# NEW ZEALAND DATA SHEET

## 1. XEOMIN (powder for injection)

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

IncobotulinumtoxinA, purified Botulinum toxin type A, free from complexing proteins

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of Xeomin powder for solution for injection contains 50 or 100 units of incobotulinumtoxinA.

Native Botulinum toxin type A is a high molecular weight complex, which, in addition to the toxin (150 kD), contains other bacterial non-toxic proteins, like haemagglutinins and non-haemagglutinins. In contrast to conventional preparations containing the botulinum toxin A complex, Xeomin contains pure (150 kD) toxin since 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.

IncobotulinumtoxinA is produced from the fermentation of Clostridium botulinum and is subsequently purified to remove complexing proteins. It consists of the purified neurotoxin which has been separated from complexing proteins (haemagglutinins and a non-toxic non-haemagglutinating protein) during production.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection.
White to off-white powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Xeomin is indicated in adults for the treatment of:

- Cervical dystonia
- Blepharospasm
- Spasticity of the upper limb
- Upper facial lines
    - Glabellar frown lines
    - Lateral periorbital lines (crow's feet)
    - Horizontal forehead lines

### 4.2 Dose and method of administration

**Dose**

Xeomin may only be administered by health care professionals with suitable qualifications and proven experience in the application of botulinum toxin and in the use of the necessary equipment

**Due to unit differences in the potency assay, Xeomin units are specific to Xeomin. Therefore, unit doses recommended for Xeomin are not interchangeable with those for other preparations of botulinum toxin. One unit of Xeomin is therefore not equivalent to one unit of other preparations of botulinum toxin (see Section 4.4 Special warnings and precautions for use).**

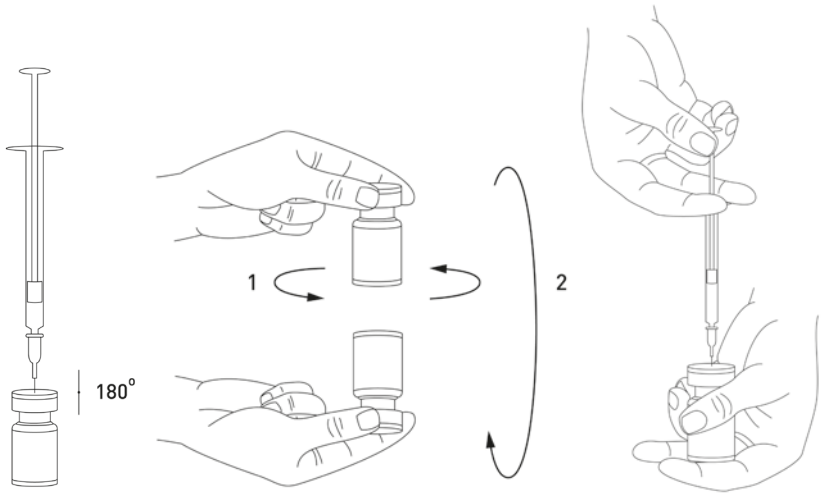
**Reconstitution**

Product is for single use in one patient only. Discard any residue.

Xeomin is reconstituted prior to use with sodium chloride 9 mg/mL (0.9%) solution for injection. A suitable sterile needle should be used for administration.

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 (see Figure 1). 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 syringe suitable for injection.

*Figure 1 Reconstitution Method*




Reconstituted Xeomin is a clear, colourless solution free of particulate matter. Xeomin should not be used if the reconstituted solution (prepared as above) has a cloudy appearance or contains floccular or particulate matter.

Reconstituted Xeomin is intended for intramuscular injection.

**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)

*Dosage*

Recommended injection volume/injection site: approximately 0.1 to 0.5 mL. Normally, 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 sitting should not be exceeded. No more than 50 U should be given at any one injection site. As with any drug treatment, initial dosing should begin at the lowest effective dose.

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: within seven days after injection.
Duration of effect: 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).

*Method of administration*

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.

Blepharospasm

*Dosage*

Initial dose and injection volume per injection site: 1.25 to 2.5 U (0.05-0.1 mL)
The initial dose should not exceed 25 U per eye.

Normally, the total dose should not exceed 100 U per treatment session.

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.

Median time to first onset of effect: 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. In a controlled clinical trial Xeomin has been efficacious and well-tolerated when injected in intervals between 6 and 20 weeks (median: 12 weeks). Treatment intervals should be determined based on the actual clinical need of the individual patient.

*Method of administration*

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).

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).

*Table 2: Standard treatment doses per muscle:*

| **Clinical Pattern**<br>*Muscle* | **Total units per muscle (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 |

For the maximum total dose for each treatment session, please refer to text below.

*Dosage*

Maximum total dose for the treatment of upper limb spasticity should not exceed 500 units per treatment session, and no more than 250 units in total should be administered to the shoulder muscles.
Median time to first onset of effect: usually within four 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.

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

*Method of administration*

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).

**Aesthetic indications**

General

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.

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

Glabellar frown lines

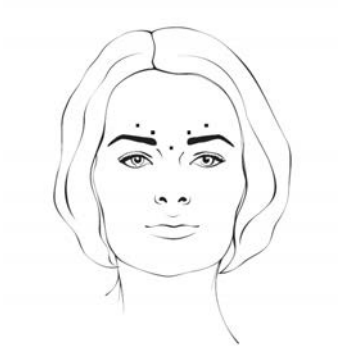
The optimum dose and number of injection sites in the treated muscle(s) should be individualised for each patient and determined by the treating doctor.

*Dosage*

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 (Figure 2).

The standard dose is 20 units. The dose may be increased by the physician to up to 30 units if required by the individual needs of the patients. Improvement in the glabellar frown lines: generally within 2 to 3 days
Maximum effect: on day 30. The effect lasts up to 4 months after the injection.
The intervals between treatments: ≥ 3 months.

*Figure 2 Injection Scheme*



*Method of administration*

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.

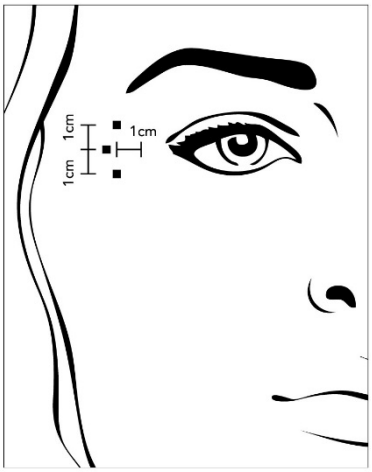
Lateral periorbital lines (crow's feet)

*Dosage for 3-point injection scheme*

Dose per injection sites: 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.

*Figure 3 Injection Scheme*

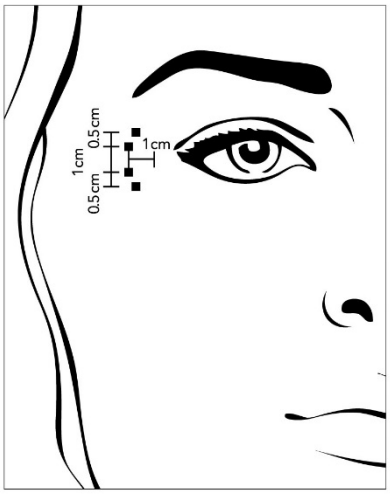



*Dosage for 4-point injection scheme*

Dose per injection sites: 3 units bilaterally into each of the 4 injection sites

- mark the 1 cm lateral from the bony orbital rim. First two injections approximately 0.5 cm above and below this point
- two injections approximately 1 cm above and below the first marked point.

*Figure 4 Injection Scheme*




Total dose: 24 units (12 units per side) may be given.
Duration of effect: up to 3 months after the injection, however, it may last longer or shorter in individual patients.

*Method of administration*

Injections too close to the zygomaticus major muscle should be avoided to prevent lip ptosis.

Horizontal forehead lines

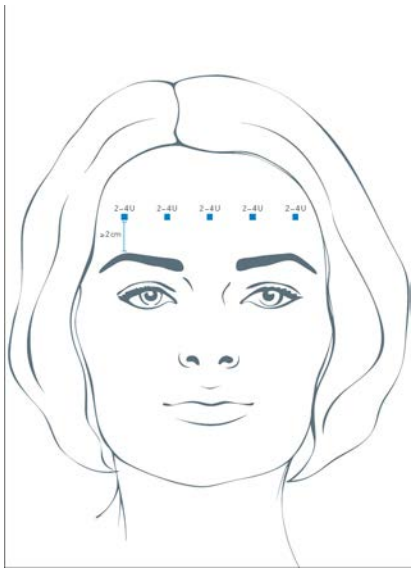
*Dosage*

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.

*Figure 5 Injection Scheme*



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

*Method of administration*

Paralysing of lower muscle fibers by injecting Xeomin near the orbital rim should be avoided to reduce the risk of brow ptosis.

**Recommendations should any incident occur during the handling of botulinum toxin**

Any spills of the product must be wiped up: either using absorbent material impregnated with any of the below listed solutions (see section 6.6) 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 below listed solutions, then dried (see also section 6.6).

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.

## 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).
- 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.

**Local and Distant Spread of Toxin Effect**

The recommended dosages and frequencies of administration for Xeomin should not be exceeded. Extensive or inappropriate doses outside the recommended dosage range may lead to an increased risk of adverse effects. Undesirable effects may occur from misplaced injections of incobotulinumtoxinA that temporarily paralyse nearby muscle groups.

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). The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalised muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to the spread of toxin effects.

The risk of symptoms is probably greatest in children treated for spasticity but symptoms can occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

Patients treated with therapeutic doses may experience excessive muscle weakness.

When treating neurological indications, some of these undesirable effects can be life threatening and there have been reports of death. Dysphagia has also been reported following injection to sites other than the cervical musculature.

Cases of iatrogenic botulism have been reported following injection of botulinum toxin products. Patients or caregivers should be advised to seek immediate medical care if they experience any signs or symptoms consistent with the spread of botulinum toxin effect or if swallowing, speech or respiratory disorders occur (see also section 4.9).

**Pre-existing Neuromuscular Disorders**

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

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.

Xeomin should be used with caution:

- in patients with amyotrophic lateral sclerosis (ALS)
- 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 toxin products. If serious (e.g. anaphylactic reaction) 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, formation of neutralising antibodies to incobotulinumtoxinA may reduce the effectiveness of Xeomin treatment by inactivating the biological activity of the toxin. The critical factors for neutralising antibody formation have not been well characterised. 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 longest feasible intervals between injections.

**Lack of interchangeability between botulinum toxin products**

**THE POTENCY UNITS OF XEOMIN ARE SPECIFIC TO THE PREPARATION AND ASSAY METHOD UTILISED. THEY ARE NOT INTERCHANCHEABLE WITH THE OTHER PREPARATIONS OF BOTULUNUM TOXIN PRODUCTS AND, THEREFORE, UNITS OF BIOLOGICAL ACTIVITY OF XEOMIN CANNOT BE COMPARED TO OR CONVERTED INTO UNITS OF ANY OTHER BOTULINUM TOXIN PRODUCTS ASSESSED WITH ANY OTHER SPECIFIC ASSAY METHOD (SEE ALSO SECTION 4.2).**

**Cervical Dystonia (Spasmodic torticollis)**

Patients should be informed that injections of Xeomin for the management of cervical dystonia (spasmodic torticollis) may cause mild to severe dysphagia with the risk of aspiration and dyspnoea. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection

that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post-marketing reports of serious breathing difficulties, including respiratory failure, in patients with cervical dystonia treated with botulinum toxin products.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscles have been reported to be at greater risk of dysphagia. In general, limiting the dose injected into the sternocleidomastoid muscle may decrease the occurrence of dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

**Blepharospasm**

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

Reduced blinking from injection of botulinum toxin products in the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with cranial nerve disorders (facial nerve). Careful testing of corneal sensation in eyes previously operated upon, avoidance of injection into the lower lid area to avoid ectropion, and vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means. Because of its anticholinergic effects, Xeomin should be used with caution in patients at risk of developing narrow angle glaucoma. To prevent ectropion, botulinum toxin products should not be injected into the medial lower eyelid area.

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

**Upper limb spasticity**

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 incobotulinumtoxinA injection has not been established.

**Risk of ptosis in patients treated with Xeomin for glabellar lines**

Do not exceed the recommended dosage and frequency of administration of Xeomin.

In order to reduce the complication of ptosis the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.

- Corrugator injections should be placed at least 1cm above the bony supraorbital ridge.

**Human albumin and transmission of viral diseases**

This product contains a small amount of human albumin. The risk of transmission of viral infection or prion-related infection such as Creutzfeldt-Jakob Disease (CJD) cannot be excluded with absolute certainty following the use of human blood or blood products.

**Use in renal, hepatic or cardiovascular impairment**

No information is available on the use of Xeomin in this population.

**Use in the elderly**

There are no additional precautions regarding the use of Xeomin in the elderly population.

**Paediatric use**

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

**Effect on laboratory tests**

No data available.

## 4.5 Interaction with other medicines and other forms of interaction

Coadministration 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.

## 4.6 Fertility, pregnancy and lactation

**Pregnancy - (Category B3)**

There are no adequate data from the use of incobotulinumtoxinA in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Xeomin should not be used during pregnancy unless clearly necessary.

Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

There was no evidence of teratogenicity in animal studies. However, Xeomin showed minor adverse effects on embryo-foetal development in rats and increased abortions in rabbits when given at doses of about 10- and 2- fold higher, respectively, than the maximum recommended human dose (MRHD) for post-stroke spasticity of the upper limb (400 U) on a dose per body weight basis. The significance of the findings are considered uncertain in humans and are consistent with those reported for other botulinum neurotoxin type A agents.

When Xeomin was administered intramuscularly to pregnant rats during organogenesis (i.e., a total of 3 injections at doses of 3, 10, or 30 U/kg on gestational day [GD] 6, 12, 19; or 14 injections at 7 U/kg on GD 6 to 19; or 5 injections at 2, 6, or 18 U/kg on GDs 6, 9, 12, 16, 19), decreases in foetal weight and skeletal ossification were observed at mater-notoxic doses. The no effect level for embryo-foetal development in rats was a total dose of 90-98 LDU/kg [i.e., 14 injections at 7 LDU/kg or 3 injections at 30 LDU/kg or 5 injections at 18 LDU/kg (11.25 to12.25-fold the MRHD for post-stroke spasticity of the upper limb on a dose per body weight basis).

Intramuscular administration to pregnant rabbits during organogenesis (1.25, 2.5, or 5 U/kg on GDs 6, 18, and 28) resulted in an increased rate of abortions at a maternally toxic dose level of 5 U/kg. In rabbits, the no effect level for abortion was 2.5 U/kg [relative exposure is 0.9-fold the MRHD for post-stroke spasticity of the upper limb (400 U) on a dose per body weight basis].

**Breast-feeding**

It is not known whether incobotulinumtoxinA is excreted into the breast milk. The use of Xeomin during lactation is not recommended.

**Fertility**

There are no clinical data from the use of incobotulinumtoxinA.

Male and female fertility was unaffected in rabbits following intramuscular doses of Xeomin starting 2 weeks prior to mating and administered every 2 weeks at ≤3.5 LDU/kg for a total of 5 and 3 doses, respectively. Relative exposure ratios were 1.3 for females and 2.2 for males, the maximum recommended human dose for post-stroke spasticity of the upper limb (400 Units) on a dose per body weight basis.

## 4.7 Effects on ability to drive and use machines

Xeomin can have an effect on the ability to use and drive machines.

Patients should be counselled that if asthenia, muscle weakness, vision disorders, dizziness or drooping eyelids occur, they should avoid driving or engaging in other potentially hazardous activities.

## 4.8 Undesirable effects

The following tables summarises the frequency of adverse events reported for Xeomin and placebo during clinical trials (Tables 4 to 9).

*Table 4: Cervical Dystonia, Adverse Events >2%*

| Adverse events | Xeomin (N=159)(%) | Placebo (N=74)(%) |
|---|---|---|
| **Musculoskeletal and Connective Tissue Disorders** | **43 (27.04)** | **8 (10.81)** |
| Neck Pain | 16 (10.06) | 3 (4.05) |
| Muscular weakness | 14 (8.81) | 1 (1.35) |
| Musculoskeletal pain | 9 (5.66) | 1 (1.35) |
| Muscle spasms | 4 (2.52) | 2 (2.70) |
| Musculoskeletal stiffness | 5 (3.14) | 1 (1.35) |
| **Gastrointestinal Disorders** | **33 (20.75)** | **5 (6.76)** |
| Dysphagia | 24 (15.09) | 2 (2.70) |
| Nausea | 6 (3.77) | 0 |
| **Nervous System Disorders** | **25 (15.72)** | **5 (6.76)** |
| Headache | 7 (4.40) | 3 (4.05) |
| Dizziness | 4 (2.52) | 1 (1.35) |
| **Infections and Infestations** | **19 (11.95)** | **9 (12.16)** |
| Sinusitis | 5 (3.14) | 2 (2.70) |
| **General Disorders and Administration Site Conditions** | **21 (13.21)** | **6 (8.11)** |
| Injection site Pain | 11 (6.92) | 4 (5.41) |
| **Respiratory, Thoracic and Mediastinal Disorders** | **17 (10.69)** | **2 (2.70)** |
| Oropharyngeal pain | 4 (2.52) | 2 (2.70) |
| Asthma | 4 (2.52) | 0 |

Note: based on pooled placebo-controlled clinical studies

*Table 5: Blepharospasm, Adverse Events >2%*

| Adverse events | Xeomin (N=74)(%) | Placebo (N=34)(%) |
|---|---|---|
| **Eye Disorders** | **31 (41.89)** | **6 (17.65)** |
| Dry eye | 14 (18.92) | 4 (11.76) |
| Eyelid ptosis | 14 (18.92) | 2 (5.88) |
| Vision blurred | 4 (5.41) | 2 (5.88) |
| Visual impairment | 6 (8.11) | 0 |
| Lacrimation increased | 2 (2.70) | 1 (2.94) |
| **Gastrointestinal Disorders** | **21 (28.38)** | **5 (14.71)** |
| Dry mouth | 11 (14.86) | 1 (2.94) |
| Diarrhoea | 6 (8.11) | 0 |
| Dysphagia | 3 (4.05) | 2 (5.88) |
| Lip disorder | 2 (2.70) | 0 |
| **Infections and Infestations** | **17 (22.97)** | **6 (17.65)** |
| Nasopharyngitis | 4 (5.41) | 2 (5.88) |
| Respiratory tract infection | 5 (6.76) | 1 (2.94) |
| Gastroenteritis viral | 2 (2.70) | 0 |
| Tooth infection | 2 (2.70) | 0 |
| Urinary tract infection | 2 (2.70) | 0 |
| **General Disorders and Administration Site Conditions** | **9 (12.16)** | **10 (8.82)** |
| Asthenia | 3 (4.05) | 0 |
| Injection site haematoma | 2 (2.70) | 1 (2.94) |
| Injection site pain | 3 (4.05) | 0 |
| **Nervous System Disorders** | **11 (14.86)** | **1 (2.94)** |
| Headache | 7 (9.46) | 1 (2.94) |
| **Respiratory, Thoracic and Mediastinal Disorders** | **8 (10.81)** | **1 (2.94)** |
| Dyspnoea | 4 (5.41) | 1 (2.94) |

| Adverse events | Xeomin (N=74)(%) | Placebo (N=34)(%) |
|---|---|---|
| **Injury, Poisoning and Procedural Complications** | **3 (4.05)** | **1 (2.94)** |
| Muscle strain | 2 (2.70) | 0 |
| **Vascular Disorders** | **2 (2.70)** | 0 |
| Hypertension | 2 (2.70) | 0 |

*Note: based on pooled placebo-controlled clinical studies*

*Table 6: Spasticity of the upper limb, Adverse Events >2%*

| Adverse events | Xeomin (N=283)(%) | Placebo (N=182)(%) |
|---|---|---|
| **Infections and infestations** | **19 (6.7)** | **12 (6.6)** |
| **Nervous System Disorders** | **16 (5.7)** | **12 (6.6)** |
| Epilepsy | 7 (2.5) | 0 |
| Headache | 3 (1.1) | 4 (2.2) |
| **Gastrointestinal disorders** | **11 (3.9)** | **8 (4.4)** |
| **Musculoskeletal and connective tissue disorders** | **10 (3.5)** | **4 (2.2)** |
| **Injury, poisoning and procedural complications** | **9 (3.2)** | **4 (2.2)** |
| **Metabolism and Nutrition Disorders** | **8 (2.8)** | **4 (2.2)** |
| **General disorders and administration site conditions** | **7 (2.5)** | **3 (1.6)** |

*Note: based on pooled placebo-controlled clinical studies*

Table 7*: Upper facial lines, Adverse Events >2%*

| Adverse events | Xeomin (N=105)(%) | Placebo (N=51)(%) |
|---|---|---|
| **Infections and Infestations** | **38 (36.2)** | **14 (27.5)** |
| Nasopharyngitis | 20 (19.0) | 10 (19.6) |
| Influenza | 5 (4.8) | 1 (2.0) |
| Cystitis | 3 (2.9) | 1 (2.0) |
| Gastroenteritis | 3 (2.9) | 0 |
| Oral herpes | 3 (2.9) | 0 |
| **Nervous system disorders** | **29 (27.6)** | **3 (5.9)** |
| Headache | 24 (22.9) | 1 (2.0) |
| **General disorders and administration site conditions** | 9 (8.6) | 5 (9.8) |
| Injection site haematoma | 4 (3.8) | 3 (5.9) |
| **Musculoskeletal and connective tissue disorders** | **8 (7.6)** | **2 (3.9)** |
| Facial asymmetry | **3 (2.9)** | 0 |
| **Eye disorders** | **7 (6.7)** | **0** |
| **Injury, poisoning and procedural complications** | **7 (6.7)** | **1 (2.0)** |
| **Gastrointestinal disorders** | **6 (5.7)** | **4 (7.8)** |
| **Surgical and medical procedures** | **5 (4.8)** | **2 (3.9)** |
| **Skin and subcutaneous tissue disorders** | **4 (3.8)** | **3 (5.9)** |
| **Respiratory, thoracic and mediastinal disorders** | **3 (2.9)** | **0** |

*Note: based on pooled placebo-controlled clinical studies*

*Table 8: Glabellar Frown Lines, Adverse Events >2%*

| Adverse events | Xeomin (N=678)(%) | Placebo (N=316)(%) |
|---|---|---|
| **Infections and Infestations** | **144 (21.2)** | **60 (19.0)** |
| Nasopharyngitis | 50 (7.4) | 31 (9.8) |
| Sinusitis | 21 (3.1) | 10 (3.2) |
| Bronchitis | 14 (2.1) | 0 |
| **Nervous System Disorders** | **103 (15.2)** | **39 (12.3)** |
| Headache | 84 (12.4) | 30 (9.5) |
| **Musculoskeletal and connective tissue disorders** | **45 (6.6)** | **10 (3.2)** |
| **Respiratory, thoracic and mediastinal disorders** | **30 (4.4)** | **6 (1.9)** |
| **Gastrointestinal disorders** | **28 (4.1)** | **9 (2.8)** |
| **Investigations** | **27 (4.0)** | **4 (1.3)** |
| **Skin and subcutaneous tissue disorders** | **27 (4.0)** | **5 (1.6)** |
| **Injury, poisoning and procedural complications** | **26 (3.8)** | **9 (2.8)** |
| **General disorders and administration site conditions** | **24 (3.5)** | **9 (2.8)** |
| **Psychiatric disorders** | **16 (2.4)** | **3 (0.9)** |
| **Eye disorders** | **14 (2.1)** | **3 (0.9)** |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **7 (1.0)** | **7 (2.2)** |

*Note: based on pooled placebo-controlled clinical studies*

*Table 9: Lateral periorbital lines (crow's feet), Adverse Events >2%*

| Adverse events | Xeomin (N=83)(%) | Placebo (N=28)(%) |
|---|---|---|
| **Infections and Infestations** | **6 (7.2)** | **1 (3.6)** |
| Viral infection | 2 (2.4) | 1 (3.6) |
| **Eye disorders** | **5 (6.0)** | **0** |
| Eyelid oedema | 3 (3.6) | 0 |
| **General Disorders and Administration Site Conditions** | **3 (3.6)** | **0** |
| Injection site haematoma | 2 (2.4) | 0 |
| **Skin and Subcutaneous Tissue Disorders** | **2 (2.4)** | **1 (3.6)** |
| **Psychiatric Disorders** | **2 (2.4)** | **0** |

*Note: based on a single placebo-controlled clinical study*

Adverse Reactions reported by 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).

Cervical dystonia (Spasmodic torticollis)

The management of cervical dystonia 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 10 : Cervical Dystonia, Adverse Reactions*

| **Body System** | **Adverse Reactions** | |
|---|---|---|
| Gastrointestinal disorders: | *Very common*:<br>*Common*: | dysphagia<br>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 disorder: | *Common*:<br>*Uncommon*: | headache, presyncope, dizziness<br>speech disorder |
| Infections and infestations: | *Common:* | upper respiratory tract infection |
| Respiratory thoracic and mediastinal disorders: | *Uncommon*: | dysphonia, dyspnoea |
| Skin and subcutaneous tissue disorders: | *Common:*<br>*Uncommon*: | hyperhidrosis<br>rash |

*Note: based on placebo-controlled, active-controlled and uncontrolled*

Blepharospasm

*Table 11: Blepharospasm, Adverse Reactions*

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

*Note: based on placebo-controlled, active-controlled and uncontrolled studies*

Spasticity of the upper limb

*Table 12: Spasticity of the upper limb, Adverse Reactions*

| **Body System** | **Adverse Reactions** | |
|---|---|---|
| Gastrointestinal disorders: | *Common*:<br>*Uncommon*: | dry mouth<br>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, dysaesthesia, hypoaesthesia |

*Note: based on placebo-controlled, active-controlled and uncontrolled studies*

Glabellar frown lines

*Table 13: Glabellar Frown Lines, Adverse Reactions*

| **Body System** | **Adverse Reactions** | |
|---|---|---|
| General disorders and administrative 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:*<br>*Uncommon*: | Mephisto sign<br>facial asymmetry (brow asymmetry), muscle spasms (above eyebrows), sensation of heaviness |
| 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 |

*Note: based on placebo-controlled, active-controlled and uncontrolled studies*

Lateral periorbital lines (crow's feet)

*Table 14: Lateral periorbital lines (crow's feet), Adverse Reactions*

| **Body System** | **Adverse Reactions** | |
|---|---|---|
| General disorders and administrative site conditions: | *Common*: | injection site haematoma |
| Eye disorders: | *Common*: | eyelid oedema, dry eye |

*Note: based on placebo-controlled, active-controlled and uncontrolled studies*

Upper facial lines

*Table 15: Upper facial lines, Adverse Reactions*

| **Body System** | **Adverse Reactions** | |
|---|---|---|
| General disorders and administrative 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: | *Very common*:<br>*Common*: | headache<br>hypoaesthesia |
| Skin and subcutaneous tissue: | *Common*: | brow ptosis |
| Musculoskeletal and connective tissue disorders: | *Common:* | facial asymmetry, Mephisto sign |
| Gastrointestinal disorders: | *Common:* | nausea |

*Note: based on placebo-controlled, active-controlled and uncontrolled studies*

Administration related adverse 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.

Adverse effects related to pharmacological class

Localised muscle weakness is one expected pharmacological effect of botulinum toxin.

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 pneumonia with fatal outcome).

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 have been rarely reported, including anaphylaxis, serum sickness, urticaria, soft tissue oedema, and dyspnoea. Some of these reactions have been reported following the use of conventional botulinum toxin A complex either alone or in combination with other agents known to cause similar reactions.

**Post-market experience**

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

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

## 4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Symptoms of overdose

Increased doses of incobotulinumtoxinA 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 an aspiration pneumonia). Symptoms of overdose are not immediately apparent post-injection.

Measures in cases of overdose

In the event of overdose or spread of toxin 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]

IncobotulinumtoxinA 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 toxin binding to cholinergic nerve terminals
- internalization of the toxin within vesicles into the nerve terminal
- translocation of the light-chain of the toxin 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 3-4 months as nerve terminals sprout and reconnect with the muscle endplate and the presynaptic neurotransmitter release mechanism becomes functional again.

**Clinical efficacy and safety**

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

**Cervical Dystonia**

Xeomin has been investigated in a Phase 3, randomised, double-blind, placebo-controlled, multi-centre 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, TWSTRS severity score ≥10, TWSTRS disability score ≥3, and TWSTRS pain score ≥1. For patients who had previously received a botulinum toxin treatment for cervical dystonia, the trial required that ≥10 weeks had passed since the most recent botulinum toxin administration. Patients with swallowing disorders or any significant neuromuscular disease that might interfere with the study were excluded from enrolment.

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). Each patient received a single administration of 4.8 mL of reconstituted study agent (Xeomin 240 Units, Xeomin 120 Units, or placebo). The investigator decided which muscles would receive injections of the study agent, the number of injection sites, and the volume at each site. The muscles most frequently injected were the splenius capitis/semispinalis, trapezius, sternocleidomastoid, scalene, and levator scapulae muscles. The median dose of Xeomin administered was 120 U, 25% of patients given Xeomin received between 186 and 300 U and 25% of patients given Botox received doses between 180 and 280 U.

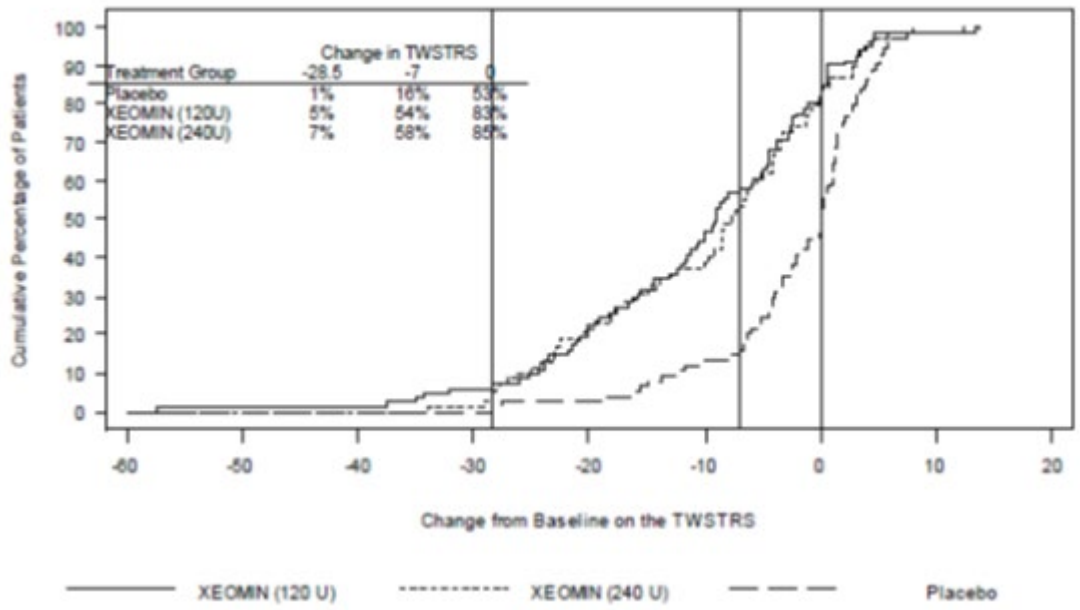
Most patients received a total of 2-10 injections into the selected muscles. Patients were assessed by telephone at one week post-injection, during clinic visits at Weeks 4 and 8, and then by telephone assessments or clinic visits every two weeks up to Week 20.

The mean age of the study patients was 53 years, and 66% of the patients were women. At study baseline, 61% of patients had previously received a botulinum toxin as treatment for cervical dystonia.

The primary efficacy endpoint was the change in the TWSTRS total score from baseline to Week 4 post-injection, in the intent-to-treat (ITT) population, with missing values replaced by the patient's baseline value. In the ITT population, the difference between the Xeomin 240 Unit group and the placebo group in the change of the TWSTRS total score from baseline to Week 4 was -9.0 points, 95% confidence interval (CI) -12.0; -5.9 points; the difference between the Xeomin 120 Unit group and the placebo group in the change of the TWSTRS total score from baseline to Week 4 was -7.5 points, 95% CI -10.4; -4.6 points.

Figure 6 illustrates the cumulative percentage of patients from each of the three treatment groups who had attained the specified change in TWSTRS Score from baseline versus 4 weeks post-injection. Three change scores have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown.

*Figure 6:* *Cumulative Percentage of Patients with Specified Changes from Baseline TWSTRS Total Score at Week 4*




The curves demonstrate that both patients assigned to placebo and Xeomin have a wide range of responses, but that the active treatment groups are more likely to show greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo.

Comparison of each Xeomin group to the placebo group was statistically significant at $p<0.001$. Initial Xeomin doses of 120 Units and 240 Units demonstrated no significant difference in effectiveness between the doses. The efficacy of Xeomin was similar in patients who were botulinum toxin naïve and those who had received botulinum toxin prior to this study.

Non-inferiority Trial

Xeomin was investigated in a Phase 3, randomised, double-blind, active-controlled, non-inferiority trial, which showed that Xeomin and botulinum toxin, type A, as a haemagglutinin complex (900kD) (active comparator) have good and similar efficacy in the treatment of cervical dystonia using a 1:1 dose ratio (see section 4.2).

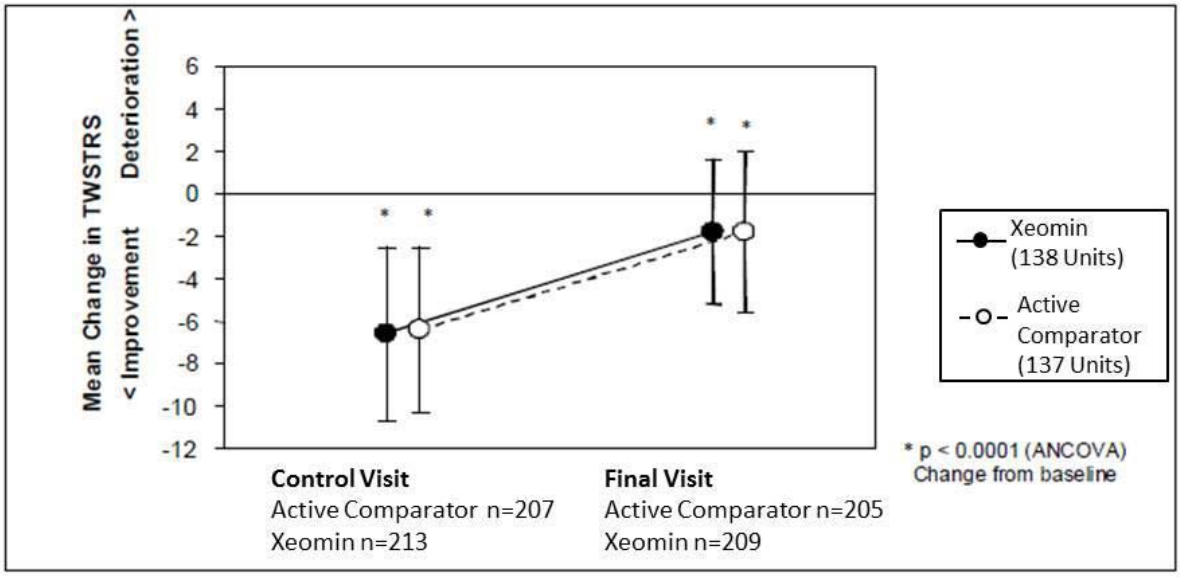
Patients in this trial were adults up to 75 years of age with spasmodic torticollis and the following TWSTRS scores: Severity ≥10, Severity (rotation) ≥2, and severity score for rotation greater than score for laterocollis, anterocollis or retrocollis. Patients had a stable therapeutic response to botulinum toxin, type A, as a haemagglutinin complex (900kD) in the last 2 injection sessions prior to trial entry, the last of which was at least 10 weeks before randomisation.

Patients were randomised (1:1) to receive a single administration of 70-300 Units of Xeomin (n=231) or active comparator (n=232). The dose chosen was equivalent to the active comparator dose used in the patients last two injection sessions. Mean doses (±SD) of 140.4±51.4 Units and 138.9± 46.8 Units were injected in the affected neck muscles for Xeomin and active comparator respectively. Patients were then monitored for up to 16 weeks following the injection and a control visit took place 4 weeks after injection.

For the primary efficacy endpoint, change from baseline to Week 4 (control visit) in TWSTRS-Severity

score, the mean change was -6.6±4.1 points in the Xeomin group, versus - 6.4±3.9 points in the active comparator group (See *Figure 7*). These changes from baseline were statistically significant and clinically meaningful, and demonstrated the comparable efficacy of each treatment (p<0.0001 for each group). The upper 95% confidence limits for Xeomin and active comparator were similar across the full range of doses, and non-inferiority of Xeomin to active comparator was shown in the final model where the LS mean difference of the TWSTRS-Severity score between the two groups was -0.33 points and the upper limit of the 95% CI was 0.38 points, which was lower than the predefined non-inferiority difference of 1.3 points.

*Figure 7: Change from Baseline in Mean TWSTRS-Severity Score*




Xeomin and active comparator also showed good and comparable efficacy with respect to the secondary efficacy parameters, including time to onset (median = 7.0 days), duration of treatment effect (median = 110 days) and time to waning of treatment (median = 11.0 weeks).

**Blepharospasm**

Xeomin has been investigated in a Phase 3, randomised, double-blind, placebo-controlled, multi-centre 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 (Botox). At least 10 weeks had to have elapsed since the most recent onabotulinumtoxinA administration. Patients with any significant neuromuscular disease that might interfere with the study were excluded from enrolment. Patients were randomised (2:1) to receive a single administration of Xeomin (n=75) or placebo (n=34). Each patient in the Xeomin group received a Xeomin treatment (dose, volume, dilution, and injection sites per muscle) that was similar to the most recent onabotulinumtoxinA injection sessions prior to study entry. The highest dose permitted in this study was 50 Units per eye; the mean Xeomin dose was 33 Units per eye. The sites of injection were: temporal area; eyebrow area; upper lid; and orbital rim.

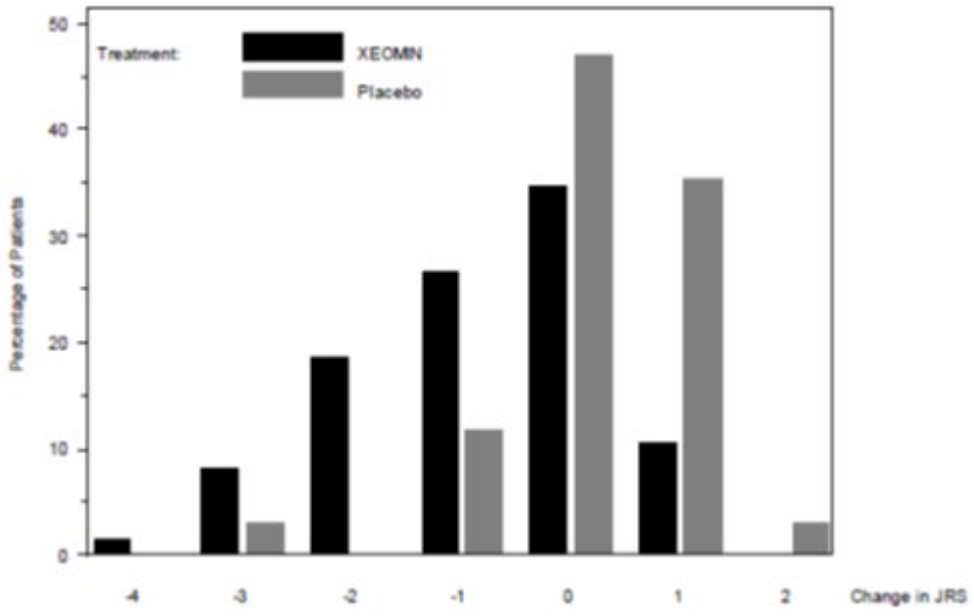
Patients were assessed during clinic visits at Weeks 3 and 6, and then by telephone or at clinic visits every two weeks up to Week 20.

The mean age of the study patients was 62 years, and 65% of the patients were women. The study was completed by 94% of study patients. Approximately one third of patients had other dystonic phenomena; in all but 1% this was limited to facial, cervical, perioral and mandibular muscles.

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 (i.e., 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 (Figure 8). Comparison of the Xeomin group to the placebo group was statistically significant at p<0.001.

*Figure 8: Frequency Distribution of Changes from Baseline JRS Severity Subscore at Week 6*




Non-inferiority Trial

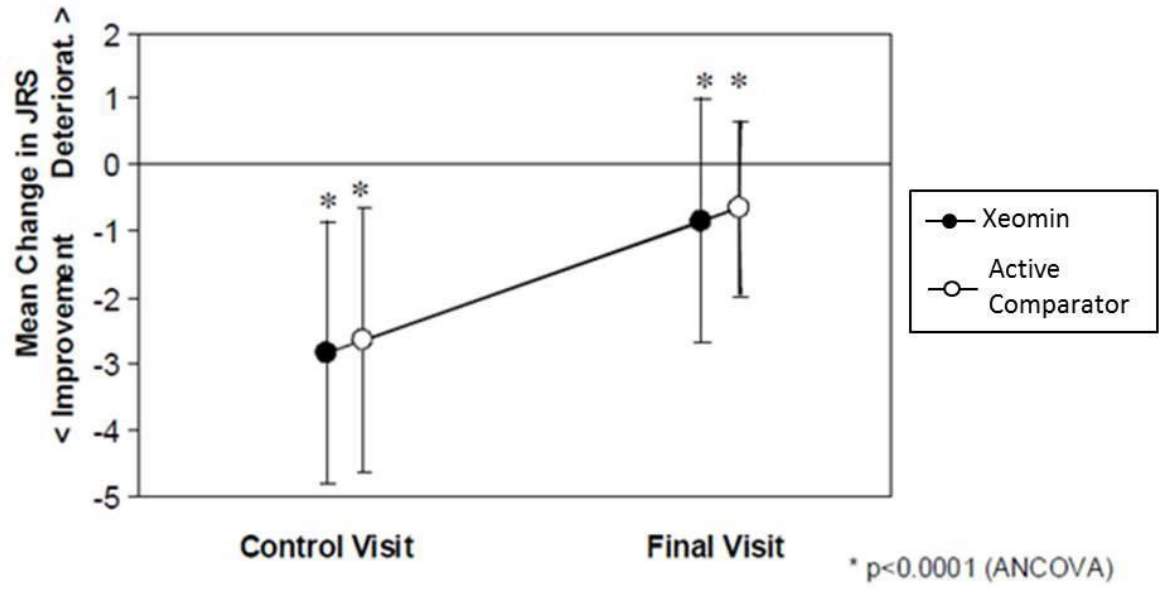
Xeomin was investigated in a Phase 3, randomised, double-blind, active-controlled trial, which showed that Xeomin and botulinum toxin, type A, as a haemagglutinin complex (900kD) (active comparator) using a 1:1 dose ratio have good and similar efficacy in the treatment of blepharospasm for both primary and secondary endpoints (see section 4.2).

Patients in this trial were adults with bilateral blepharospasm and a stable clinical response at the two most recent previous injection sessions with botulinum toxin, type A, as a haemagglutinin complex (900kD). Patients were monitored for up to 16 weeks following the injection and a control visit took place 3 weeks after baseline.

Patients were randomised (1:1) to receive a single intramuscular injection dose of ≤35 Units per eye of Xeomin (n=148) or active comparator (n=152). Patients in the Xeomin group received a mean total dose (both eyes) of 41 Units and the active comparator group received a mean total dose of 42 Units.

For the primary efficacy endpoint, change from baseline to Week 3 (control visit) in JRS sumscore, the decrease (adjusted change) in mean JRS sumscore seen for Xeomin was -2.90 and for active comparator was -2.67. Both were statistically significant (p<0.0001) and clinically meaningful, demonstrating the comparable efficacy of the two treatments (Figure 9). Non-inferiority of Xeomin to active comparator was shown, where the difference in JRS sumscore between the two adjusted group means was -0.23 and the upper confidence bound of the 95% CI of this difference was 0.22, which was less than the predefined limit of 0.8 for non-inferior efficacy.

*Figure 9: Change from Baseline in JRS Sumscore at the Control (Week 3) and Final Visit (up to Week 16)*




Further, Xeomin and active comparator showed consistent good and comparable efficacy with respect to the secondary efficacy parameters, including time to onset (median = 4.0 days), time to waning of treatment effect (median = 11.0 weeks), and duration of treatment effect (median = 110 days).

**Spasticity of the upper limb**

Xeomin has been investigated in a Phase 3, randomised, double-blind, placebo-controlled, multi-centre trial in a total of 148 patients (Xeomin: n = 73; placebo n = 75) with a confirmed diagnosis of post-stroke spasticity of the upper limb. All patients had clinical patterns for flexed wrist and clenched fist with an Ashworth score of ≥ 2. Besides these, flexed elbow, pronated forearm, and thumb-in-palm had to be treated if the Ashworth score was ≥ 2 and could also be treated if the Ashworth score was at least 1. Dosing followed the recommended doses for initial treatment as provided in section 4.2.

The mean age of the study patients was 55.6 years, and 64.2% of the patients were male.

The primary outcome measure of efficacy was a responder analysis at Week 4 for patients with at least a 1-point improvement (reduction) from baseline in the Ashworth score for wrist flexors. Amongst others secondary outcome variables, the extent of functional impairment was measured by the Disability Assessment Scale (DAS).

In the ITT population, the responder rate in the Xeomin group (50 patients, 68.5%) was significantly higher ($p<0.001$) than in the placebo group (28 patients 37.3%). There was a statistically significant and clinically relevant higher likelihood that a patient treated with Xeomin had at least 1-point improvement in the Ashworth Scale score for wrist flexors compared with placebo (Odds Ratio Xeomin: Placebo for all covariates = 3.97; 95% CI: [1.90; 8.30], $p<0.001$). The responder rate in favour of Xeomin remained significant at all post-injection visits until Week 12. Median time to onset of treatment effect was 4 days for patients given Xeomin.

Xeomin was investigated in a second Phase 3 randomised, double-blind, placebo-controlled, multicentre trial in patients with a confirmed diagnosis of post-stroke spasticity of the upper limb. The study included an initial double-blind phase and a subsequent open-label phase. Patients were eligible for enrolment in the study if at least three months had elapsed since the stroke event leading to spasticity, if the spasticity score was ≥2 on the Ashworth Scale (AS) in the wrist flexors, finger flexors and elbow flexors; ≥2 points on the Disability Assessment Scale (DAS) in the principal target domain; required a total dose of 400 Units of Xeomin based on clinical need; and were treatment-naïve.

The double-blind treatment period consisted of one treatment injection session with a total fixed dose of 400 U Xeomin or matching volume of placebo into the affected upper limb and a subsequent 12-week observation period with control visits at 4 weekly intervals. For each individual subject, one primary target clinical pattern was selected from flexed elbow, flexed wrist, or clenched fist. Efficacy analyses were performed on 259 subjects randomised and treated (Xeomin n=171; placebo n=88). The primary efficacy variable was the change from baseline in AS determined 4 weeks after the treatment. The co-primary efficacy variable was the Investigator's Global Impression of Change at week 4 after treatment. The primary analysis showed a statistically significant ($p<0.001$) and clinically relevant difference in favour of Xeomin. The results for the co-primary efficacy variable confirmed the result of the primary efficacy analysis. The overall efficacy of Xeomin on upper limb spasticity as rated by the investigator after 4 weeks of treatment was superior to placebo (Least Squares (mean ± standard error: Xeomin 1.2 ± 0.07; placebo: 0.9 ± 0.09; $p=0.003$). Trends for more pronounced improvement with Xeomin than with placebo were also seen for both primary and co-primary endpoints. Additionally, the results of the secondary and the tertiary efficacy endpoints were consistent with the results of the primary efficacy endpoint.

Open-label treatment with Xeomin was continued for a further 36 weeks (Week 12 to Week 48). A total of 299 subjects entered the open-label phase and 248 subjects (82.9%) completed the study. The mean cumulative total dose of Xeomin, for all injections and muscles treated, was 1120.2 ± 217.5 Units. Efficacy of Xeomin in repeated treatment was shown using changes in AS score for each treated muscle group, ≥1-point improvement in the AS score, changes in Disability Assessment Scale (DAS), changes in Carer Burden Scale, investigator's, patient's and carer's global impression of change at Week 4 of all injection cycles, EuroQol 5- dimensions questionnaire (EQ-5D), and the investigator's, patient's and carer's global assessment of efficacy. The results of the open-label period were consistent with the results of the double-blind phase.

Xeomin was further investigated in another Phase 3 open-label, non-randomised, single-arm, dose titration trial to investigate the safety and efficacy of Xeomin in 155 subjects deemed to require total body doses of up to 800 Units for the treatment of upper limb and lower limb spasticity of the same body side due to cerebral causes. Subjects with a focal spasticity with an AS score of ≥2 points in the joint associated with the selected target clinical pattern. Three injection cycles of Xeomin were administered and each cycle was followed by an observation period of 12-16 weeks. Injections were administered into limbs of the same body side only, and the same body side was injected throughout the study. In cycle 1 and Cycle 2, injection of the cycle dose was planned in the upper limb only, in the lower limb only, or into both limbs (fixed total body dose; Cycle 1: 400 Units, Cycle 2: 600 Units). In Cycle 3, the total body dose was injected into both the upper limb and the lower limb (800 Units if clinically justified although a lower dose 600-800 Units was allowed). Efficacy was assessed as changes in AS, Resistance to passive movement (REPAS) scale, Functional ambulation classification (FAC) scale, DAS, global assessment of efficacy and EuroQoL 5-dimensions questionnaire relative to baseline and control visit scores.

For all clinical upper limb (internally rotated or extended or adducted shoulder, flexed elbow, extended elbow, pronated forearm, flexed wrist, clenched fist, thumb-in-palm) and lower limb patterns treated in a given injection cycle, a shift to lower AS scores and a decrease in mean AS scores (indicating improvement of the subjects' condition) was discernible between injection cycle baseline visits and control visits 1 of the respective injection cycle. Additionally, for all of the efficacy variables assessed in this study, clinically relevant shifts across injection cycles towards improvement of the subjects' condition were observed, especially with the Resistance to passive movement scale (REPAS) and the Goal attainment scale (GAS). 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.

**Glabellar Frown Lines**

Two identically designed randomised, double-blind, multi-centre, placebo-controlled Phase 3 clinical trials (Study 1 and Study 2) were conducted to evaluate Xeomin for the use in the temporary improvement of moderate to severe glabellar lines. The studies included a total of 547 subjects of which 193 subjects were > 50 years of age and 55 subjects were male. The study patients received either 20 units Xeomin or an equal amount of placebo. The total dose was delivered in 5 equally divided aliquots of 4 units each to specific injection sites.

Overall, treatment success was defined as a 2-point improvement at maximum frown on Day 30 on a 4-point scale (Facial Wrinkle Scale, FWS, 0=none, 1=mild, 2=moderate, 3=severe) compared to baseline for both the investigator's and patient's assessments (composite endpoint).

At Day 30, Xeomin improved wrinkles significantly better than placebo (2-point simultaneous improvement on investigator and patient assessment). There was a statistically significant ($p < 0.0001$) response rate between Xeomin and placebo for the composite endpoint.

Xeomin also consistently showed better efficacy than placebo at maximum frown based on both the investigator's and patient's rating on the 4-point scale. Secondary efficacy endpoints support the results of the primary endpoint.

The highest response rates were observed on Day 30 (subjects were evaluated on the efficacy assessment at baseline and Days 7, 30, 60, 90 and 120) and then decreased until nearly all subjects had lost response by Day 120.

*Table 16: Treatment Success at Day 30 (at Least 2 Grades Improvement from Baseline at Maximum Frown)*

| | **GL-1** | | **GL-2** | |
|---|---|---|---|---|
| | Xeomin (N=184) | Placebo (N=92) | Xeomin (N=182) | Placebo (N=89) |
| Composite Treatment Success* | 111 (60%) | 0 (0%) | 87 (48%) | 0 (0%) |
| Investigator Assessment | 141 (77%) | 0 (0%) | 129 (71%) | 0 (0%) |
| Subject Assessment | 120 (65%) | 0 (0%) | 101 (55%) | 1 (1%) |

* *Success on both the Investigator and Subject Assessments*

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 3 study over a treatment period of up to two years with up to 8 consecutive injection cycles for a total of 796 subjects. Response rates were continuously high and constant in all cycles, and a stable and enduring treatment effect was obvious, even with repeated treatments, indicating that the dose of 20 U of Xeomin per cycle is appropriate for this indication.

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 4 study in subjects with glabellar frown lines (n=250). The primary efficacy variable was a response defined as ≥1 point improvement from baseline on the FWS at maximum frown as rated by an independent masked panel of physicians specifically qualified to assess subject photographs at 1 month from treatment. At 1 month post-treatment, the response rate of subjects in the Xeomin and onabotulinumtoxinA group was 95.7% and 99.2%, respectively. The two-sided 95% Newcombe-Wilson confidence interval computed around the difference in response rates of -3.5% fell within the pre-specified equivalence margin. 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)**

A randomized, double-blind, placebo-controlled, Phase 3 study was conducted to evaluate Xeomin for the use in subjects with moderate to severe lateral periorbital lines. A total of 111 subjects (Xeomin: n=83, placebo=28) received Xeomin 12 Units per eye or placebo using a three or four injection point scheme. The primary efficacy endpoint was the treatment response rate, where treatment response was defined as an improvement of at least 1 point on the 4-point scale for lateral periorbital wrinkles at maximum smile at visit 4 (week 4) compared to the assessment at baseline. Treatment response in terms of a reduction of at least 1 point in independent rater assessment score for Crow's Feet since baseline was seen in 69.9% of Xeomin subjects for the 3-injection application scheme and in 68.7% of Xeomin subjects for the 4 injection application scheme. The difference in proportion of responders compared to the placebo group was 48.5% for the 3-injection application scheme and 54.4% for the

4-injection application scheme (p<0.0001). The 3-injection scheme and 4-injection scheme were found to be equivalent. Efficacy results were also positive for the secondary efficacy endpoints.

**Upper facial lines**

A randomized, double-blind, placebo-controlled, Phase 3 study was conducted in 156 subjects (Xeomin: n=105, placebo n=51) for the combined treatment of upper facial lines (horizontal forehead lines, glabellar frown lines, and lateral periorbital lines). A Xeomin dose of 54 to 64 Units were distributed to three anatomical areas: the forehead (flexible individual dose range from 10 to 20 U), the lateral eye area (12 Units per each eye side), and the glabellar area (20 Units), allowing the assessment of each area separately for efficacy. The primary efficacy variables were response at maximum contraction, as assessed by the investigator according to the MAS, i.e., a score of none (0) or mild (1), individually for the three treated areas, as well as response at maximum contraction at Day 30 simultaneously for all three treatment areas, i.e., a sum score of 3 or lower. Results for the primary endpoint were statistically significant: Response for the three treated areas showed a statistically significant difference between Xeomin and placebo (p<0.0001) for all three areas. Response for all three treatment areas combined showed a statistically significant difference between Xeomin and placebo as well (p=0.0001). Efficacy was also shown for all secondary efficacy variables.

## 5.2 Pharmacokinetic properties

Classical absorption, distribution, metabolism and elimination studies cannot be conducted with incobotulinumtoxinA because the active substance is applied in such small quantities (picograms per injection), and because it binds so rapidly and irreversibly to cholinergic nerve terminals.

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, 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 in rabbits nor direct effects on embryo-foetal or on pre- and postnatal 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

Each vial of Xeomin powder for solution for injection also contains 4.7 mg sucrose and 1.0 mg albumin (human).

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

Unopened vial

36 months

Reconstituted solution

24 hours

## 6.4 Special precautions for storage

Unopened vial

Store below 30 °C.

Reconstituted solution

To reduce microbiological hazard, use as soon as practicable after reconstitution. lf storage is necessary, hold at 2-8°C for not more than 24 hours.

## 6.5 Nature and contents of container

Xeomin is presented as a type I glass vial sealed with a bromobutyl rubber stopper and tamper-proof aluminium cap.

The formulated product solution is sterile filtered prior filling into vials and subsequent lyophilisation. The final product which is sealed under nitrogen in Type I glass vials. Xeomin is reconstituted for use using 0.9% physiological saline.

Each pack contains 1 vial Xeomin 50 units or 100 units.

## 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, residual reconstituted solution in the vial and/or syringe should be autoclaved or inactivated by adding one of the following solutions: 70% ethanol, 50% isopropanol, diluted sodium hydroxide solution (0.1 N NaOH), or diluted sodium hypochlorite solution (at least 0.1% NaOCl).

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

# 7. MEDICINE SCHEDULE

Prescription Medicine (S4)

## 8. SPONSOR

Healthcare Logistics
58 Richard Pearse Drive
Mangere
Auckland 2022
New Zealand

## 9. DATE OF FIRST APPROVAL

18 December 2014

## 10. DATE OF REVISION OF THE TEXT

16 December 2025

| Section changed | Summary of new information |
|---|---|
| 4.4 | Updated warning that cases of iatrogenic botulism have been reported following injection of botulinum toxin products and action for patients and caregivers to take in the event of signs or symptoms consistent with spread of botulinum toxin effect. |
| 4.8 | Updated warning regarding toxin spread |
| 4.9 | Amended to include management where spread of toxin is suspected. |