▼ This medicine is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – XEOMIN®

(incobotulinumtoxinA) powder for solution for injection

1 Name of the medicine

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 List of excipients.

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 (spasmodic torticollis)
- Blepharospasm
- Spasticity of the upper limb
- Chronic sialorrhea due to neurological disorders
- Upper facial lines
  - Glabellar frown lines
  - Lateral periorbital lines (crow's feet)
  - Horizontal forehead lines

Xeomin is indicated in children and adolescents aged 2 years to 17 years for the symptomatic treatment of:

- Chronic sialorrhea due to neurological/neurodevelopmental disorders
- Spasticity of the lower and/or upper limbs

4.2 Dose and method of administration

Xeomin may only be administered by medical practitioners 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.

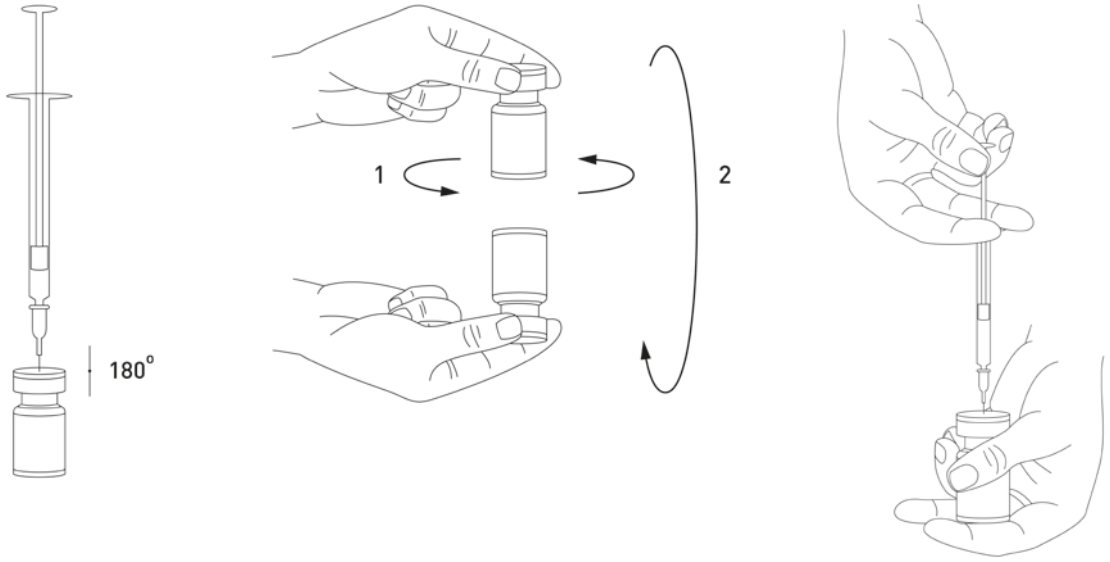
Reconstitution

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 needle should be used for reconstitution. A short bevel needle is recommended. 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

Figure 1: Reconstitution Method



and the required amount of solution should be drawn up with a new syringe suitable for injection.
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 and intraglandular (intra-salivary gland) 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, including patient's response to previous treatment, and/or adverse event history with botulinum toxins.

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	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) (adults)

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 (adults)

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 50 U per eye per treatment session. Repeated treatment should generally be no more frequent than every 12 weeks.

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.

Median time to first onset of effect: within four days after injection.

Duration of effect: up to 3-5 months, however, it may last significantly longer or shorter in individual patients.

Treatment intervals and doses 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.

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 intramuscularly 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 (adults)

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 *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

Dosage

Maximum total dose for the treatment of upper limb spasticity in adults should not exceed 500 units per treatment session, and no more than 250 units 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).

Chronic sialorrhea (adults)

Dosage

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:

Table 3: Dosing by Gland for Treatment of Chronic Sialorrhea (adults)

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 and total maximum 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.

Method of administration

Reconstituted Xeomin 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.

Spasticity of the lower and upper limb (children and adolescents aged 2 years to 17 years)

Dosage

Reconstituted Xeomin at a concentration between 1.25 units/0.1 mL and 5 units/0.1 mL is recommended.

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

For children and adolescents with a body weight of less than 25 kg, dose ranges for muscles and injection site numbers per clinical pattern are subject to body weight-adjusted ranges and need to be calculated. A maximum dose of 25 units and a maximum volume of 0.5 mL per injection site should not be exceeded.

For children and adolescents with a body weight equal to or greater than 25 kg, a maximum dose of 50 units and a maximum volume of 1 mL per injection site should not be exceeded.

Maximum effect: usually within 4 weeks.

Duration of effect: usually up to 14 weeks, however, it may last longer (up to 36 weeks) or shorter (12 weeks) in individual patients. Repeat treatment should generally be no more frequent than every 12 weeks. Treatment intervals should be determined based on the actual clinical need of the individual patient.

Spasticity of the lower limb (children/adolescents)

Initial treatment recommendation:

For uni- or bilateral treatment in patients not previously treated with a botulinum toxin the recommended initial dose is 2 units per kg body weight with a maximum of 50 units per clinical pattern. In clinical studies up to two clinical patterns have been treated simultaneously in the lower limbs. The total initial dose is 4 units per kg body weight with a maximum dose of 100 units.

The following dose ranges for initial treatment of the clinical patterns pes equinus, adducted thigh and flexed knee are recommended.

Table 4: Initial Dosing by Muscle for Treatment of Lower Limb Spasticity (children/adolescents)

Clinical Pattern *Muscle*	Units per kg BW	Maximum Dose (Units)	Number of Injection Sites per Muscle
Total Dose for Lower Limb	4	100	
Pes Equinus:	2	50	
Gastrocnemius (medial and lateral)	0.75-1.5	37.5	2-6

Clinical Pattern *Muscle*	Units per kg BW	Maximum Dose (Units)	Number of Injection Sites per Muscle
Soleus	0.5-1	25	1-4
Tibialis posterior	0.5-0.75	18.75	1-3
Flexor digitorum longus/flexor hallucis longus	0.25-0.75	18.75	1-3
Flexed Knee:	2	50	
Semitendinosus	0.5-1	25	1-4
Semimembranosus	0.5-1	25	1-4
Biceps femoris	0.5-1	25	1-4
Gracilis	0.5-0.75	18.75	1-3
Adducted Thigh:	2	50	
Gracilis	0.5-0.75	18.75	1-3
Adductor longus/brevis	1-1.5	37.5	2-6
Adductor magnus	0.5-1	25	1-4

Repeated treatment recommendation:

With repeated treatments, doses for uni- or bilateral treatment may be increased if required by the individual needs of the patient. Doses of 2-8 units per kg BW and a maximum dose of 200 units should be injected per lower limb clinical pattern at repeat treatment sessions.

Total doses of 4-16 units per kg BW should be given, with a maximum dose of 400 units. The following dose ranges for repeated treatment of the clinical patterns pes equinus, adducted thigh and flexed knee are recommended.

Table 5: Repeat Dosing by Muscle for Treatment of Lower Limb Spasticity (children/adolescents)

Clinical Pattern *Muscle*	Units per kg BW	Maximum Dose (Units)	Number of Injection Sites per Muscle
Total Dose for Lower Limb	4-16	400	
Pes Equinus:	2-8	200	
Gastrocnemius (medial and lateral)	0.75-6	150	2-6
Soleus	0.5-4	100	1-4
Tibialis posterior	0.5-3	75	1-3
Flexor digitorum longus/flexor hallucis longus	0.25-3	75	1-3
Flexed Knee:	2-8	200	
Semitendinosus	0.5-4	100	1-4
Semimembranosus	0.5-4	100	1-4
Biceps femoris	0.5-4	100	1-4
Gracilis	0.5-3	75	1-3

Clinical Pattern *Muscle*	Units per kg BW	Maximum Dose (Units)	Number of Injection Sites per Muscle
Adducted Thigh:	2-8	200	
Gracilis	0.5-3	75	1-3
Adductor longus/brevis	1-6	150	2-6
Adductor magnus	0.5-4	100	1-4

Spasticity of the upper limb (children/adolescents)

Initial treatment recommendation:

For uni- or bilateral treatment in patients not previously treated with a botulinum toxin the recommended initial dose is 2 units per kg BW with a maximum dose of 50 units per single upper limb. The total initial dose for bilateral treatment is 4 units per kg BW with a maximum dose of 100 units. The following dose ranges per single upper limb for initial treatment of the clinical patterns flexed elbow, flexed wrist, pronated forearm, clenched fist, and thumb-in-palm are recommended.

Table 6: Initial Dosing by Muscle for Treatment of Upper Limb Spasticity (children/adolescents)

Clinical Pattern *Muscle*	Units per kg BW	Maximum Dose (Units)	Number of Injection Sites per Muscle
Total Dose for Upper Limb	4	100	
Total Dose per Single Upper Limb	2	50	
Flexed Elbow:			
Brachioradialis	0.3-0.5	12.5	1-2
Biceps	0.5-0.8	20.0	1-3
Brachialis	0.3-0.5	12.5	1-2
Flexed Wrist:			
Flexor carpi radialis	0.3	7.5	1
Flexor carpi ulnaris	0.3	7.5	1
Pronated Forearm:			
Pronator quadratus	0.1	2.5	1
Pronator teres	0.3-0.5	12.5	1-2
Clenched Fist:			
Flexor digitorum superficialis	0.3	7.5	1
Flexor digitorum profundus	0.3	7.5	1
Thumb-in-Palm:			
Flexor pollicis longus	0.3	7.5	1
Adductor pollicis/flexor pollicis brevis/opponens	0.1	2.5	1

Repeated treatment recommendation:

With repeated treatments, doses for uni- or bilateral treatment may be increased if required by the individual needs of the patient. Doses of 2-8 units per kg BW up to a maximum dose of 200 units should be injected per single upper limb at repeat treatment sessions. Total doses for bilateral treatment of 4-16 units per kg BW should be given up to a maximum dose of

400 units. The following dose ranges per single upper limb for repeated treatment of the clinical patterns flexed elbow, flexed wrist, pronated forearm, clenched fist, and thumb-in-palm are recommended.

Table 7: Repeat Dosing by Muscle for Treatment of Upper Limb Spasticity (children/adolescents)

Clinical Pattern *Muscle*	Units per kg BW	Maximum Dose (Units)	Number of injection sites per muscle
Total Dose for Upper Limb	4-16	400	
Dose per Single Upper Limb	2-8	200	
Flexed Elbow:			
Brachioradialis	0.3-2	50	1-2
Biceps	0.5-3	75	1-3
Brachialis	0.3-2	50	1-2
Flexed Wrist:			
Flexor carpi radialis	0.3-1	25	1
Flexor carpi ulnaris	0.3-1	25	1
Pronated Forearm:			
Pronator quadratus	0.1-0.5	12.5	1
Pronator teres	0.3-2	50	1-2
Clenched Fist:			
Flexor digitorum superficialis	0.3-1	25	1
Flexor digitorum profundus	0.3-1	25	1
Thumb-in-Palm:			
Flexor pollicis longus	0.3-1	25	1
Adductor pollicis/flexor pollicis brevis/opponens	0.1-0.5	12.5	1

Combined spasticity of the lower and upper limb (children/adolescents)

Multi-pattern / multi-level spasticity treatment of the lower in combination with the upper limb should be performed based on the above doses and recommendations for initial and repeated treatment.

Initial treatment recommendation:

The recommended total dose for the initial combined treatment in patients not previously treated with a botulinum toxin of the lower and upper limb is 8 units per kg BW (maximum total dose of 200 units). This initial total dose is to be divided between lower limb (4 units per kg BW, maximum 100 units) and upper limb (4 units per kg BW, maximum 100 units).

Repeated treatment recommendation:

If required by the individual needs of the patient maximum total doses can be increased at repeated sessions for combined treatment of the lower and upper limb:

- In case of ambulatory patients with Gross Motor Function Classification System (GMFCS) levels I-III, doses of 8-20 units per kg BW up to a maximum dose of 500 units should be administered. No more than 16 units per kg BW (maximum 400 units) should be applied for lower limb or upper limb spasticity treatment.
- In cases of non-ambulatory patients with GMFCS levels IV-V, doses of 8-16 units per kg BW up to a maximum dose of 400 units should be given.

Method of administration

After reconstitution Xeomin is injected intramuscularly using a suitable sterile needle (e.g. 30 gauge / 0.30 mm diameter / 25 mm length, for superficial muscles and a longer needle, e.g. 27 gauge / 0.40 mm diameter / 37 mm length, for deeper musculature). Localisation of the involved muscles with techniques such as electromyographic guidance, nerve stimulation, or ultrasound is recommended.

Chronic sialorrhea (children and adolescents aged 2 years to 17 years)

Dosage

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. Treatment doses should be administered by body weight class and the total dose should not exceed 75 units per treatment session. For children weighing less than 12kg no data are available and therefore no dosing recommendations can be made for children weighing less than 12 kg.

Table 8: Dosing by Body Weight and Gland for Treatment of Chronic Sialorrhea (children/adolescents)

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.

Method of administration

Reconstituted Xeomin is injected intraglandularly using a suitable sterile needle (e.g. 27-30 gauge/0.30- 0.40 mm diameter/12.5 mm length). Ultrasound guidance should be used for the localization of the involved salivary glands. Local anaesthesia (such as local anaesthetic cream), sedation, or anaesthesia in combination with sedation may be offered to children prior to injection after a careful benefit-risk evaluation and per local site practice.

Aesthetic indications

General

Possible dilutions of Xeomin for the treatment of aesthetic indications are indicated in the following table.

Table 9: 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

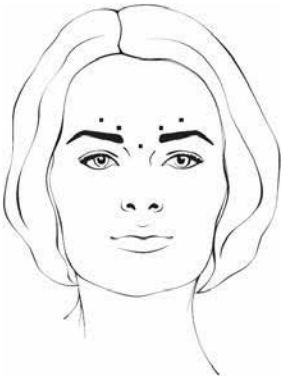
Dose per injection site: 4 units into each of the 5 injection sites: two injections in each corrugator muscle and one injection in the procerus muscle (Figure 2).

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.

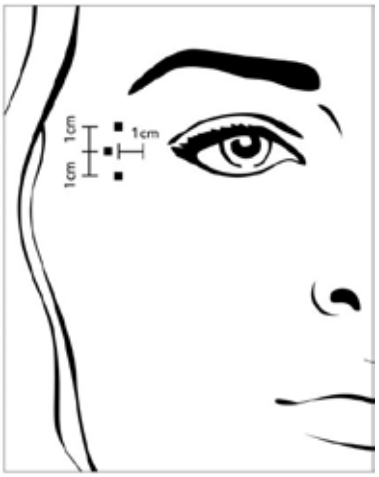
Lateral periorbital lines (crow's feet)

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

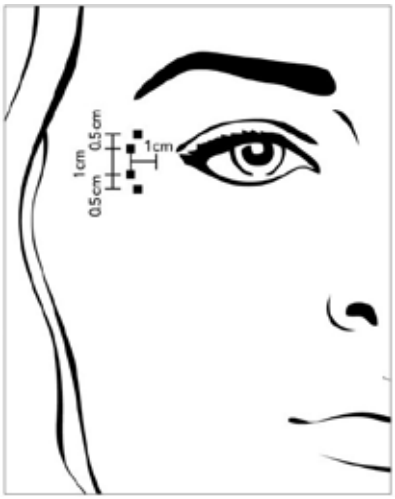


Dosage for 4-point injection scheme

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.

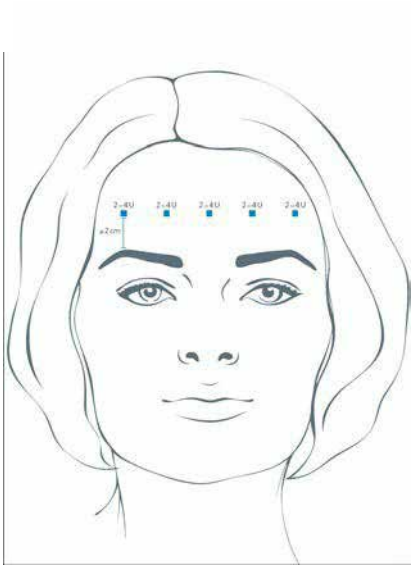
Horizontal forehead lines

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 Special Precautions for disposal) 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 Section 6.6 Special Precautions for disposal).

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 Adverse Effects, Toxin spread). 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.

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

Pre-existing Neuromuscular Disorders

Patients with neuromuscular disorders may be at increased risk of excessive muscle weakness. The botulinum 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 the 150kDa Toxin may reduce the effectiveness of Xeomin treatment by inactivating the biological activity of the toxin. The critical factors for neutralising antibody formation are continuing to be characterised. Higher foreign protein load, higher doses and shorter treatment intervals 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, reducing protein load injected and injecting with the lowest effective dose given at the longest feasible intervals between injections. Treatment immunogenicity is of particular concern as many indications are chronic and require regular, usually life-long, therapy.

Lack of interchangeability between botulinum toxin products

THE POTENCY UNITS OF XEOMIN ARE SPECIFIC TO THE PREPARATION AND ASSAY METHOD UTILISED. THEY ARE NOT INTERCHANGEABLE WITH THE OTHER PREPARATIONS OF BOTULINUM 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 Dose and method of administration).

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 muscle should be avoided to reduce the occurrence of ptosis. Diplopia may develop as a result of incobotulinumtoxinA diffusion into the inferior oblique muscle. 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.

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.

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

The safety and efficacy of Xeomin in indications other than those described for children and adolescents in Section 4.1 has not been established, see Section 4.1 Therapeutic indications. 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.

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 LDU/kg) 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 LDU/kg and above. Whether this finding was a male or female mediated effect could not be conclusively clarified. A no-effect dose for adverse effects on development in juvenile animals was not established. Accordingly, safety margins with regard to clinical therapy were generally low in terms of high clinical dose.

Effect on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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.

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.

4.6 Fertility, pregnancy and lactation

Effects on 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.

Use in pregnancy – 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].

Use in lactation

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

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 Adverse effects (Undesirable effects)

The following tables summarises the frequency of adverse events reported for Xeomin and placebo during clinical trials (Tables 9 to 14).

Table 10: 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)

Note: based on pooled placebo-controlled clinical studies

Table 11: 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)
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 12: 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)
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)
Gastrointestinal Disorders	11 (3.9)	8 (4.4)
General disorders and administration site conditions	7 (2.5)	3 (1.6)

Note: based on pooled placebo-controlled clinical studies

Table 13: 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

Table 14: Glabellar Frown Lines, Adverse Events >2%

Adverse events	Xeomin (N=678)(%)	Placebo (N=316)(%)
Infections and Infestations Nasopharyngitis Sinusitis Bronchitis	144 (21.2) 50 (7.4) 21 (3.1) 14 (2.1)	60 (19.0) 31 (9.8) 10 (3.2) 0
Nervous System Disorders Headache	103 (15.2) 84 (12.4)	39 (12.3) 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)

Note: based on pooled placebo-controlled clinical studies

Table 15: Lateral periorbital lines (crow's feet), Adverse Events >2%

Adverse events	Xeomin (N=83)(%)	Placebo (N=28)(%)
Infections and Infestations Viral infection	6 (7.2) 2 (2.4)	1 (3.6) 1 (3.6)
Eye disorders Eyelid oedema	5 (6.0) 3 (3.6)	0 0
General Disorders and Administration Site Conditions Injection site haematoma	3 (3.6) 2 (2.4)	0 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 16: Cervical Dystonia, Adverse Reactions

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

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

Blepharospasm

Table 17: Blepharospasm, Adverse Reactions

Body System	Adverse Reactions	
Nervous system disorders:	*Uncommon*:	headache, facial paresis
Eye disorders:	*Very common:* *Common*: *Uncommon*:	eyelid ptosis, dry eyes, vision blurred, visual impairment diplopia, lacrimation increased
Gastrointestinal disorders:	*Common*: *Uncommon*:	dry mouth dysphagia
General disorders and administration site conditions:	*Common*: *Uncommon*:	injection site pain 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 (adults)

Table 18: Spasticity of the upper limb, Adverse Reactions (adults)

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

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

Chronic sialorrhea (adults)

Table 19: Chronic sialorrhea (adults), Adverse Reactions

Body System	Adverse Reactions	
Nervous system disorders:	*Common:* *Uncommon:*	paraesthesia speech disorder
Gastrointestinal disorders:	*Common:* *Uncommon:*	dry mouth, dysphagia altered (thickened) saliva, dysgeusia

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)

Table 20: Chronic sialorrhea (children/adolescents), Adverse Reactions

Body System	Adverse Reactions	
Gastrointestinal disorders:	*Uncommon:*	dysphagia
	Not known:	altered (thickened) saliva, dry mouth, oral pain, dental caries

Spasticity of the lower and upper limb (children/adolescents)

Table 21: Spasticity of the lower and upper limb, Adverse Reactions (children/adolescents)

Body System	Adverse Reactions	
Musculoskeletal and connective tissue disorders:	*Uncommon:*	muscular weakness, myofascial pain syndrome, pain in extremity
General disorders and administration site conditions:	*Uncommon:*	injection site pain, injection site erythema, influenza like illness
Injury, poisoning and procedural complication:	*Uncommon:*	fall
Skin and subcutaneous tissue disorder:	*Uncommon:*	rash

Glabellar frown lines

Table 22: 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:* *Uncommon*:	Mephisto sign 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 23: 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 24: 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*: *Common*:	headache 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 pneumonitis with fatal outcome in some cases).

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

Hypersensitivity reactions

Serious and/or immediate hypersensitivity reactions 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 registration 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 at www.tga.gov.au/reporting-problems.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 Overdose

Contact the Poisons Information Centre on telephone in Australia on 13 11 26 or in New Zealand on 0800 POISON or 0800 764766 for advice on management of overdose.

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 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

Mechanism of action

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 Trials

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.

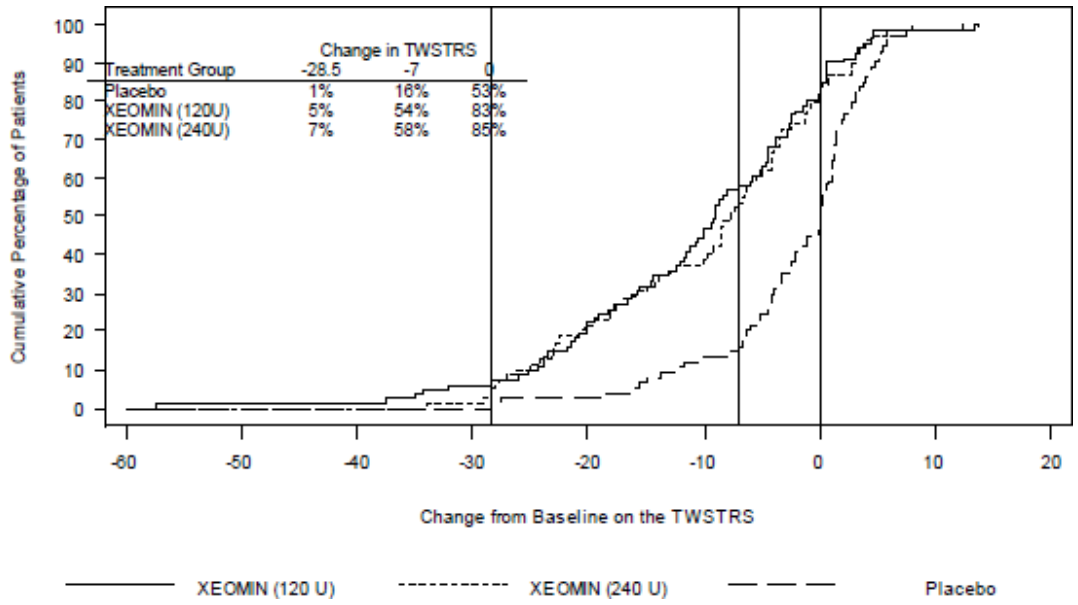
The mean age of the study patients was 53 years, and 66% of the patients were women. At study baseline, 61% of patients had previously received a botulinum toxin as treatment for cervical dystonia.

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 (Note this is for cervical dystonia)

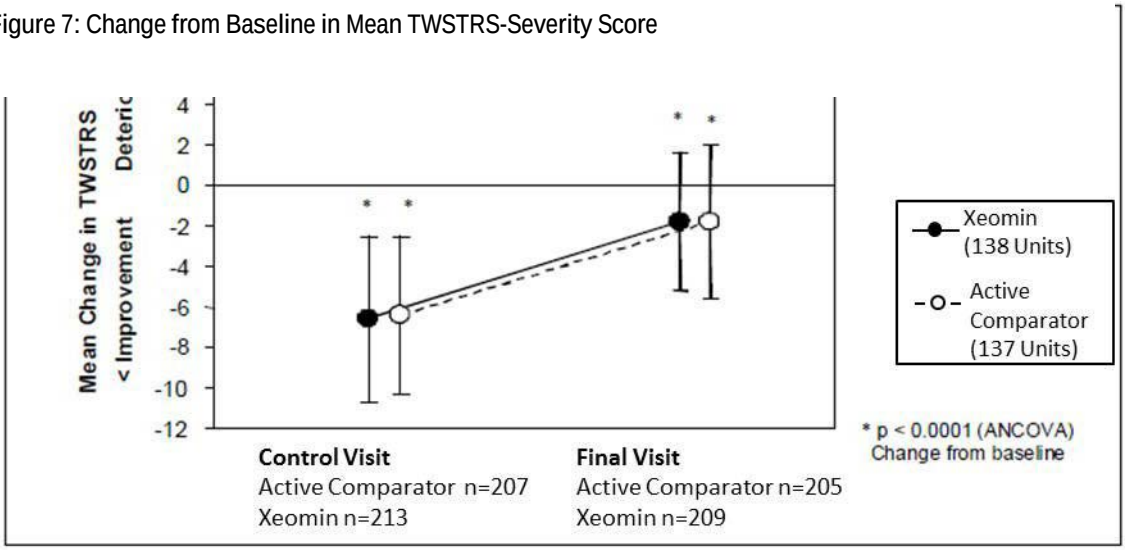
Xeomin was investigated in a Phase 3, randomised, double-blind, active-controlled, non-inferiority trial, which showed that Xeomin and botulinum toxin, type A, as a haemagglutinin complex (900kD) (active comparator) have good and similar efficacy in the treatment of cervical dystonia using a 1:1 dose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

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

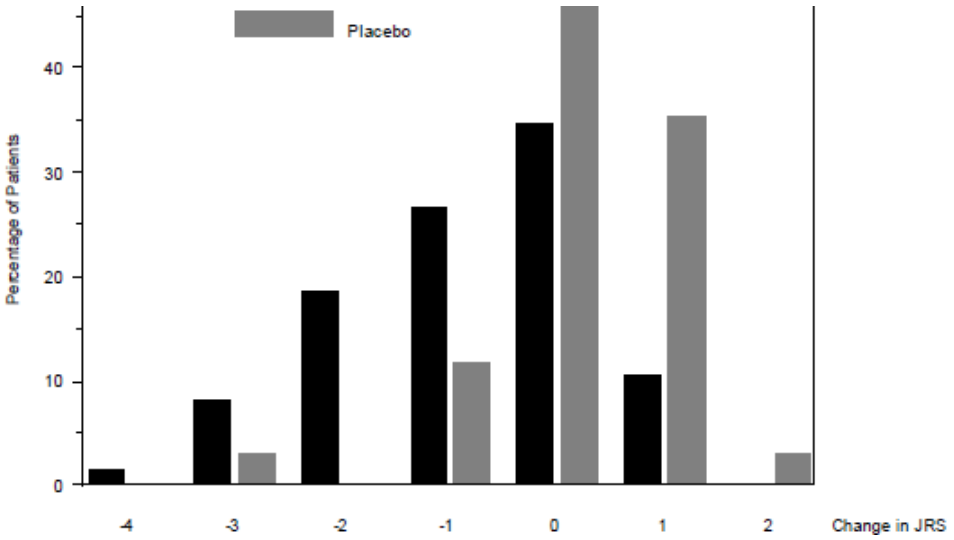
Xeomin has been investigated in a Phase 3, randomised, double-blind, placebo-controlled, multi- centre trial in a total of 109 patients with blepharospasm. Patients had a clinical diagnosis of benign essential blepharospasm, with baseline Jankovic Rating Scale (JRS) severity subscore ≥2, and a stable 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 32 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



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.

Non-inferiority Trial (Note this is for Blepharospasm)

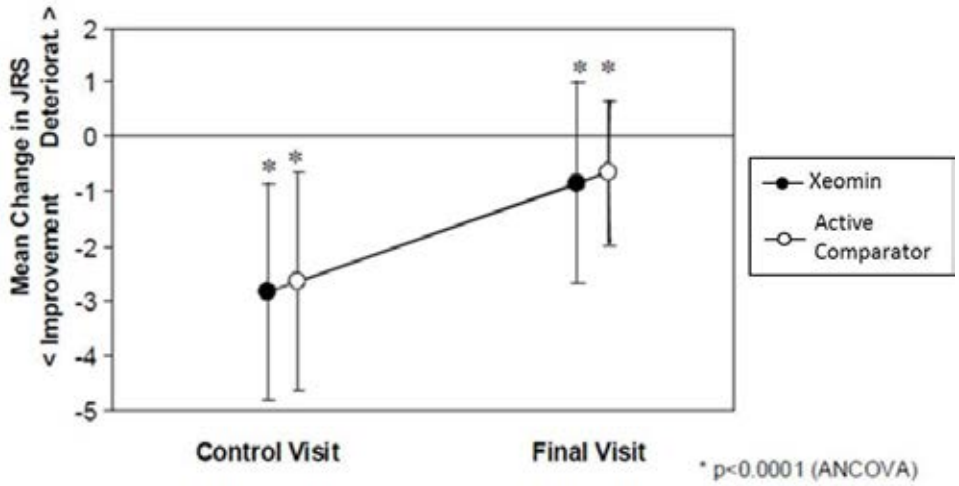
Xeomin was investigated in a Phase 3, randomised, double-blind, active-controlled trial, which showed that Xeomin and botulinum toxin, type A, as a haemagglutinin complex (900kD) (active comparator) using a 1:1 dose ratio have good and similar efficacy in the treatment of blepharospasm for both primary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

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 (adults)

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 Dose and method of administration.

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.

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.

Table 25: Change in Unstimulated Salivary Flow Rate and Global Impression of Change Scale at Week 4, Week 8, Week 12 and Week 16

		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.

Spasticity of the lower and upper limb (children/adolescents)

In one 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 limb and lower limb spasticity due to cerebral palsy were treated with Xeomin. In the main period with one injection cycle (12 16 weeks) Xeomin treatment was administered in three parallel treatment groups (2 units/kg body weight max. 50 units, 6 units/kg body weight max. 150 units and 8 units/kg body weight max. 200 units per treated upper limb). As clinically needed, upper and lower limb treatment was administered uni- or bilaterally and subjects received Xeomin injections up to the maximum total dose of up to 20 units/kg body weight (max. 500 units).

The primary efficacy variable showed clinically relevant treatment response on the Ashworth Scale for the primary clinical target pattern, i.e., elbow flexors or wrist flexors, in all three Xeomin treatment groups 4 weeks after injection with statistically significant superiority of the high dose group over the low dose group. These positive results were confirmed by the co-primary variable, demonstrating clinically meaningful improvements on the Investigator's Global Impression of Change Scale for the upper limb after 4 weeks in all three Xeomin dose groups. Essentially, similar results were seen for the other treated patterns in the upper limb (pronated forearm, clenched fist, thumb-in-palm) and lower limb (pes equinus, flexed knee, adducted thigh). Overall improvement of upper and lower limb spasticity was confirmed in all three treatment groups by the investigator's, child's/adolescent's and parent's/caregiver's Global Impression of Change Scales. Spasticity-related pain (as measured by the Questionnaire on Pain caused by Spasticity) improved as well as performance and satisfaction with occupational problems (as measured by the Canadian Occupational Performance Measure).

In the open-label extension of this study with three injection cycles (each 12 16 weeks) all eligible subjects continued treatment with Xeomin doses as in the highest dose group of the main period. The results showed that repeated injections of Xeomin had a consistent and persistent treatment effect with accumulating improvements over the course of the study.

No subjects developed secondary nonresponse due to neutralising antibodies (no antibody measurements were performed in subjects with less than 20 kg body weight).

A favourable long-term safety profile was demonstrated for each of the 4 treatment cycles and overall in the treatment of upper limb and combined upper and lower limb spasticity with doses of 20 units/kg body weight of Xeomin (max. 500 units).

The open-label long-term safety and efficacy Phase III clinical trial enrolled a total of 370 children and adolescents (age 2-17 years) with uni- or bilateral lower limb spasticity or with combined unilateral upper and uni- or bilateral lower limb spasticity. Each of the 4 injection cycles comprised 14 +/- 2 weeks observation after treatment. Long-term efficacy of the four injections of Xeomin was clearly and consistently demonstrated in the treated clinical patterns of the lower limb (pes equinus, flexed knee, adducted thigh) and upper limb (flexed elbow, flexed wrist, clenched fist, pronated forearm, thumb-in palm) 4 weeks after each injection based on the Ashworth Scale, Global Impression of Change of Plantar Flexor Spasticity Scale, and Global Impression of Change Scales (assessments by investigator, child/adolescent and parent/caregiver). Spasticity-related pain (as measured by the Questionnaire on Pain caused by Spasticity), as well as motor function (as measured by the Gross Motor Function Measure – 66) improved over the course of the study. No subjects developed secondary nonresponse due to neutralizing antibodies (no antibody measurements were performed in subjects with less than 20 kg body weight).

A favourable long-term safety profile was demonstrated for each of the 4 treatment cycles and overall in the treatment of lower limb spasticity with doses of 16 units/kg BW of Xeomin (max. 400 units) and in the treatment of combined lower and upper limb spasticity with treatment doses of up to 20 units/kg BW of Xeomin (max. 500 units) in children and adolescents.

Spasticity of the lower limb (children/adolescents)

The double-blind, parallel-group, dose-response Phase III clinical trial enrolled a total of 311 children and adolescents (age 2 – 17 years) with uni- or bilateral lower limb spasticity due to cerebral palsy. The results of the primary and co-primary efficacy variables showed a positive clinical treatment response, i.e., spasticity improvements of the pes equinus in the three treatment groups of Xeomin (4 units/kg BW max. 100 units, 12 units/kg BW max. 300 units and 16 units/kg BW max. 400 units) 4 weeks after first injection as demonstrated by the Ashworth Scale and the Global Impression of Change of Plantar Flexor Spasticity Scale assessment. In consistency with this result, spasticity improvements in all treatment groups were evident in the 2 injection cycles (12-36 weeks) of the study in the clinical patterns of the pes equinus, flexed knee and

adducted thigh as demonstrated by the Ashworth Scale. Overall improvement of lower limb spasticity was confirmed in all three treatment groups by the investigator's, child's/adolescent's and parent's/caregiver's Global Impression of Change Scales. Furthermore, less spasticity-related pain was reported (as measured by the Questionnaire on Pain caused by Spasticity) and improvement of motor function was noted (as measured by the Gross Motor Function Measure – 66) in all of the three treatment groups after treatment. No subjects developed secondary nonresponse due to neutralizing antibodies (no antibody measurements were performed in subjects with less than 20 kg body weight). The favourable safety and tolerability profile of XEOMIN was demonstrated at intervals from 12-36 weeks for all three treatment groups in both injection cycles of this study.

In a supportive open-label, parallel-group, comparative clinical trial efficacy and safety of Xeomin (4 units/kg BW unilateral, 8 units/kg BW bilateral) compared to a comparator product containing the conventional Botulinum toxin type A complex onabotulinumtoxinA (900 kD) were investigated in children with spastic equine and equinovarus foot deformation in paediatric cerebral palsy. A total of 64 children (age 2-11 years) were enrolled. The study showed comparable reduction of plantar flexor muscle tone in both treatment arms as measured by the Modified Ashworth Scale in the gastrocnemius muscle of the examined lower limb. Treatment with Xeomin was safe and well tolerated.

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 6-17 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.

Table 26: Change in Unstimulated Salivary Flow Rate and Global Impression of Change Scale at Week 4, Week 8, Week 12 and Week 16

		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.

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 25: 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 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.

Genotoxicity

No genotoxicity studies have been conducted with Xeomin.

Carcinogenicity

No long term carcinogenicity studies in animals have been conducted with Xeomin injection.

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

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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. If storage is necessary, hold at 2-8°C for not more than 24 hours.

6.5 Nature and contents of container

Xeomin contains 50 or 100 units of incobotulinumtoxinA in 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 is sealed under nitrogen in Type I glass vials. Xeomin is reconstituted for use using 0.9% physiological saline.

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

6.6 Special precautions for disposal

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.

6.7 Physicochemical properties

Chemical structure

The active ingredient is synthesised by Clostridium botulinum type A as a single chain protein (1,296 amino acid residues), which is subsequently split between residues 448 and 449 by an endogenous protease, during post translational modification. This results in a heavy chain, with a molecular weight of ~100 kD, and a light chain, with a molecular weight of ~50 kD. These separate chains are covalently linked via a disulfide bond. The light chain is associated with one atom of zinc. The protein exists in a monomeric form under normal conditions.

CAS number

93384-43-1nts.

7 Medicine Schedule (Poisons Standard)

Schedule 4 – Prescription Only Medicine

8 Sponsor

Australia

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New Zealand

9 Date of first approval

21 March 2014

10 Date of revision

DD Month YYYY

Summary Table of Changes

Section Changed	Summary of new information
4.1	Added following indications in adults: • treatment of chronic sialorrhea due to neurological disorders Added following indications in in children and adolescents (age 2 - 17 years):
	• treatment of chronic sialorrhea due to neurological / neurodevelopmental disorders • treatment of spasticity of the lower limb(s) or of combined spasticity of upper and lower limb
4.2	Added intraglandular injection (sialorrhea indication). Added dosage and administration information for new indications listed in 4.1
4.4	Added and updated warnings and precautions applicable to new indications listed in 4.1
4.5	Added interaction with anticholinergics and radiotherapy as applicable to sialorrhea indication
4.8	Added adverse event information for new indications listed in 4.1 and updated information for blepharospasm indication
5.1	Added information regarding clinical trials for new indications listed in 4.1
8	Update to Australian Sponsor address