0.001$, ITT population).

This fixed dose study was not designed to differentiate between female and male patients, nevertheless in a post-hoc analysis the response rates were higher in female (89.3 %) compared to male (55.6%) patients, the difference being statistically significant for women only. However, in male patients response rates in Ashworth Scale after 4 weeks in XEOMIN treated patients were consistently higher in all muscle groups treated compared to placebo. Based on the patient's request for retreatment, the median duration of effect in this pivotal study followed by the open-label extension period was 14 weeks (Interquartile ranges: 13 to 17 weeks) and in the majority of injection cycles (95.9%) the time to retreatment was between 12 and 28 weeks.

Responder rates were similar in men compared to women in the open label extension period of the pivotal study (flexible dosing was possible in this trial period) in which 145 patients were enrolled and up to 5 injection cycles were performed, as well as in the observer-blind study (EudraCT Number 2006-003036-30) in which efficacy and safety of XEOMIN in two different dilutions in 192 patients were assessed in patients with upper limb spasticity of diverse aetiology.

Another double-blind, placebo-controlled Phase III clinical trial enrolled a total of 317 treatment-naïve patients with spasticity of the upper limb who were at least three months post-stroke. During the Main Period (MP) a fixed total dose of XEOMIN (400 units) was administered intramuscularly to the defined primary target clinical pattern chosen from among the flexed elbow, flexed wrist, or clenched fist patterns and to other affected muscle groups (n=210). The confirmatory analysis of the primary and co-primary efficacy variables at week 4 post-injection demonstrated statistically significant improvements in the responder rate of the Ashworth score, or changes from baseline in the Ashworth score and the Investigator's Global Impression of Change.
296 treated patients completed the MP and participated in the first Open-label Extension (OLEX) cycle. During the Extension Period patients received up to three injections. Each OLEX cycle consisted of a single treatment session (400 units of XEOMIN total dose, distributed flexibly among all affected muscles) followed by a 12 week observation period. The overall study duration was 48 weeks.

Moderate to severe Vertical Lines between the Eyebrows seen at frown (Glabellar Frown Lines)
A total of 994 subjects with moderate to severe glabellar frown lines at maximum frown participated

in studies with XEOMIN in the indication glabellar frown lines. Of these, 169 subjects (≥ 18 years) were treated with XEOMIN in the Main Period of the pivotal Phase III double-blind placebo controlled trial and 236 subjects were treated in the Open-label Extension (OLEX) of that study. Treatment success was defined as a 'none' or 'mild' assessment on a 4-point Facial Wrinkle Scale assessed by the investigator at week 4 at maximum frown. The study demonstrated a statistically significant and clinically relevant efficacy of 20 units XEOMIN when compared to placebo. The overall success rate was 51.5% in the XEOMIN group vs. 0% in the placebo group. No worsening was observed in any patient treated with XEOMIN in the pivotal study. This was validated by the higher number of responders at Day 30 according to the Facial Wrinkle Scale at maximum frown by both the investigator and the patient's assessment showing a significantly higher proportion of responders among the patients receiving 20 units XEOMIN compared to placebo.

Subgroup analysis showed that efficacy in patients older than 50 years is lower compared to younger patients. Of those, 113 subjects were in the age of 50 years or younger and 56 subjects were older than 50 years of age. Efficacy in men is lower compared to women. Of those, 33 subjects were male and 136 subjects were female.

Therapeutic equivalence of XEOMIN as compared to a comparator product Vistabel/Botox containing botulinum toxin type A complex (onabotulinumtoxin A, 900 kD) was shown in two comparative, prospective, multicentre, randomised, double-blind studies (n=631) using single-doses (20 and 24 units, respectively). Study results demonstrated that XEOMIN and the comparator product have a similar efficacy and safety profile in patients with moderate to severe glabellar frown lines when used with a dosing conversion ratio of 1:1 (see section 4.2).

Long-term safety in repeat-dose (20 units) treatment of glabellar frown lines has been demonstrated in a Phase III study over a treatment period of up to two years with up to 8 consecutive injection cycles (MRZ 60201-0609, n=796) [Rzany et al., 2013].

5.2 Pharmacokinetic properties

General characteristics of the active substance

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

Native botulinum toxin type A is a high molecular weight complex which, in addition to the neurotoxin (150 kD), contains other non-toxic proteins, like haemagglutinins and non-haemagglutinins. In contrast to conventional preparations containing the botulinum toxin type A complex, XEOMIN contains pure (150 kD) neurotoxin because it is free from complexing proteins and thus has a low foreign protein content. The foreign protein content administered is considered as one of the factors for secondary therapy failure.

Botulinum neurotoxin type A has been shown to undergo retrograde axonal transport after intramuscular injection. However, retrograde transsynaptic passage of active botulinum neurotoxin type A into the central nervous system has not been found at therapeutically relevant doses.

Receptor-bound botulinum neurotoxin type A is endocytosed into the nerve terminal prior to reaching its target (SNAP 25) and is then degraded intracellularly. Free circulating botulinum neurotoxin type A molecules, which have not bound to presynaptic cholinergic nerve terminal receptors, are phagocytosed or pinocytosed and degraded like any other free circulating protein.

Distribution of the active substance in patients

Human pharmacokinetic studies with XEOMIN have not been performed for the reasons detailed above.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of cardiovascular and intestinal safety pharmacology.

The findings from repeated-dose toxicity studies on the systemic toxicity of XEOMIN after intramuscular injection in animals were mainly related to its pharmacodynamic action, i.e. atony, paresis and atrophy of the injected muscle.
Similarly, the weight of the injected submandibular salivary gland was reduced at all dose levels, and salivary gland acinar atrophy was seen at the highest dose of 40 units/kg after four repeated injections of XEOMIN at 8 weeks intervals in rats.

No evidence of local intolerability was noted. Reproductive toxicity studies with XEOMIN did neither show adverse effects on male or female fertility in rabbits nor direct effects on embryo-foetal or on pre- and postnatal development in rats and/or rabbits. However, the administration of XEOMIN at daily, weekly or biweekly intervals in embryotoxicity studies at dose levels exhibiting maternal body weight reductions increased the number of abortions in rabbits and slightly decreased foetal body weight in rats. Continuous systemic exposure of the dams during the (unknown) sensitive phase of organogenesis as a pre-requisite for the induction of teratogenic effects cannot necessarily be assumed in these studies.

In a post-weaning juvenile toxicity study in rats, atrophy of the testicular germinal epithelium and hypospermia were observed at the highest dose tested (30 units/kg/adm) without any impact on male fertility. When males and females were paired at 14 weeks of age, mating performance was reduced in high dose males possibly due to the limb weakness or the markedly lower body weight. In the absence of any effect on the mean number of corpora lutea, preimplantation loss was increased at 10 units/kg/adm and above. Whether this finding was a male or female mediated effect could not be conclusively clarified.

Accordingly, safety margins with regard to clinical therapy were generally low in terms of high clinical doses.

No genotoxicity or carcinogenicity studies have been conducted with XEOMIN.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, human serum albumin

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

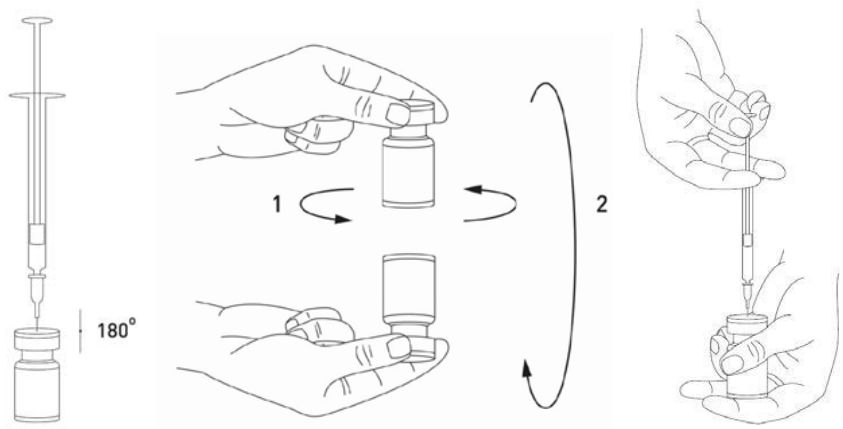
6.5 Nature and contents of container

Clear glass vial (type 1 glass) with a bromobutyl rubber stopper sealed and crimped with an aluminium cap. Pack size:1, 2, 3 or 6 vials
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution
XEOMIN is reconstituted prior to use with 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 reconstitute the vial contents and prepare the syringe over plastic-lined paper towels to catch any spillage. An appropriate amount of sodium chloride solution (see dilution table) is drawn up into a syringe. A 20-27 gauge needle is recommended for reconstitution. After vertical insertion of the needle through the rubber stopper, the solvent is injected gently into the vial in order to avoid foam formation. If the vacuum does not pull the solvent into the vial, the vial should be discarded. The syringe should be removed from the vial and XEOMIN should be mixed with the solvent by carefully swirling and inverting/flipping the vial – The solution should not be shaken vigorously. If needed, the needle used for reconstitution should remain in the vial and the required amount of solution should be drawn up with a new sterile syringe suitable for injection.



Reconstituted XEOMIN is a clear, colourless solution.

XEOMIN must not be used if the reconstituted solution has a cloudy appearance or contains floccular or particulate matter.

Care should be taken to use the correct solvent volume for the presentation chosen to prevent accidental overdose. If different vial sizes of XEOMIN are being used as part of one injection procedure, care should be taken to use the correct amount of solvent when reconstituting a particular number of units per 0.1 ml. The amount of solvent varies between XEOMIN 50 units and XEOMIN 100 units. Each syringe should be labelled accordingly.

Possible concentrations for XEOMIN 50 and 100 units are indicated in the following table:

Resulting dose (in units per 0.1 ml)	**Solvent added** (sodium chloride 9 mg/ml (0.9%) solution for injection)	
	Vial with 50 units	**Vial with 100 units**
20 units	0.25 ml	0.5 ml
10 units	0.5 ml	1 ml
8 units	0.625 ml	1.25 ml
5 units	1 ml	2 ml
4 units	1.25 ml	2.5 ml
2.5 units	2 ml	4 ml
2 units	2.5 ml	5 ml
1.25 units	4 ml	Not applicable

Any solution for injection that has been stored for more than 24 hours as well as any unused solution for injection should be discarded.

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

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

Recommendations should any incident occur during the handling of botulinum toxin type A

- Any spills of the product must be wiped up: either using absorbent material impregnated with any of the above listed solutions in case of the powder, or with dry, absorbent material in case of reconstituted product.
- The contaminated surfaces should be cleaned using absorbent material impregnated with any of the above solutions, then dried.
- If a vial is broken, one should proceed as mentioned above by carefully collecting the pieces of broken glass and wiping up the product, avoiding any cuts to the skin.
- If the product comes into contact with skin, the affected area should be rinsed abundantly with water.
- If product gets into the eyes, they should be rinsed thoroughly with plenty of water or with an ophthalmic eyewash solution.
- If product comes into contact with a wound, cut or broken skin, the skin should be rinsed thoroughly with plenty of water . Appropriate medical steps according to the dose injected should be taken.

These instructions for use, handling and disposal should be strictly followed.

7. MANUFACTURER
Merz Pharma GmbH & Co. KGaA
Eckenheimer Landstrate 100, 60318 Frankfurt/Main, Germany

8. MARKETING AUTHORISATION HOLDER

Alphamedix Ltd.
25 Bazel St. POB
10256
Petach Tikva 49002, Israel

9. MARKETING AUTHORISATION NUMBER(S)

XEOMIN 50: 161-95-35383-00
XEOMIN 100: 161-96-35384-00

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