Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

XEOMIN 200 units powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XEOMIN 200 units powder for solution for injection
One vial contains 200 units of Clostridium Botulinum neurotoxin type A (150 kD), 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 powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

XEOMIN is indicated for the symptomatic treatment in adults of

- blepharospasm and hemifacial spasm,
- cervical dystonia of a predominantly rotational form (spasmodic torticollis),
- spasticity of the upper limb,
- chronic sialorrhea due to neurological disorders.

XEOMIN is indicated for the symptomatic treatment in children and adolescents aged 2 to 17 years and weighing ≥ 12 kg of

- chronic sialorrhea due to neurological / neurodevelopmental disorders.

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.

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

The optimum dose, frequency and number of injection sites 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 and hemifacial spasm

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 50 units per eye per treatment session. 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.

The median time to first onset of effect is observed within four days after injection. The effect of a XEOMIN treatment generally lasts approximately 3-5 months, however, it may last significantly longer or shorter.

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.

Patients with hemifacial spasm should be treated as for unilateral blepharospasm.

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.

Spasticity of the upper limb
The exact dose 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.

Recommended 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
Internally Rotated/Extended/Adducted Shoulder		
Deltoideus, pars clavicularis	20-150	1-3
Latissimus dorsi	25-150	1-4
Pectoralis major	20-200	1-6
Subscapularis	15-100	1-4
Teres major	20-100	1-2

The maximum total dose for the treatment of upper limb spasticity should not exceed 500 units per treatment session, and no more than 250 units should be administered to the shoulder muscles.

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.

Chronic sialorrhea (adults)
A reconstituted solution at a concentration of 5 units/0.1 ml should be used.

XEOMIN is injected into the parotid and submandibular glands on both sides (per treatment four injections in total). The dose is divided with a ratio of 3:2 between the parotid and submandibular glands as follows:

Glands	**Units**	**Volume**
Parotid glands	30 per side	0.6 ml per injection
Submandibular glands	20 per side	0.4 ml per injection

The injection site should be close to the centre of the gland.

The recommended dose per treatment session is 100 units. This maximum dose should not be exceeded.
Treatment intervals should be determined based on the actual clinical need of the individual patient.
Repeat treatment more frequent than every 16 weeks is not recommended.

Chronic sialorrhea (children/adolescents)
A reconstituted solution at a concentration of 2.5 units/0.1 ml should be used.

XEOMIN is injected into the parotid and submandibular glands on both sides (per treatment four injections in total). The body-weight adjusted dose is divided with a ratio of 3:2 between the parotid and submandibular glands as indicated in the table below.

No dosing recommendations can be made for children weighing less than 12 kg.

Body weight	**Parotid gland, each side**		**Submandibular gland, each side**		**Total dose, both glands, both sides**
	Dose per gland	**Volume per injection**	**Dose per gland**	**Volume per injection**	
[kg]	[Units]	[ml]	[Units]	[ml]	[Units]
≥ 12 and < 15	6	0.24	4	0.16	20
≥ 15 and < 19	9	0.36	6	0.24	30
≥ 19 and < 23	12	0.48	8	0.32	40
≥ 23 and < 27	15	0.60	10	0.40	50
≥ 27 and < 30	18	0.72	12	0.48	60
≥ 30	22.5	0.90	15	0.60	75

The injection site should be close to the centre of the gland.

Treatment intervals should be determined based on the actual clinical need of the individual patient. Repeat treatment should be no more frequent than every 16 weeks.

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

- 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

Paediatric population

The safety and efficacy of XEOMIN in indications other than the one described for the paediatric population in section 4.1 have not been established. No recommendations on posology can be made for indications other than chronic sialorrhea in children and adolescents aged 2 to 17 years and weighing ≥ 12 kg.

Currently available paediatric clinical data with XEOMIN are described in section 5.1.

Method of administration

All indications

For instructions on reconstitution of the medicinal product before administration, see section 6.6. After reconstitution, XEOMIN should be used for only one injection session and for only one patient.

XEOMIN is intended for intramuscular and intraglandular (intra-salivary gland) use.

Blepharospasm and hemifacial spasm

After reconstitution, the XEOMIN solution is injected intramuscularly 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.

In cases of unilateral blepharospasm the injections should be confined to the affected eye.

Patients with hemifacial spasm should be treated as for unilateral blepharospasm.

There is no experience with injections in the lower facial area from clinical studies with XEOMIN. Muscles in the lower facial area should not be injected due to pronounced risk of local weakness as reported in literature after injections of botulinum toxin into this area in patients with hemifacial spasm.

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.

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).

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.

Chronic sialorrhea (adults/children/adolescents)

After reconstitution the XEOMIN solution is injected intraglandularly using a suitable sterile needle
(e.g. 27-30 gauge/0.30-0.40 mm diameter/12.5 mm length).

In adults, anatomic landmarks or ultrasound guidance are both possible for the localisation of the involved salivary glands, however the ultrasound guided method should be preferred, because it could result in a better therapeutic outcome (see section 5.1).

For the treatment of children and adolescents ultrasound guidance should be used. Local anaesthesia (such as local anaesthetic cream), sedation, or anaesthesia in combination with sedation may be offered to children and adolescents prior to injection after a careful benefit-risk evaluation and per local site practice.

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.

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 and hemifacial spasm

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.

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 muscle 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.

Chronic sialorrhea (adults/children/adolescents)

In cases of medication-induced sialorrhea (e.g. by aripiprazole, clozapine, pyridostigmine) first of all the possibility of replacement, reduction or even termination of the inducing medication should be considered before using XEOMIN for the treatment of sialorrhea.

Efficacy and safety of XEOMIN in patients with medication-induced sialorrhea were not investigated.

If cases of "dry mouth" develop in association with the administration of XEOMIN reduction of the dose should be considered.

A dental visit at the beginning of treatment is recommended. The dentist should be informed about sialorrhea treatment with XEOMIN to be able to decide about appropriate measures for caries prophylaxis.

4.5 Interaction with other medicinal products and other forms of interactions

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.

In addition, when used for the treatment of chronic sialorrhea, irradiation to the head and neck including salivary glands and/or co-administration of anticholinergics (e.g. atropine, glycopyrronium, scopolamine) may increase the effect of the toxin. The treatment of sialorrhea with XEOMIN during radiotherapy is not recommended.

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.

Breastfeeding
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.

Toxin spread
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).

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. 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); 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

Hemifacial spasm

Similar adverse reactions as for blepharospasm can be expected with hemifacial spasm.

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.

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	Unknown

Chronic sialorrhea (adults)

System Organ Class	**Adverse Reaction**	**Frequency**
Nervous system disorders	Paraesthesia	Common
	Speech disorder	Uncommon
Gastrointestinal disorders	Dry mouth, dysphagia	Common
	Altered (thickened) saliva, dysgeusia	Uncommon

Cases of persistent dry mouth (> 110 days) of severe intensity have been reported, which could cause further complications as gingivitis, dysphagia and caries.

Chronic sialorrhea (children/adolescents)

System Organ Class	Adverse Reaction	Frequency
Gastrointestinal disorders	Dysphagia	Uncommon
	Altered (thickened) saliva, dry mouth, oral pain, dental caries	Not known

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. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance
Website: **www.hpra.ie**

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 NT 201 ranged between 10.14 (1st interval) and 12.00 weeks (2nd to 5th 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 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 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 NT 201 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.

Spasticity of the upper limb (adults)
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.

Treatment of shoulder muscles was investigated in an open-label Phase III study which included 155 patients with a clinical need for treatment of combined upper and lower limb spasticity. The study protocol allowed for administration of doses up to 600 units of XEOMIN to the upper limb.
This study showed a positive relationship between increasing doses of XEOMIN 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.

Spasticity of the lower and upper limb due to cerebral palsy (children/adolescents)
Lower limb evaluation
In a double-blind, parallel-group, dose-response Phase III clinical study 311 children and adolescents (aged 2-17 years) with uni- or bilateral lower limb spasticity due to cerebral palsy were enrolled. For treatment of lower limb spasticity XEOMIN was administered in three treatment groups (4 units/kg body weight with a maximum of 100 units, 12 units/kg body weight with a maximum of 300 units or 16 units/kg body weight with a maximum of 400 units, respectively) for treatment of two selected lower limb clinical patterns (pes equinus, flexed knee, adducted thigh).
In this study the low dose group was intended to act as control group. No statistically significant differences were demonstrated in the comparison of the high dose vs low dose neither regarding the primary nor the co-primary efficacy endpoint. LS-Mean change (SE, 95% CI) from baseline in Ashworth Scale of plantar flexors 4 weeks after injection was -0.70 (0.061, 95% CI: -0.82; -0.58) for the high dose and -0.66 (0.084, 95% CI: -0.82; -0.50) for the low dose with a p-value of 0.650. Improvement in muscle tone was not reflected in an effect on function or Investigator's Global Impression of Change. Adequate posology of XEOMIN for the treatment of lower limb spasticity in children and adolescents cannot be determined.

No unexpected adverse events were observed in the double-blind treatment and open-label long-term treatment with XEOMIN over four injection cycles.

Upper limb evaluation
In a second double-blind, parallel-group, dose-response Phase III study a total of 350 children and adolescents (aged 2-17 years) with upper limb spasticity alone or with combined upper and lower limb spasticity due to cerebral palsy were treated with XEOMIN. For treatment of upper limb (flexed elbow, flexed wrist, clenched fist, pronated forearm, thumb-in-palm) or combined upper and lower limb spasticity (pes equinus, flexed knee, adducted thigh) XEOMIN was administered in three treatment groups in the Main Period with one injection cycle: 2 to 5 units/kg body weight with a maximum of 50 to 125 units, 6 to 15 units/kg body weight with a maximum of 150 to 375 units and 8 to 20 units/kg body weight with a maximum of 200 to 500 units. Patients continued with the highest dose in the Open-label Extension Period of the study with three injection cycles. A statistical significant difference between the low and high dose was seen in change from baseline in Ashworth Scale for elbow flexor or wrist flexor at week 4 post injection (-0.22 [95% CI -0.4;-0.04] p=0.017). Improvements in muscle tone was not reflected in an effect on function and Investigator's Global Impression of Change.Adequate posology of XEOMIN for the treatment of upper limb spasticity in paediatric patients can therefore not be determined from this study.

No unexpected safety concerns were reported in the upper limb and lower limb spasticity treatment with XEOMIN up to four injection cycles (14± 2 weeks each).

Chronic sialorrhea (adults)
The pivotal double-blind, placebo-controlled Phase III clinical trial enrolled a total of 184 patients suffering at least three months from sialorrhea resulting from Parkinson's disease, atypical parkinsonism, stroke or traumatic brain injury. During the Main Period (MP) a fixed total dose of XEOMIN (100 or 75 units) or placebo was administered intraglandularly at a defined dose ratio of 3:2 into parotid and submandibular salivary glands, respectively.

		uSFR (g/min)		**GICS (score points)**	
Treatment	**Timepoint**	**n obs**	**LS mean (SE)**	**n obs**	**LS mean (SE)**
Placebo	Week 4	36	-0.04 (0.033)	36	0.67 (0.186)
100 units	Week 4	73	-0.13 (0.026)	74	1.25 (0.144)
100 units	Week 8	73	-0.13 (0.026)	74	1.30 (0.148)
100 units	Week 12	73	-0.12 (0.026)	74	1.21 (0.152)
100 units	Week 16	73	-0.11 (0.027)	74	0.93 (0.152)

uSFR: Unstimulated Salivary Flow Rate; GICS: Global Impression of Change Scale
n obs: Number observed; LS: Mean difference to baseline; SE: Standard Error

At week 4, at least 1 point improvement on GICS (co-primary endpoint) was observed in 73% of patients treated with 100 units of XEOMIN compared to 44% of patients in the placebo group. The confirmatory analysis of both co-primary efficacy variables (uSFR and GICS at week 4 post-injection) demonstrated statistically significant improvements of the 100 units treatment group compared to placebo. Improvements in efficacy parameters at weeks 8 and 12 post-injection could be shown and were maintained up to the last observation point of the MP at week 16. Co-primary efficacy variables at week 4 demonstrated superior results for ultrasound guided application in comparison with anatomic landmark method (uSFR p-value 0.019 vs 0.099 and GICS 0.003 vs 0.171).
173 treated patients completed the MP and entered the Extension Period (EP). The EP consisted of three dose-blinded cycles each with a single treatment session (100 or 75 units of XEOMIN total dose, with the same dose ratio as in the MP) followed by a 16 week-observation period. 151 patients completed the EP. Results from the EP confirmed the findings of the MP showing continued treatment benefits of 100 units XEOMIN.

Chronic sialorrhea (children/adolescents)
In one double-blind, placebo-controlled Phase III clinical trial, a total of 255 children and adolescents (aged 2-17 years) with a body weight (BW) of at least 12 kg suffering from chronic sialorrhea associated with neurological disorders and/or intellectual disability were treated. During the Main Period (MP), 220 patients aged 617 years received XEOMIN treatment according to BW class and up to 75 U, or placebo. Treatment was administered ultrasound guided intraglandularly with a defined dose ratio of 3:2 into the parotid and submandibular salivary glands, respectively.

		uSFR (g/min)		**GICS (score points)**	
Treatment	**Timepoint**	**n obs**	**LS mean (SE)**	**n obs**	**LS mean (SE)**

Placebo	Week 4	72	-0.07 (0.015)	72	0.63 (0.104)
XEOMIN according to BW class	Week 4	148	-0.14 (0.012)	148	0.91 (0.075)
	Week 8	146	-0.16 (0.012)	146	0.94 (0.068)
	Week 12	147	-0.16 (0.013)	147	0.87 (0.073)
	Week 16	145	-0.15 (0.013)	146	0.77 (0.070)

uSFR: Unstimulated Salivary Flow Rate; GICS: Global Impression of Change Scale; BW: Body Weight;
n obs: Number observed; LS: Mean difference to baseline; SE: Standard Error

The confirmatory analysis of the co-primary efficacy variables (uSFR and GICS at week 4 post-injection) demonstrated statistically significant and clinically relevant improvements of the XEOMIN group compared to placebo. For both efficacy parameters, statistically significant differences between treatment groups were observed until the end of the MP at week 16. All 35 children aged 2-5 years were treated with XEOMIN according to their BW class, no placebo arm was used as control showing an improvement in the investigated efficacy variables similar to those observed in the 6-17 years XEOMIN treatment group.
247 patients participated in the subsequent first cycle of the Open-label Extension Period (OLEX). The OLEX consisted of three additional cycles, each with a single treatment session followed by a 16-week observation period. All patients received XEOMIN according to the same pre-determined dosing scheme and the same dose ratio used in the MP. A total of 222 patients completed the OLEX. Results from the OLEX confirmed the findings of the MP showing continued treatment benefits. No new or unexpected safety concerns were identified.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with XEOMIN:

- in all subsets of the paediatric population in the treatment of dystonia
- in infants and toddlers from 0-24 months in the treatment of muscle spasticity and chronic sialorrhea.

See section 4.2 for information on paediatric use.

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

Human albumin
Sucrose

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

XEOMIN 200 units powder for solution for injection: 3 years

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

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

XEOMIN 200 units powder for solution for injection: Pack sizes of 1, 2, 3, 4 or 6 vials, each containing 200 units

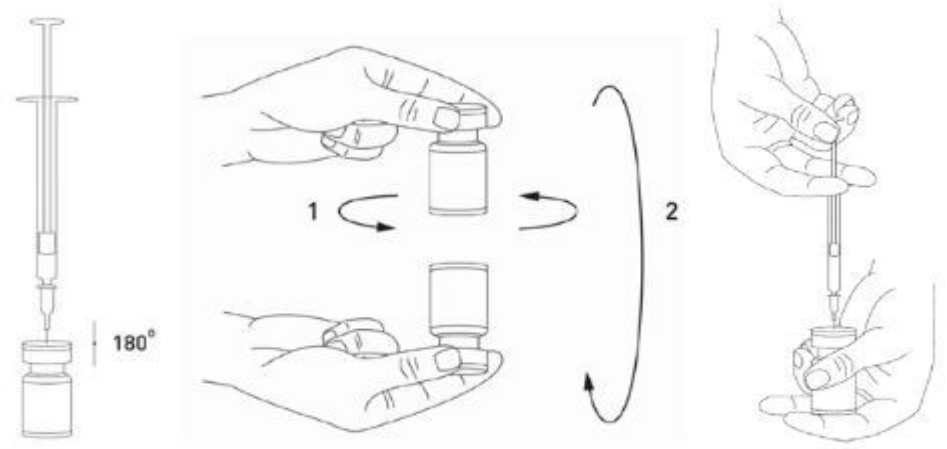
Not all pack sizes may be marketed.

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 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. 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, XEOMIN 100 units and XEOMIN 200 units. Each syringe should be labelled accordingly.

Possible concentrations for XEOMIN 50, 100, and 200 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**	**Vial with 200 units**
20 units	0.25 ml	0.5 ml	1 ml
10 units	0.5 ml	1 ml	2 ml
8 units	0.625 ml	1.25 ml	2.5 ml
5 units	1 ml	2 ml	4 ml
4 units	1.25 ml	2.5 ml	5 ml
2.5 units	2 ml	4 ml	Not applicable
2 units	2.5 ml	5 ml	Not applicable
1.25 units	4 ml	Not applicable	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 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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