1. NAME OF THE MEDICINAL PRODUCT

XEOMIN powder for solution for injection 50 units
XEOMIN powder for solution for injection 100 units

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 50 or 100 units of Clostridium Botulinum neurotoxin type A (150kD), free from complexing proteins*

* Botulinum neurotoxin type A, purified from cultures of Clostridium Botulinum (Hall strain)

3. PHARMACEUTICAL FORM

Powder for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

XEOMIN is indicated in adults for the treatment of:
- Cervical dystonia (spasmodic torticollis)
- Blepharospasm
- Spasticity of the upper limb

XEOMIN is indicated for the temporary improvement in the appearance of moderate to severe
- Upper facial lines
    - Glabellar frown lines
    - Lateral periorbital lines (crow's feet lines)
    - Horizontal forehead lines

in adults below 65 years of age.

4.2 Posology and method of administration

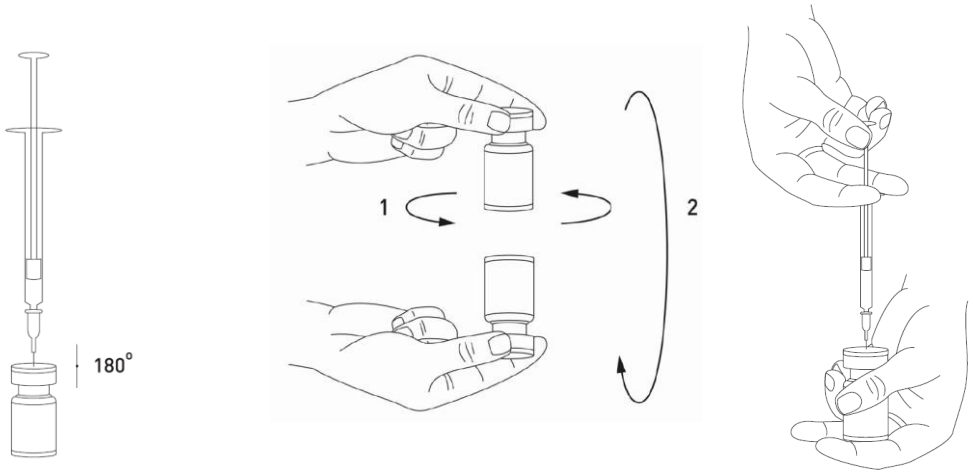
4.2.1 Method of administration

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

XEOMIN may only be administered by health care professionals with suitable qualifications and proven experience in the application of Botulinum neurotoxin type A.

XEOMIN is reconstituted prior to use with sodium chloride 9 mg/ml (0.9%) solution for injection.

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 is drawn up into a syringe. A 20-27 G short bevel 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. The vial must be discarded if the vacuum does not pull the solvent into the vial. Remove the syringe from the vial and mix XEOMIN with the solvent by carefully swirling and inverting/flipping the vial – do not shake 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 free of particulate matter.

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

Reconstituted XEOMIN is intended for intramuscular injection.

Neurological indications

Cervical dystonia (spasmodic torticollis)
A suitable sterile needle (e.g. 25-30 gauge / 0.30-0.50 mm diameter / 37mm 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.

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 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 U are administered into this muscle.

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.

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.

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).

In case of any difficulty in isolating the individual muscles, injections should be made under electromyographic assistance. 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.

Aesthetic indications

Reconstituted XEOMIN is injected using a thin sterile needle (e.g. 30-33 gauge needle / 0.20-0.30 mm diameter / 13 mm length).

Glabellar frown lines
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.

Lateral periorbital lines (Crow's Feet lines)
Injection should be done intramuscularly into the orbicularis oculi muscle, directly under the dermis to avoid diffusion of Xeomin. Injections too close to the zygomaticus major muscle should be avoided to prevent lip ptosis.

Horizontal forehead lines
Paralyzing of lower muscle fibers by injecting XEOMIN near the orbital rim should be avoided to reduce the risk of brow ptosis.

4.2.2 Posology

Neurological indications

General
The optimum dosage, frequency and number of injection sites in the treated muscle(s) should be individualised for each patient and determined by the physician.

Possible dilutions for the treatment of neurological indications are indicated in the following table:

Table 1: Diluent Volumes for Reconstitution of XEOMIN for the Treatment of Neurological Indications

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**
40 units	0.125 ml	0.25 ml
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

Cervical dystonia (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.

Injection volume per injection site: approximately 0.1 to 0.5 ml.
Total dose: should not exceed 200 units in the first treatment session.
Dose: up to 300 units may be given in subsequent injection sessions.
No more than 50 units should be given at any single injection site.

XEOMIN is usually injected into the sternocleidomastoid, levator scapulae, splenius capitis, scalenus, and/or the trapezius muscle(s). This list is not exhaustive as any of the muscles responsible for controlling head position may require treatment.

Median time to first onset of effect: usually within seven days after injection.
Duration of effect: up to 3-4 months, however, it may last significantly longer or shorter.

Treatment intervals should be determined based on the actual clinical need of the individual patient. Improved patient benefit may be achieved by retreating when symptoms return to a clinically significant level of discomfort and severity. Duration of action is dependent on dosing,

injection technique, and other variables. Generally, the patient should be treated using the lowest effective dose at the longest clinically indicated intervals between injections.

If in individual cases the duration of effect is shorter than 12 weeks, the next injection can be given earlier, upon consideration of the risk-benefit ratio. Injection intervals should not be shorter than 6 weeks, and one single injection given earlier than 12 weeks does not indicate a general need for regular earlier re-injection. If an injection interval reduction is necessary, the following recommendations should be followed:

1. Active request from the patient
2. An objective confirmation of the necessity for an injection
3. Absence of adverse reactions to the previous injection

The dose should not be increased when the interval is reduced. In case of intervals reduction below 12 weeks, a close monitoring of adverse reaction should be performed. In a controlled clinical trial XEOMIN has been efficacious and well-tolerated when injected in intervals between 6 and 20 weeks (median: 12 weeks).

Blepharospasm

Initial dose and injection volume per injection site: 1.25 to 2.5 units (0.05-0.1 ml).
Dosing:

- The initial dose should not exceed 25 units per eye.
- Normally, the total dose should not exceed 100 units per treatment session.

XEOMIN is injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi muscle 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.

Median time to first onset of effect: usually within four days after injection.
Duration of effect: up to 3-4 months, however, it may last significantly longer or shorter in individual patients. Treatment intervals should be determined based on the actual clinical need of the individual patient. Improved patient benefit may be achieved by retreating when symptoms return to a clinically significant level of discomfort and severity. Duration of action is dependent on dosing, injection technique, and other variables. Generally, the patient should be treated using the lowest effective dose at the longest clinically indicated intervals between injections.
If in individual cases the duration of effect is shorter than 12 weeks, the next injection can be given earlier, upon consideration of the risk-benefit ratio. Injection intervals should not be shorter than 6 weeks, and one single injection given earlier than 12 weeks does not indicate a general need for regular earlier re-injection. If an injection interval reduction is necessary, the following recommendations should be followed:

1. Active request from the patient
2. An objective confirmation of the necessity for an injection
3. Absence of adverse reactions to the previous injection

The dose should not be increased when the interval is reduced. In case of intervals reduction below 12 weeks, a close monitoring of adverse reaction should be performed. In a controlled clinical trial XEOMIN has been efficacious and well-tolerated when injected in intervals between 6 and 20 weeks (median: 12 weeks).

Spasticity of the upper limb
Injection volume per injection site: approximately 0.2 to 1 ml (can be exceeded to 1.5 ml in selected cases).

The exact dosage and number of injection sites should be tailored to the individual patient based on the size, number and location of involved muscles, the severity of spasticity, and the presence of local muscle weakness.

Table 2: Standard treatment doses 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	25-100	2
Flexor digitorum profundus	25-100	2
Flexed Elbow		
Brachioradialis	25-100	1-3
Biceps	50-200	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

This list is not exhaustive as any of the muscles of the upper limb may require treatment, e.g. shoulder.

The total recommended dose is up to 400 units per treatment session.
Median time to first onset of effect: usually within 4 days after injection.
Maximum effect: usually within 4 weeks. Duration of effect: usually up to 12 weeks, however, it may last longer or shorter in individual patients.

Repeat 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.

Aesthetic indications

Possible dilutions of XEOMIN for the treatment of aesthetic indications are indicated in the following table:

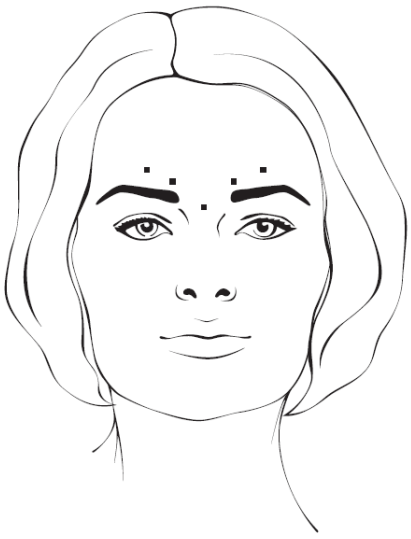
Table 3: Diluent Volumes for Reconstitution of XEOMIN for the Treatment of Aesthetic Indications

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**
4 units	1.25 ml	2.5 ml
5 units	1 ml	2 ml

The intervals between aesthetic indications treatments should not be shorter than 3 months.

Glabellar frown lines
Dose per injection site: 4 units 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.

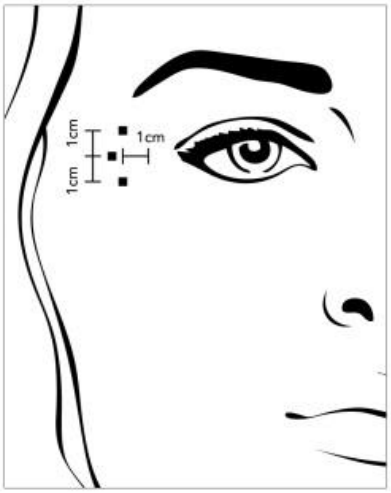
The dose may be increased by the physician to up to 30 units if required by the individual needs of the patients, with at least 3-months' interval between treatments.



Duration of effect: up to 4 months after the injection, however, it may last longer or shorter in individual patients.

Lateral periorbital lines (Crow's Feet lines)
Dose per injection site: 4 units bilaterally into each of the 3 injection sites

- one injection approximately 1 cm lateral from the bony orbital rim
- two injections approximately 1 cm above and below the area of the first injection

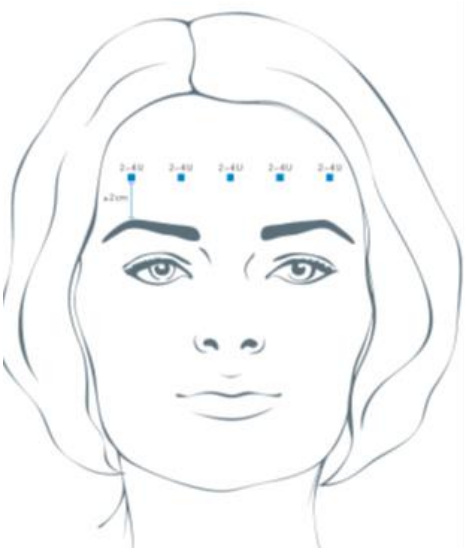


Total dose: 24 units (12 units per side) may be given.
Duration of effect: up to 4 months after the injection, however, it may last longer or shorter in individual patients.

No efficacy and safety data are currently available for more than two injections in lateral periorbital lines seen at maximum smile separated by a 4-month interval.

Horizontal forehead lines
Total dose: 10 to 20 units may be given according to the individual needs of the patients.
Dose per injection sites:

- 10 to 20 units into the frontalis muscle in five horizontally aligned injection sites at least 2 cm above the orbital rim
- 2 units, 3 units, or 4 units per injection point, respectively.



Duration of effect: up to 4 months after injection, however, it may last longer or shorter in individual patients.
Currently available efficacy and safety data in horizontal forehead lines seen at maximum contraction are limited to two injection cycles separated by a 4 to 5-month interval.

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

- For Blepharospasm, Spasmodic torticollis, spasticity of the upper limb only: clinical verification of the neurotoxin effect on the injected muscle: e.g. an electromyographic investigation in a specialised facility.
- Analysis of the reason 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) EMG guidance,
  3) the recommended minimum interval between the initial and repeat treatment is followed

4.2.3 Special populations

There are limited clinical data from phase 3 studies of XEOMIN in patients over 65 years of age for the treatment of upper facial lines. Until further studies have been conducted in this age group, XEOMIN is not recommended for use in patients over 65 years of age in these indications.

4.2.4 Paediatric population

XEOMIN has not been studied in the paediatric population and is therefore not recommended in the paediatric age group.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome).
- Presence of infection or inflammation at the proposed injection sites.

4.4 Special warnings and precautions for use

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.

For the treatment of aesthetic indications: if proposed injection sites are marked with a pen, the product must not be injected through the pen marks; otherwise a permanent tattooing effect may occur.

For the treatment of cervical dystonia and spasticity of the upper limb XEOMIN should be injected carefully when injected at sites close to sensitive structures, such as the carotid artery, lung apices and oesophagus.

XEOMIN should be used with caution:
- If bleeding disorders of any type exist
- In patients receiving anticoagulant therapy or other substances in anticoagulant doses.
- in patients suffering from amyotrophic lateral sclerosis (ALS)
- in patients with other diseases which result in peripheral neuromuscular dysfunction
- in targeted muscles which display pronounced weakness or atrophy

The recommended single doses of XEOMIN should not be exceeded.

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

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 injected muscles and marginally varying toxin activity resulting from the biological testing procedure employed or secondary non-response.

Cervical dystonia (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).

In general, 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.

Blepharospasm
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.

Because of its anticholinergic effects, XEOMIN should be used with caution in patients at risk of developing 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 injection of Botulinum toxin products into the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration, especially in patients with cranial nerve disorders (facial nerve).

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

Spasticity of the upper limb
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 neurotoxin injection has not been established.

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.

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 the toxin to sites distant from the injection site (see section 4.8).
Patients treated with therapeutic doses may experience excessive muscle weakness.

When treating neurological indications, some of these effects can be life threatening and there have been reports of death, which in some cases was associated with dysphagia, pneumonia and/or significant debility. Dysphagia has been reported following injection to sites other than the cervical musculature.

In general, patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

Pre-existing neuromuscular disorders

Patients with neuromuscular disorders may be at increased risk of excessive muscle weakness. The Botulinum neurotoxin 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.

Patients with a history of dysphagia and aspiration should be treated with extreme caution when treated for neurological indications.

The treatment for aesthetic indications with XEOMIN is not recommended for patients with a history of dysphagia and aspiration.

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

Antibody formation
As with all therapeutic proteins, there is a potential for immunogenicity. Too frequent doses may increase the risk of antibody formation, which can result in treatment failure even if the product is being used to treat other indications.

The potential for antibody formation may be minimised by injecting with the lowest effective dose given at the indicated minimum intervals between injections.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of XEOMIN and aminoglycoside antibiotics or other agents interfering with neuromuscular transmission, e.g., tubocurarine-type muscle relaxants, should only be performed with caution as these agents may potentiate the effect of the toxin.

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.

Breastfeeding
It is not known whether Botulinum neurotoxin type A is excreted into the breast milk. Therefore, the use of XEOMIN during lactation cannot be recommended.

Fertility

There are no clinical data from the use of Botulinum neurotoxin type A. In an animal study no adverse effects on male or female fertility were detected (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.

Due to the nature of the disease being treated, the ability to drive and to operate machines may be reduced. Due to the latency of onset, some of the therapeutic and/or adverse effects of XEOMIN, which may also interfere with the ability to drive and operate machinery.

Consequently affected persons should avoid these tasks until their faculties are fully recovered.

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.

4.8.1 Undesirable effects independent from indication

Application related undesirable effects
As it is expected for any injection procedure 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 neurotoxin type A. Blepharoptosis which can be caused by injection technique is associated with the pharmacological effect of XEOMIN.

Toxin spread
When treating neurological indications, side effects related to spread of toxin distant from the site of administration have been reported very rarely to produce symptoms consistent with Botulinum toxin effects (excessive muscle weakness, dysphagia, and aspiration pneumonitis with a fatal outcome in some cases).

Undesirable effects such as these cannot be completely ruled out with the use of XEOMIN in aesthetic indications.

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.

Post-Marketing Experience
Flu-like symptoms and hypersensitivity reactions like swelling, oedema (also apart from injection site), erythema, pruritus, rash (local and generalised) and dyspnoea have been reported.

4.8.2 Undesirable effects dependent on indication

Based on clinical experience, information on the frequency of adverse reactions for the individual indications is given below. The 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); unknown (cannot be estimated from the available data).

Cervical dystonia (Spasmodic torticollis)
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. Dysphagia appears to be dose-dependent.

Table 4: Adverse reactions based on clinical experience with cervical dystonia

Body System	**Adverse Reaction**	
Gastrointestinal disorders:	Very common	dysphagia
	Common:	dry mouth, nausea
General disorders and administration site conditions:	Common:	injection site pain, asthenia
Musculoskeletal and connective tissue disorders:	Common:	neck pain, muscular weakness, myalgia, musculoskeletal stiffness, muscle spasms
Nervous system disorders:	Common:	headache, presyncope, dizziness
	Uncommon:	speech disorder
Infections and infestations:	Common:	upper respiratory tract infection
Respiratory thoracic and mediastinal disorders:	Uncommon:	dysphonia, dyspnoea
Skin and subcutaneous tissue	Common:	hyperhidrosis

disorders:	Uncommon:	rash

Blepharospasm

Table 5: Adverse reactions based on clinical experience with blepharospasm

Body System	**Adverse Reaction**	
Nervous system disorders:	Uncommon:	headache, facial paresis
Eye disorders:	Very common:	eyelid ptosis,
	Common:	dry eyes, vision blurred, visual impairment
	Uncommon	diplopia, lacrimation increased
Gastrointestinal disorders:	Common:	dry mouth
	Uncommon	dysphagia
General disorders and administration site conditions:	Common:	injection site pain,
	Uncommon	fatigue
Musculoskeletal and connective tissue disorders:	Uncommon:	muscular weakness
Skin and subcutaneous tissue disorders:	Uncommon:	rash

Spasticity of the upper limb

Table 6: Adverse reactions based on clinical experience with upper limb spasticity

Body System	**Adverse Reaction**	
Gastrointestinal disorders:	Common:	dry mouth
	Uncommon:	dysphagia, nausea
General disorders and administration site conditions:	Uncommon:	asthenia
Musculoskeletal and connective tissue disorders:	Uncommon:	muscular weakness, pain in extremity, myalgia

Nervous system disorders:	Uncommon:	headache, hypoaesthesia

Glabellar Frown Lines

Table 7: Adverse reactions based on clinical experience with glabellar frown lines

Body System	**Adverse Reaction**	
General disorders and administration site conditions:	Uncommon:	injection site bruising, influenza like illness, (local) tenderness, fatigue, injection site pain, discomfort (heavy feeling of eyelid/eyebrow)
Musculoskeletal and connective tissue disorders:	Common:	Mephisto sign
	Uncommon:	facial asymmetry (brow asymmetry), muscle spasms (above eyebrows)
Nervous system disorders:	Common:	headache
Eye disorders:	Uncommon:	eyelid oedema, vision blurred, eyelid ptosis
Skin and subcutaneous tissue disorders:	Uncommon:	pruritus, brow ptosis
Infections and infestations:	Uncommon:	nasopharyngitis
Vascular disorders:	Uncommon:	haematoma

Lateral Periorbital Lines (Crow's Feet Lines)

Table 8: Adverse reactions based on clinical experience with crow's feet

Body System	**Adverse Reaction**	
General disorders and administration site conditions:	Common:	injection site haematoma
Eye disorders:	Common:	eyelid oedema, dry eye

Upper Facial Lines

Table 9: Adverse reactions based on clinical experience with upper facial lines

Body System	**Adverse Reaction**	
General disorders and administration site conditions:	Common:	injection site haematoma, injection site pain, injection site erythema, discomfort (heavy feeling of frontal area)
Eye disorders:	Common:	eyelid ptosis, dry eye
Nervous system disorders:	Very common:	headache
	Common:	hypoaesthesia
Skin and subcutaneous tissue disorders	Common:	brow ptosis
Musculoskeletal and connective tissue disorders:	Common:	facial asymmetry, Mephis to sign
Gastrointestinal disorders:	Common:	nausea

4.9 Overdose

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. Symptoms of overdose are not immediately apparent post-injection.

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 from peripheral cholinergic nerve terminals.

This inhibition occurs according to the following sequence:

- heavy chain of neurotoxin binding to cholinergic nerve terminals
- internalisation of the neurotoxin within vesicles into the nerve terminal
- translocation of the light-chain of the neurotoxin molecule into the cytosol of the nerve terminal
- enzymatic cleavage of SNAP25, the presynaptic target protein essential for the release of acetylcholine.

Complete recovery of endplate function/impulse transmission after intramuscular injection normally occurs within 3 to 4 months as nerve terminals sprout and reconnect with the muscle endplate and the presynaptic neurotransmitter release mechanism becomes functional again.

Results of clinical studies

Cervical dystonia (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. 39% of the patients were treatment naïve. Patients were randomised (1:1:1) to receive a single administration of 240 units of XEOMIN (n=81), 120 units of XEOMIN (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 NT 201 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 U vs. placebo, and -7.5 points for 120 U vs. placebo in the full statistical model.

Patients could continue with the Extension Period if a new injection was required.
During the Extension Period, they received up to five additional injections of 240 units of XEOMIN (n=111) or 120 units of Xeomin (n=103) with a minimum interval between two injections of at least six weeks. The overall study duration was 68-89 weeks. Over the entire study, the median injection interval in patients treated with Xeomin ranged between 10.00 and 13.14 weeks.

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 onabotulinumtoxinA 900kD (Botox).

Patients were randomised (2:1) to receive a single administration of XEOMIN (n=75) at a similar dose to the most recent onabotulinumtoxinA injections sessions prior to study entry or placebo (n=34). The highest dose permitted in this study was 50 units per eye; the mean 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. During the Extension Period, they received up to five injections of XEOMIN (n=82) with a minimum interval between two injections of at least six weeks and a maximum dose of 50 units per eye. The overall study duration was 68-89 weeks. Over the entire study, the median injection interval in patients treated with Xeomin ranged between 10.14 and 12.00 weeks.

Cervical dystonia and Blepharospasm

Therapeutic equivalence of XEOMIN as compared to a comparator product containing the conventional Botulinum toxin type A complex onabotulinumtoxinA (900 kD) was shown in two comparative single-dose 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 suggest that XEOMIN and this comparator product have a similar efficacy and safety profile in patients with blepharospasm or cervical dystonia when used in a dosing conversion ratio of 1:1 (see section 4.2).

Spasticity of the upper limb

One double-blind, placebo-controlled Phase III clinical trial (MRZ 60201/SP/3001) 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 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 Main Period 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.

A second double-blind, placebo-controlled Phase III clinical trial (MRZ 60201-0410) enrolled a total of 148 patients with post-stroke spasticity of the upper limb. During the Main Period a fixed total dose of XEOMIN (90 and 80 units, respectively) was administered intramuscularly to the clinical patterns of flexed wrist and clenched fist (n=73). Additionally, if other upper limb spasticity patterns were present, the elbow, forearm and thumb muscles could be treated with fixed doses per muscle with a total dose of up to 400 units. The difference between the XEOMIN group and the placebo group in the change of the Ashworth Scale score was statistically significant. 145 patients continued in an Open-label Extension (OLEX) period of this study with flexible dosing (up to 400 units per injection session) and up to 5 injection cycles. The overall maximum study duration was 89 weeks.

In a supportive observer-blind, active-controlled Phase III clinical trial (MRZ 60201-0607) a total of 192 patients with spasticity of the upper limb were enrolled. Thereof, 97 patients received a high-volume dilution (20 units/ml) and 95 patients received a low-volume dilution (50 units/ml) of XEOMIN. Results demonstrated non-inferiority of the 20 U/ml dilution to the 50 U/ml dilution of XEOMIN as well as a statistically significant and clinically relevant efficacy and safety of both dilutions in the treatment of spasticity with various etiologies.

In another supportive uncontrolled, open-label Phase III study (MRZ 60201-3053) the safety and efficacy of XEOMIN was investigated for the treatment of upper and lower limb spasticity due to different cerebral causes in 155 patients with a clinical need for a total body dose of 800 units. This study showed a positive relationship between increasing doses of XEOMIN of up to 800 units and improvement of the patients' condition as assessed by Ashworth Scale and other efficacy variables without compromising the patients' safety or the tolerability of XEOMIN.

More than 3500 patients have been treated with XEOMIN in clinical trials for different indications.

Glabellar Frown Lines

The two identically designed double-blind, placebo-controlled Phase III clinical trials (MRZ 60201-0741 and MRZ 60201-0724) enrolled a total of 547 subjects with moderate to severe glabellar frown lines as assessed on the 4-point Facial Wrinkle Scale (FWS). Subjects were treated with 20 units of XEOMIN (n=366) or placebo (n = 181). Results demonstrated a statistically significant and clinically relevant efficacy of XEOMIN when compared to placebo. Another double-blind, placebo-controlled Phase III clinical trial (MRZ 60201-0520) enrolled a total of 256 subjects with moderate to severe glabellar frown lines as assessed on the 4-point Facial Wrinkle Scale (FWS). Thereof, 169 subjects were treated with 20 units of XEOMIN in the Main Period and 236 subjects were treated in the Open-label Extension (OLEX) Period of that study. Results demonstrated a statistically significant and clinically relevant efficacy of XEOMIN when compared to placebo.

Long-term safety in repeat-dose (20 units) treatment of moderate to severe glabellar frown lines as assessed on the 4-point Facial Wrinkle Scale (FWS) has been demonstrated in a Phase III study (MRZ 60201-0609) over a treatment period of up to two years with up to 8 consecutive injection cycles for a total of 796 subjects.

Therapeutic equivalence of XEOMIN as compared to a comparator product containing the conventional Botulinum toxin type A complex onabotulinumtoxinA (900 kD) was shown in one comparative Phase IV study (MUS 60201-4096_1) in subjects with glabellar frown lines (n=250). Study results demonstrated that XEOMIN and this comparator product have a similar efficacy and safety profile in subjects with moderate to severe glabellar frown lines when used with a dosing conversion ratio of 1:1.

Lateral Periorbital Lines (Crow's Feet lines)

In a Phase III study, 111 subjects with moderate to severe crow's feet lines at maximum smile were treated during 1 cycle with 12 units XEOMIN or placebo per side (right/left eye area) with a comparison of a 3-point and a 4-point injection schemes. Treatment success was defined as an improvement of at least 1 point on a 4-point scale assessed by an independent rater at week 4 using standardised digital photographs taken at maximum smile for either eye area compared to

baseline. Both the 3-point injection and 4-point injection schemes showed superiority over placebo. For the 3-point injection scheme, the success rate was 69.9% in the XEOMIN group vs. 21.4% in the placebo group, and for the 4-point injection scheme, 68.7% vs. 14.3%, respectively. No worsening was observed in any patient treated with XEOMIN. This was validated by the higher number of responders at Day 30 according to a 4-point scale at maximum smile by both the investigator and the patient's assessment showing a significantly higher proportion of responders among the patients receiving 12 units of XEOMIN per eye area compared to placebo.

Upper Facial Lines
The double-blind placebo controlled Phase III clinical trial (MRZ 60201-3076) enrolled a total of 156 subjects with moderate to severe upper facial lines as assessed on the 5-point Merz Aesthetics Scales (MAS). Thereof, 105 subjects were treated with 54 to 64 units XEOMIN in the Main Period of the study and 139 subjects were treated in the Open-label Extension (OLEX) Period of that study. Results demonstrated a statistically significant and clinically relevant efficacy of XEOMIN when compared to placebo with regard to the individual treatment areas alone (glabellar frown lines, lateral periorbital lines and horizontal forehead lines) as well as for all areas combined (upper facial lines).

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 it binds so rapidly and irreversibly to 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.

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 revealed no special hazard for humans based on conventional studies of cardiovascular safety pharmacology.

The findings from repeat-dose toxicity studies on systemic toxicity of XEOMIN in animals were mainly related to its pharmacodynamic action, i.e. atony, paresis and atrophy of the injected muscle.

No evidence of local intolerability was noted.

Reproductive toxicity studies with XEOMIN did neither show adverse effects on male or female fertility nor direct effects on embryo-foetal or on pre- and post-natal development in rats and/or rabbits. However, the administration of XEOMIN in embryotoxicity studies at dose levels exhibiting

maternal toxicity increased the number of abortions in rabbits and slightly decreased foetal bodyweights in rats.

In a post-weaning juvenile toxicity study in rats, atrophy of the testicular germinal epithelium and hypospermia were observed at the highest dose tested but no frank systemic toxicity, other than growth retardation, was detected at the dose level of 10 units/kg and below.

No genotoxicity or carcinogenicity studies have been conducted with XEOMIN.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sucrose

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
Refer to 'EXP DATE' on outer carton.

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

Unopened vial: Do not store above 30°C.

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

6.5 Nature and contents of container

Vial (type 1 glass) with a stopper (bromobutyl rubber) and tamper-proof seal (aluminium).

Pack size of 1, 2, 3, 4 or 6 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Procedure to follow for a safe disposal of vials, syringes and materials used
Any unused vials or remaining Xeomin 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), sodium hydroxide solution (0.1 N NaOH), or 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 neurotoxin type A

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

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

7. PRODUCT OWNER

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