XEOMIN- botulinum toxin type a injection, powder, lyophilized, for solution
Merz Pharmaceuticals, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XEOMIN® safely and effectively. See full prescribing information for XEOMIN.

XEOMIN (incobotulinumtoxinA)
for injection, for intramuscular use
Initial U.S. Approval: 2010

WARNING: DISTANT SPREAD OF TOXIN EFFECT

See full prescribing information for complete boxed warning. The effects of XEOMIN and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms. (5.1)

INDICATIONS AND USAGE

XEOMIN is an acetylcholine release inhibitor and neuromuscular blocking agent indicated for the:

- treatment of adults with cervical dystonia, to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients (1.1).
- treatment of blepharospasm in adults previously treated with onabotulinumtoxinA (Botox®) (1.2).
- temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients (1.3).

DOSAGE AND ADMINISTRATION

Reconstituted XEOMIN is intended for intramuscular injection. For the indications of cervical dystonia and blepharospasm, the optimum dose and number of injection sites in the treated muscle(s) should be individualized for each patient and determined by the physician (2.1, 2.2).

Cervical Dystonia (2.1):

- The recommended total dose is 120 Units per treatment session. Higher doses did not provide additional efficacy and were associated with an increased incidence of adverse reactions.
- Usually injected into the sternocleidomastoid, splenius capitis, levator scapulae, scalenus, and/or the trapezius muscle(s)
- Dose, number, and location of injection sites should be based on the number and location of muscles involved, severity of dystonia, and response to any previous botulinum toxin injections.

Blepharospasm (2.2):

- When initiating XEOMIN therapy, the dose, number, and location of injections should be based on the previous dosing of onabotulinumtoxinA (Botox). In clinical trials of XEOMIN for blepharospasm, XEOMIN was not administered to patients who had not previously received onabotulinumtoxinA (Botox).
- If the previous dose of onabotulinumtoxinA (Botox) is not known, the recommended starting dose is 1.25-2.5 Units per injection site.
- In the XEOMIN clinical trials, the mean dose per injection site was 5.6 Units, the mean number of injections per eye was 6, and the mean dose per eye was 33.5 Units.

Glabellar Lines (2.3):

- The total recommended XEOMIN dose is 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each. The five injection sites are: two injections in each corrugator muscle and one injection in the procerus muscle.
- Retreatment with XEOMIN should be administered no more frequently than every three months.

DOSAGE FORMS AND STRENGTHS

- 50 Units, lyophilized powder in single-use vial (3)
- 100 Units, lyophilized powder in single-use vial (3)

CONTRAINDICATIONS

- Known hypersensitivity to the active substance botulinum neurotoxin type A or to any of the excipients (4.1)
- Infection at the proposed injection sites (4.2)

WARNINGS AND PRECAUTIONS

For All Indications:

- The potency Units of XEOMIN are not interchangeable with other preparations of botulinum toxin products. Therefore, Units of biological activity of XEOMIN cannot be compared to or converted into Units of any other botulinum toxin products (5.2).
- Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties (5.1, 5.4).
- Use with caution in patients with compromised respiratory function or dysphagia (5.4).
- Concomitant neuromuscular disorders may exacerbate clinical effects of treatment (5.5).

Cervical Dystonia (5.4):

- Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscles are at greater risk of dysphagia.
- Limiting the dose injected into the sternocleidomastoid muscle may decrease the occurrence of dysphagia.

Blepharospasm (5.6):

- Corneal exposure and ulceration
- Injection of XEOMIN into the orbicularis oculi muscle may lead to reduced blinking and corneal exposure with possible ulceration or perforation.
- Lower lid injections should not be repeated if diplopia occurred with previous botulinum toxin injections.

Glabellar Lines (5.7):

- Risk of ptosis (5.7).

ADVERSE REACTIONS

Cervical Dystonia: The most commonly observed adverse reactions (≥5% of patients and > placebo) are dysphagia, neck pain, muscle weakness, injection site pain, and musculoskeletal pain (6.1).
Blepharospasm: The most commonly observed adverse reactions (≥5% of patients and > placebo) are eyelid ptosis, dry eye, dry mouth, diarrhea, headache, visual impairment, dyspnea, nasopharyngitis, and respiratory tract infection (6.1).
Glabellar Lines: The most commonly observed adverse reaction (>1% of patients and > placebo) is headache (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merz Pharmaceuticals, LLC at 888-493-6646 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Concomitant treatment of XEOMIN and aminoglycoside antibiotics, spectinomycin, or other agents that interfere with neuromuscular transmission (e.g., tubocurarine-like agents), or muscle relaxants, should be observed closely because the effect of XEOMIN may be potentiated (7).

USE IN SPECIFIC POPULATIONS

- Pregnancy: based on animal data, may cause fetal harm (8.1)
- Pediatric Use: XEOMIN has not been studied in the pediatric age group and is therefore not recommended in pediatric patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2015

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FULL PRESCRIBING INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of XEOMIN and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, 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. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses *[see Warnings and Precautions (5.1)]***.**

1 INDICATIONS AND USAGE

1.1 Cervical Dystonia

XEOMIN (incobotulinumtoxinA) is indicated for the treatment of adults with cervical dystonia to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients.

1.2 Blepharospasm

XEOMIN (incobotulinumtoxinA) is indicated for the treatment of adults with blepharospasm who were previously treated with onabotulinumtoxinA (Botox).

1.3 Glabellar Lines

XEOMIN (incobotulinumtoxinA) is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

2 DOSAGE AND ADMINISTRATION

The potency Units of XEOMIN (incobotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with 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 Warnings and Precautions (5.2) and Description (11)]*.

2.1 Cervical Dystonia

The recommended initial total dose of XEOMIN for cervical dystonia is 120 Units. In a placebo-controlled trial utilizing initial XEOMIN doses of 120 Units and 240 Units, no meaningful difference in effectiveness was demonstrated between the doses *[see Clinical Studies (14.1)]*. In previously treated patients, their past dose, response to treatment, duration of effect, and adverse event history should be taken into consideration when determining the XEOMIN dose.

In the treatment of cervical dystonia, 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 *[see Clinical Studies (14.1)]*.

The dose and number of injection sites in each treated muscle should be individualized based on the number and location of the muscle(s) to be treated, the degree of spasticity/dystonia, muscle mass, body weight, and response to any previous botulinum toxin injections.

The frequency of XEOMIN repeat treatments should be determined by clinical response, but should generally be no more frequent than every 12 weeks *[see Clinical Studies (14.1)]*.

2.2 Blepharospasm

The recommended initial total dose of XEOMIN should be the same dose as the patient's previous treatment of onabotulinumtoxinA (Botox), although responses to XEOMIN and onabotulinumtoxinA (Botox) may differ in individual patients. In a placebo-controlled trial in which patients were dosed with the same number of Units as they had received previously with onabotulinumtoxinA (Botox), the mean dose per eye was about 33 Units (range 10-50 Units), and the mean number of injections per eye was 6. The maximum dose per eye in the controlled trials was 50 Units, with a range of 10-50 Units. In the controlled trial, few patients received a total dose of greater than 75 Units.

If the previous dose of Botox is not known, the initial dose of XEOMIN should be between 1.25-2.5 Units/injection site.

The total initial dose of XEOMIN in both eyes should not exceed 70 Units (35 Units/eye).

The number and location of injection sites should be based on the severity of blepharospasm, and previous dose and response to onabotulinumtoxinA (Botox) injections. Subsequent dosing should be tailored to the individual patient, based on response, up to a maximum dose of 35 Units per eye *[see Clinical Studies 14.2]*. XEOMIN dosing has not been established in patients with blepharospasm who have not been previously treated with onabotulinumtoxinA (Botox).

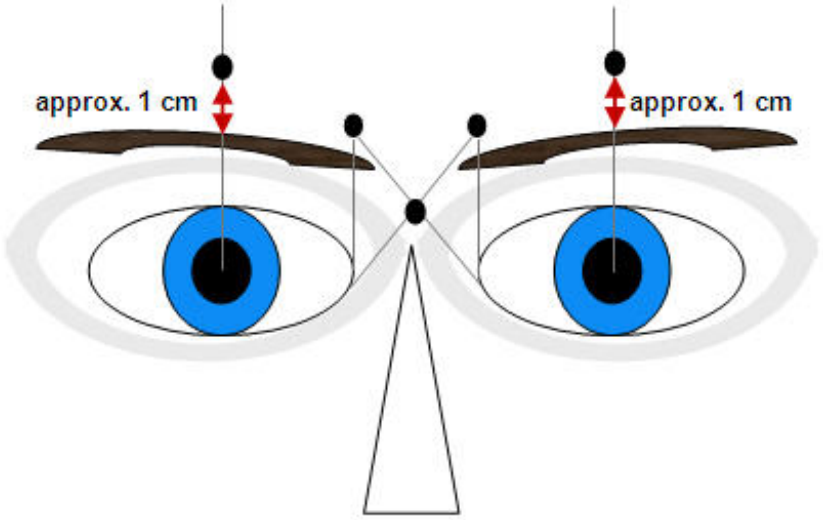
The frequency of XEOMIN repeat treatments should be determined by clinical response but should generally be no more frequent than every 12 weeks *[see Clinical Studies (14.2)]*.

2.3 Glabellar Lines

The total recommended XEOMIN dose is 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each. The five injection sites are: two injections in each corrugator muscle and one injection in the procerus muscle.

Retreatment with XEOMIN should be administered no more frequently than every three months.

Figure 1: Injection Sites for Glabellar Lines



2.4 Special Populations

The safety and effectiveness of XEOMIN in the treatment of cervical dystonia, blepharospasm, and glabellar lines in patients below 18 years of age have not been assessed *[see Warnings and Precautions (5.1)]*.

2.5 Preparation and Reconstitution Technique

Prior to injection, reconstitute each vial of XEOMIN with sterile, preservative-free 0.9% Sodium Chloride Injection, USP. Draw up an appropriate amount of preservative-free 0.9% Sodium Chloride Injection, USP into a syringe (see Table 1). Clean the exposed portion of the rubber stopper of the vial with alcohol (70%) prior to insertion of the needle. Gently inject the saline solution into the vial. If the vacuum does not pull the solvent into the vial, then XEOMIN must be discarded. Gently mix XEOMIN with the saline by rotating the vial. Reconstituted XEOMIN is a clear, colorless solution free of particulate matter. XEOMIN should not be used if the reconstituted solution has a cloudy appearance or contains floccular or particulate matter.

Diluent volumes for reconstitution of XEOMIN are indicated in Table 1.

Table 1: Diluent Volumes for Reconstitution of XEOMIN

Volume of Preservative-free 0.9% Sodium Chloride Injection, USP	**50 Unit Vial: Resulting dose in Units per 0.1 mL**	**100 Unit Vial: Resulting dose in Units per 0.1 mL**
0.25 mL	20 Units	-
0.5 mL	10 Units	20 Units
1 mL	5 Units	10 Units
1.25 mL	4 Units	8 Units
2 mL	2.5 Units	5 Units
2.5 mL	2 Units	4 Units
4 mL	1.25 Units	2.5 Units
5 mL	1 Unit	2 Units
8 mL	-	1.25 Units

Reconstituted XEOMIN solution should be administered within 24 hours after dilution. During this time period, reconstituted XEOMIN should be stored in a refrigerator 2-8°C (36-46°F) *[see How Supplied/Storage and Handling (16.2)]*.

2.6 Administration

Reconstituted XEOMIN is intended for intramuscular injection only. After reconstitution, XEOMIN should be used for only one injection session and for only one patient.

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.

The number of injection sites is dependent upon the size of the muscle to be treated and the volume of reconstituted XEOMIN injected.

XEOMIN should be injected carefully when injected at sites close to sensitive structures, such as the carotid artery, lung apices and esophagus. Before administering XEOMIN, the physician should be familiar with the patient's anatomy and any anatomic alterations, e.g., due to prior surgical procedures.

<u>Cervical Dystonia</u>

A suitable sterile needle (e.g., 26-gauge (0.45 mm diameter), 37 mm length for superficial muscles; or 22-gauge (0.70 mm diameter), 75 mm length for injections into deeper muscles) should be used in the administration in the treatment of cervical dystonia.

Localization of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful.

Blepharospasm

A suitable sterile needle (e.g., 26-gauge (0.45 mm diameter), 37 mm length for superficial muscles; or 22-gauge (0.70 mm diameter), 75 mm length for injections into deeper muscles) should be used in the administration in the treatment of blepharospasm.

Glabellar Lines

A suitable sterile needle 30-33 gauge (0.3-0.2 mm diameter), 13 mm length should be used in the administration in the treatment of glabellar lines.

2.7 Monitoring to Assess Effectiveness

The median first onset of XEOMIN effect occurs within seven days after injection. The typical duration of effect of each treatment is up to 3 months; however, the effect may last significantly longer, or shorter, in individual patients.

3 DOSAGE FORMS AND STRENGTHS

Single-use, sterile 50 Units or 100 Units lyophilized powder for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection, USP, prior to injection.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Use in patients with a known hypersensitivity to the active substance botulinum neurotoxin type A, or to any of the excipients (human albumin, sucrose), could lead to a life-threatening allergic reaction. XEOMIN is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions (5.3) and Description (11)]*.

4.2 Infection at Injection Site

Use in patients with an infection at the injection site could lead to severe local or disseminated infection. XEOMIN is contraindicated in the presence of infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Toxin Effect

Postmarketing safety data from XEOMIN and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized 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 or caregivers should be advised to seek immediate medical care if swallowing, speech, or

respiratory disorders occur.

5.2 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of XEOMIN are specific to the preparation and assay method utilized. 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 Description (11)]*.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with botulinum toxin products (anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea). If serious and/or immediate hypersensitivity reactions occur further injection of XEOMIN should be discontinued and appropriate medical therapy immediately instituted.

5.4 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with XEOMIN and other botulinum toxin products can result in swallowing or breathing difficulties. 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 *[See Warnings and Precautions (5.1)]*.

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 *[See Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

5.5 Pre-existing Neuromuscular Disorders and other Special Populations

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of XEOMIN *[See Adverse Reactions (6.1)]*.

5.6 Corneal Exposure, Corneal Ulceration, and Ectropion in Patients Treated with XEOMIN for Blepharospasm

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 VII nerve disorders. 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.

5.7 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 1 cm above the bony supraorbital ridge.

5.8 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

6 ADVERSE REACTIONS

The following adverse reactions to XEOMIN are discussed in greater detail in other sections of the labeling:

- Hypersensitivity [*see Contraindications (4) and Warnings and Precautions (5.3)]*
- Dysphagia and Breathing Difficulties in Treatment of cervical dystonia [*see Warnings and Precautions (5.4)*]
- Spread of Effects from Toxin *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in practice.

Cervical Dystonia

The data described below reflect exposure to a single intramuscular dose of XEOMIN in a placebo-controlled, Phase 3 trial in patients with cervical dystonia [*see Clinical Studies (14.1)*]. In this study, 159 patients received XEOMIN (78 were randomized to receive a total dose of 120 Units, and 81 were randomized to receive a total dose of 240 Units). XEOMIN-treated patients were 18 to 79 years old (mean 53 years), and were predominantly female (66%) and Caucasian (91%). At study baseline, approximately 25% had mild, 50% had moderate, and 25% had severe cervical dystonia. Approximately 61% of XEOMIN-treated patients had previously received another botulinum toxin type A product. Common adverse events (≥5% in any XEOMIN treatment group) observed in patients who received XEOMIN (120 Units or 240 Units) included dysphagia, neck pain, muscle weakness, injection site pain, and musculoskeletal pain.

Table 2: Most Common TEAEs (≥5%) and Greater than Placebo: Double-Blind Phase of Clinical Trial

	Double-Blind Phase	
	XEOMIN 120	XEOMIN 240

System Organ Class Preferred Term	XEOMIN 120 Units (N=77)	XEOMIN 240 Units (N=82)	Placebo (N=74)
Any TEAEs	57%	55%	42%
Musculoskeletal and connective tissue disorders	23%	32%	11%
Neck pain	7%	15%	4%
Muscular weakness	7%	11%	1%
Musculoskeletal pain	7%	4%	1%
Gastrointestinal disorders	18%	24%	4%
Dysphagia	13%	18%	3%
Nervous system disorders	16%	17%	7%
General disorders and administration site conditions	16%	11%	11%
Injection site pain	9%	4%	7%
Infections and infestations	14%	13%	11%
Respiratory, thoracic and mediastinal disorders	13%	10%	3%

Blepharospasm

In the placebo-controlled Phase 3 trial in patients with blepharospasm previously treated with onabotulinumtoxinA (Botox) *[see Clinical Studies (14.2)]*, 74 patients received XEOMIN at a mean dose of approximately 33 Units per eye (minimum 10 Units, maximum 50 Units). XEOMIN-treated patients were 22 to 79 years of age (mean 62 years), predominantly female (65%), Caucasian (79%), and had a mean time since diagnosis of approximately 5 years.

The adverse events occurring in ≥5% of XEOMIN-treated patients and greater than placebo in the Phase 3 study were eyelid ptosis, dry eye, dry mouth, diarrhea, headache, visual impairment, dyspnea, nasopharyngitis, and respiratory tract infection. No serious adverse events occurred in patients who received XEOMIN; one placebo-treated patient experienced a serious adverse event (dyspnea).

Table 3: Most Common TEAEs (≥5%) and Greater than Placebo: Double-Blind Phase of Clinical Trial

	Double-Blind Phase	
System Organ Class Preferred Term	XEOMIN (N=74)	Placebo (N=34)
Subjects with TEAEs	70%	62%
Eye disorders	38%	21%
Eyelid ptosis	19%	9%
Dry eye	16%	12%
Visual impairment*	12%	6%
Gastrointestinal disorders	30%	15%
Dry mouth	16%	3%
Diarrhoea	8%	-
Infections and infestations	20%	15%
Nasopharyngitis	5%	3%
Respiratory tract infection	5%	3%
Nervous system disorders	14%	9%
Headache	7%	3%

General disorders and administration site conditions	11%	9%
Respiratory, thoracic and mediastinal disorders	11%	3%
Dyspnoea	5%	3%

* including vision blurred

Glabellar Lines

In three placebo-controlled trials in 803 subjects with glabellar lines, 535 subjects received a single dose of 20 Units XEOMIN and 268 subjects received placebo. XEOMIN treated subjects were 24 to 74 years old, and were predominantly female (88%). The most frequent adverse reactions in XEOMIN treated subjects were: headache 29 (5.4%), facial paresis 4 (0.7%), injection site hematoma 3 (0.6%) and eyelid edema 2 (0.4%). Four serious adverse events occurred in two placebo-treated subjects. Six XEOMIN treated subjects experienced six serious adverse events. All serious adverse events were assessed as unrelated to study drug.

The adverse reactions below reflect exposure to XEOMIN with glabellar lines in placebo-controlled studies. Adverse reactions are adverse events in which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Table 4: Adverse Reactions in Placebo-Controlled Trials

Adverse reactions	XEOMIN (N=535) (%)	Placebo (N=268) (%)
Nervous system disorders	**33 (6.1)**	**6 (2.2)**
Headache[1]	29 (5.4)	6 (2.2)
Facial paresis (brow ptosis)	4 (0.7)	0
General disorders and administration site conditions	**5 (0.9)**	**2 (0.7)**
Injection site hematoma	3 (0.6)	0
Injection site pain	1 (0.2)	0
Facial pain	1 (0.2)	0
Injection site swelling	0	1 (0.4)
Sensation of pressure	0	1 (0.4)
Eye disorders	**5 (0.9)**	**0**
Eyelid edema	2 (0.4)	0
Blepharospasm	1 (0.2)	0
Eye disorder	1(0.2)	0
Eyelid ptosis	1(0.2)	0

In open label, multiple dose trials, adverse reactions were reported for 105 of the 800 subjects (13.1%). Headache was the most common adverse reaction, reported for 57 subjects (7.1%), followed by injection site hematoma in 8 subjects (1.0%). Adverse reactions reported in less than 1% of subjects were: facial paresis (brow ptosis), muscle disorder (elevation of eyebrow), injection site pain, and eyelid edema.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

The incidence of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies across products in this class may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval use with XEOMIN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: eye swelling, eyelid edema, dysphagia, nausea, flu-like symptoms, injection site pain, injection site reaction, allergic dermatitis, localized allergic reactions like swelling, edema, erythema, pruritus or rash, herpes zoster, muscular weakness, muscle spasm, dysarthria, myalgia and hypersensitivity.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with XEOMIN.

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.

Use of anticholinergic drugs after administration of XEOMIN may potentiate systemic anticholinergic effects.

The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of XEOMIN.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

There are no adequate and well-controlled studies in pregnant women. XEOMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. XEOMIN was embryotoxic in rats and increased abortions in rabbits when given at doses higher than the maximum recommended human dose (MRHD) for cervical dystonia (120 Units) on a body weight basis.

When XEOMIN was administered intramuscularly to pregnant rats during organogenesis (3, 10, or 30 Units/kg on gestational days [GDs] 6, 12, and 19; or 7 Units/kg on GDs 6 to 19; or 2, 6, or 18 Units/kg on GDs 6, 9, 12, 16, and 19), decreases in fetal body weight and skeletal ossification were observed at doses that were also maternally toxic. The no-effect level for embryotoxicity in rats was 6 Units/kg (3 times the MRHD for cervical dystonia on a body weight basis). Intramuscular administration to pregnant rabbits during organogenesis (1.25, 2.5, or 5.0 Units/kg on GDs 6, 18, and 28) resulted in an increased rate of abortion at the highest dose, which was also maternally toxic. In rabbits, the no-effect level for increased abortion was 2.5 Units/kg (similar to the MRHD for cervical dystonia on a body weight basis).

8.3 Nursing Mothers

It is not known whether botulinum toxin type A is excreted in human milk. Because many drugs are

excreted in human milk, caution should be exercised when XEOMIN is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of XEOMIN in patients less than 18 years of age have not been established *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Cervical Dystonia

In the Phase 3 study in cervical dystonia *[see Clinical Studies (14.1)]*, 29 patients were older than 65 years of age, including 19 patients who received XEOMIN and 10 patients who received placebo. Of these, ten (53%) XEOMIN-treated patients and four (40%) placebo-treated patients experienced an adverse event. For patients over 65 years of age treated with XEOMIN, the most common adverse events were dysphagia (4 patients, 21%) and asthenia (2 patients, 11%). One XEOMIN-treated patient (5%) experienced severe dizziness.

Blepharospasm

In the Phase 3 study in blepharospasm *[see Clinical Studies (14.2)]*, 41 patients were older than 65 years of age, including 29 of 75 patients (39%) who received XEOMIN and 12 of 34 patients (35%) who received placebo. Of these patients, 22 of 29 (76%) XEOMIN-treated patients, compared with 7 of 12 (58%) placebo-treated patients, experienced an adverse event. One XEOMIN-treated patient experienced severe dysphagia.

Glabellar Lines

There are limited clinical data with XEOMIN in subjects over 65 years of age and over in clinical studies with glabellar lines. Of the total number of subjects in the placebo-controlled clinical studies GL1 and GL2, 21 (4%) subjects were 65 and over. Efficacy was observed in 20% (3/15) of XEOMIN subjects 65 years and over. For the entire safety database of geriatric subjects, there was no increase in the incidence of adverse events related to treatment with XEOMIN.

10 OVERDOSAGE

Excessive doses of XEOMIN may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of the respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis *[See Warnings and Precautions (5.1, 5.4)]*. Symptomatic treatment may be necessary.

Symptoms of overdose are not likely to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis.

There is no significant information regarding overdose from clinical studies in cervical dystonia and blepharospasm.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 770-488-7100. More information can be obtained at http://www.cdc.gov/ncidod/srp/drugs/formulary.html#1a.

11 DESCRIPTION

The active ingredient of XEOMIN is botulinum toxin type A produced from fermentation of Hall strain *Clostridium botulinum* serotype A. The botulinum toxin complex is purified from the culture supernatant and then the active ingredient is separated from the proteins (hemagglutinins and non-hemagglutinins) through a series of steps yielding the active neurotoxin with molecular weight of 150 kDa, without accessory proteins. XEOMIN is a sterile white to off-white lyophilized powder intended for intramuscular injection after reconstitution with preservative-free 0.9% Saline for Injection. One vial of XEOMIN contains 50 or 100 Units of incobotulinumtoxinA, 1 mg of human albumin, and 4.7 mg sucrose.

The primary release procedure for XEOMIN uses a cell-based potency assay to determine the potency relative to a reference standard. One Unit corresponds to the median intraperitoneal lethal dose (LD_{50}) in mice. As the method for conducting the assay is specific to XEOMIN, Units of biological activity of XEOMIN cannot be converted into Units of any other botulinum toxin assessed with other specific assays.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

XEOMIN blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine from peripheral cholinergic nerve endings. This inhibition occurs according to the following sequence: neurotoxin binding to cholinergic nerve terminals, internalization of the neurotoxin into the nerve terminal, translocation of the light-chain part of the molecule into the cytosol of the nerve terminal, and enzymatic cleavage of SNAP25, a presynaptic target protein essential for the release of acetylcholine. Impulse transmission is re-established by the formation of new nerve endings.

12.2 Pharmacodynamics

In patients, recovery from paralysis after intramuscular injection normally occurs within 3-4 months as nerve terminals sprout and reconnect with the muscle endplate.

12.3 Pharmacokinetics

General characteristics of the active substance:

Using currently available analytical technology, it is not possible to detect XEOMIN in the peripheral blood following intramuscular injection at the recommended doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies to evaluate the carcinogenic potential of XEOMIN have not been conducted.

Mutagenesis

Genotoxicity studies have not been conducted for XEOMIN.

Impairment of Fertility

In a fertility and early embryonic development study in rabbits, males and females were dosed with XEOMIN (1.25, 2.5, or 3.5 Units/kg) intramuscularly every two weeks for 5 and 3 doses, respectively, beginning 2 weeks prior to mating. No effects on mating or fertility were observed . The highest dose tested is approximately twice the maximum recommended human dose for cervical dystonia (120 Units) on a body weight basis.

14 CLINICAL STUDIES

14.1 Cervical Dystonia

XEOMIN has been investigated in a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial in a total of 233 patients with cervical dystonia. Patients had a clinical diagnosis of predominantly rotational cervical dystonia, with baseline Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) total score ≥20, 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 enrollment. Patients were randomized (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 at each site 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. **Table 5** indicates the average XEOMIN dose, and percentage of total dose, injected into specific muscles in the pivotal clinical trial.

Table 5: XEOMIN 120 Units Initial Dose (Units and % of the Total Dose) by Unilateral Muscle Injected During Double Blind Pivotal Phase 3 Study

		XEOMIN Dose Injected	
	Number of Patients Injected Per Muscle	**Median XEOMIN Units**	**75th percentile XEOMIN Units**
Sternocleidomastoid	63	25	35
Splenius capitis/ Semispinalis capitis	78	48	63
Trapezius	55	25	38
Levator scapulae	49	25	25
Scalenus (medius and anterior)	27	20	25

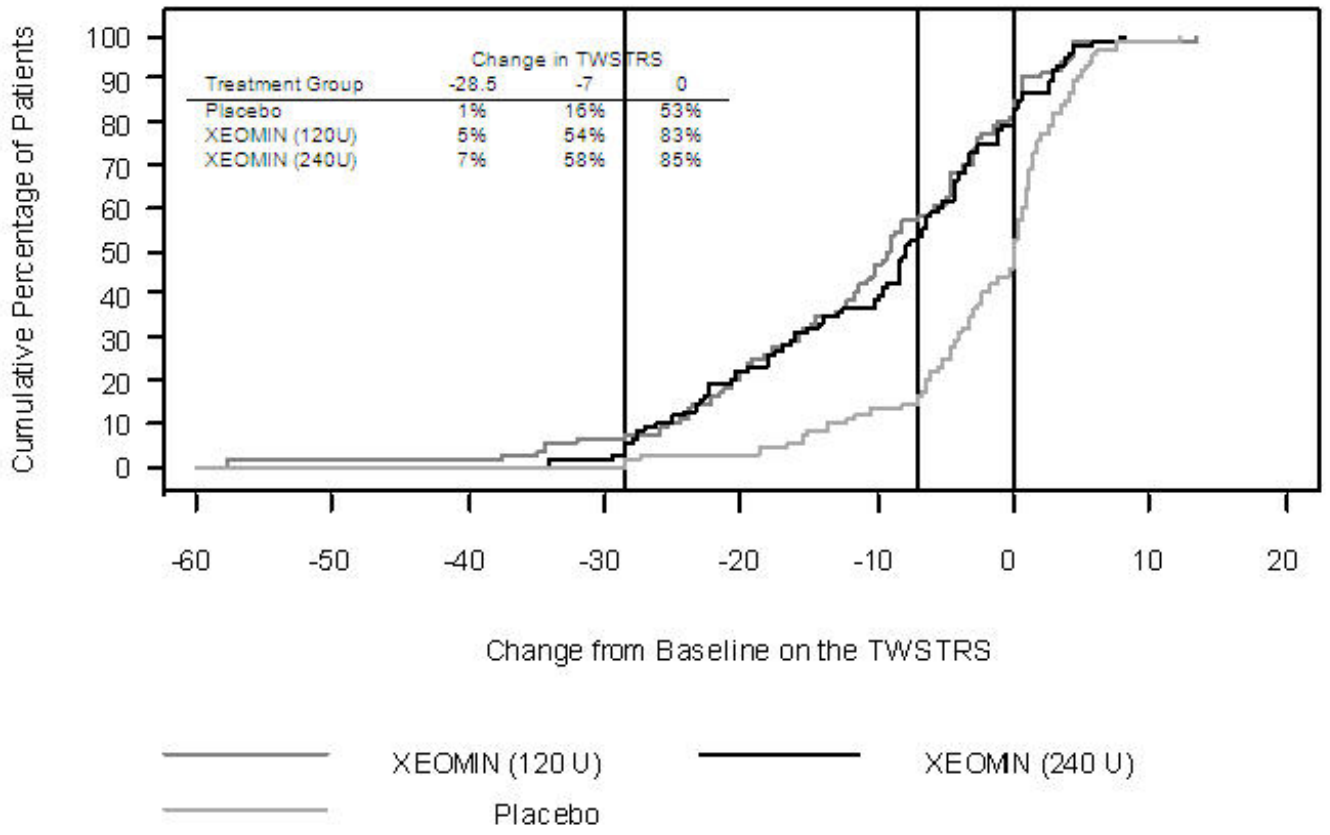
Most patients received a total of 2-10 injections into the selected muscles. Patients were assessed by telephone at one week post-injection, during clinic visits at Weeks 4 and 8, and then by telephone assessments or clinic visits every two weeks up to Week 20.

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 study was completed by 94% of study patients. Three patients discontinued the study prematurely due to adverse events: two patients in the 240 Unit group experienced musculoskeletal pain and muscle weakness, and one patient in the 120 Unit group experienced nausea and dizziness.

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 2 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 2: 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.

Examination of age and gender subgroups did not identify differences in response to XEOMIN among these subgroups. There were too few African-American patients to adequately assess efficacy in that population.

14.2 Blepharospasm

XEOMIN has been investigated in a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial in a total of 109 patients with blepharospasm. Patients had a clinical diagnosis of benign essential blepharospasm, with baseline Jankovic Rating Scale (JRS) Severity subscore ≥2, and a stable satisfactory therapeutic response to previous administrations of onabotulinumtoxinA (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 enrollment.

Patients were randomized (2:1) to receive a single administration of XEOMIN (n=75) or placebo (n=34). Each patient in the XEOMIN group received a XEOMIN treatment (dose, volume, dilution, and injection sites per muscle) that was similar to the most recent onabotulinumtoxinA injection sessions prior to study entry. The highest dose permitted in this study was 50 Units per eye; the mean XEOMIN dose was 33 Units per eye.

In Table 6 the most frequently injected sites, the median dose per injection site, and the median number (and range) of injection sites per eye are presented.

Table 6: Median Dose and Median Number of Injection Sites per Eye (Blepharospasm)

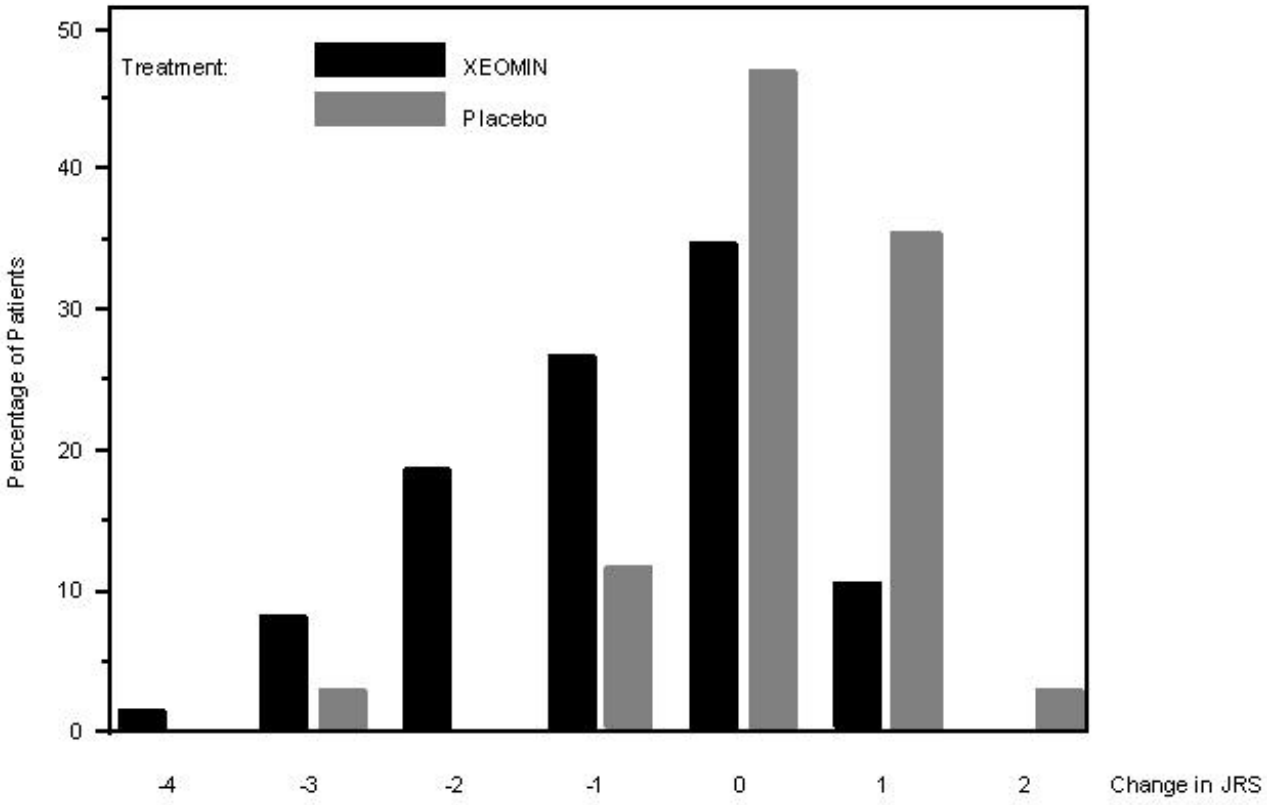
Injection Area	Median Units XEOMIN	Median Number of Injection Sites (Min-Max)
Temporal Area	13	2 (1 – 6)
Eyebrow Area	5	1 (1 – 4)
Upper Lid Area	10	2 (1 – 4)
Lower Lid Area	8	2 (1 – 3)
Orbital Rim	5	1 (1 – 3)

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. No patients discontinued the study prematurely due to adverse events.

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. Comparison of the XEOMIN group to the placebo group was statistically significant at $p<0.001$.

Figure 3: Frequency Distribution of Changes from Baseline JRS Severity Subscore at Week 6



Examination of age and gender subgroups did not identify substantial differences in response to XEOMIN among these subgroups. There were too few African-American patients to assess efficacy in that population.

14.3 Glabellar Lines

Two identically designed randomized, double-blind, multi-center, placebo controlled clinical trials (Studies GL-1 and GL-2) were conducted to evaluate XEOMIN for use in the temporary improvement of moderate to severe glabellar lines. The studies enrolled 547 healthy patients (≥18 years old) with glabellar lines of at least moderate severity at maximum frown. Three hundred sixty six subjects were treated with 20 U of XEOMIN and 181 subjects were treated with placebo. Subjects were excluded if they had marked ptosis, deep dermal scarring, or an inability to lessen glabellar lines, even by physically spreading them apart. The mean age of study subjects was 46 years. The majority of patients were female (86% and 93% in Studies GL-1 and GL-2, respectively), and predominantly Caucasian (89% and 65% respectively). The study subjects received either 20 U of XEOMIN or an equal amount of placebo. The total dose was delivered in 5 equally divided intramuscular injections of 4 Units each to specific sites (see Figure 1). Subjects were followed up for 120 days.

Investigators and subjects assessed efficacy at maximum frown on Day 30 of treatment using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe). Composite treatment success was defined as a 2-grade improvement on this scale compared to baseline for both the investigator's and subject's assessments on Day 30. The percentage of subjects with treatment success was greater on the XEOMIN arm than the placebo arm at Day 30 in both studies (see Table 7). The percentage of subjects with composite treatment success at each visit are presented in Figure 4.

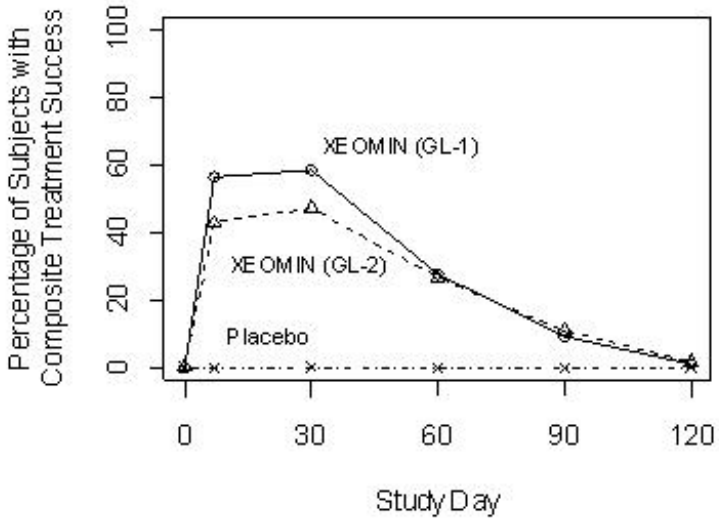
Table 7: Treatment Success at Day 30 (at Least 2 Grades Improvement from Baseline at Maximum Frown)

	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

Figure 4: Percentage of Subjects with Composite Treatment Success by Visit – Observed Cases (GL-1 and GL-2)



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Type 1 borosilicate glass single-use vials with latex-free bromobutyl rubber closures and tamper-proof aluminum seals in the following pack sizes:

Cervical Dystonia and Blepharospasm

Package	XEOMIN 50 Units	XEOMIN 100 Units
single vial pack	NDC 0259-1605-01	NDC 0259-1610-01

Glabellar Lines

Package	XEOMIN 50 Units	XEOMIN 100 Units
single vial pack	NDC 46783-161-01	NDC 46783-160-01

16.2 Storage

Unopened vials of XEOMIN can be stored at room temperature 20 to 25°C (68 to 77° F), in a refrigerator at 2 to 8°C (36 to 46°F), or a freezer at -20 to -10°C (-4 to 14°F) for up to 36 months. Do not use after the expiration date on the vial. Reconstituted XEOMIN should be stored in a refrigerator at 2 to 8°C (36 to 46°F) and administered within 24 hours.

16.3 Handling

XEOMIN is reconstituted prior to use with sterile preservative-free 0.9% Sodium Chloride Injection, USP *[see Dosage and Administration (2.5)]*.

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

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

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Provide a copy of the Medication Guide and review the contents with the patient.

17.1 General

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Previously immobile or sedentary patients should be reminded to gradually resume activities following the injection of XEOMIN for the treatment of cervical dystonia and blepharospasm.

Patients should be informed that injections of XEOMIN may cause dyspnea, or mild to severe dysphagia, with the risk of aspiration *[see Boxed Warning and Warnings and Precautions (5.1, 5.4)]*.

Patients should be counseled that if loss of strength, muscle weakness, blurred vision, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Patients should be informed that injections of XEOMIN may cause reduced blinking or effectiveness of blinking, and that they should seek immediate medical attention if eye pain or irritation occur following treatment.

Manufactured by:
Merz Pharma GmbH & Co., KGaA
Am Pharmapark
D-06861 Dessau-Rosslau
Germany

Distributed by:
Merz Pharmaceuticals, LLC
4215 Tudor Lane
Greensboro, NC 27410

and

Merz North America, Inc.
4133 Courtney Road, Suite 10
Franksville, WI 53126

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Patent pending.

Botox® is a registered trademark of Allergan, Inc.

Medication Guide
XEOMIN® (Zeo-min)
(incobotulinumtoxinA)
for injection, for intramuscular use

Read this Medication Guide before you start receiving XEOMIN® and each time XEOMIN® is given to you. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. You should share this information with your family

members and caregivers.

What is the most important information that I should know about XEOMIN®?

XEOMIN® may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems after treatment with XEOMIN®:

- **Problems with swallowing, speaking, or breathing**. **These problems can happen hours to weeks after an injection of XEOMIN®** if the muscles that you use to breathe and swallow become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with XEOMIN®.
- People with certain breathing problems may need to use muscles in their neck to help them breathe. These patients may be at greater risk for serious breathing problems with XEOMIN®.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving XEOMIN® have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
  - loss of strength and muscle weakness all over the body
  - double vision
  - blurred vision and drooping eyelids
  - hoarseness or change or loss of voice
  - trouble saying words clearly
  - loss of bladder control
  - trouble breathing
  - trouble swallowing

These symptoms can happen hours to weeks after you receive an injection of XEOMIN®.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving XEOMIN®?"

What is XEOMIN®?

XEOMIN® is a prescription medicine that is injected into muscles and used:

- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat abnormal spasm of the eyelids (blepharospasm) in adults who have had prior treatment with onabotulinumtoxinA (BOTOX).
- to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults for a short period of time (temporary).

It is not known whether XEOMIN® is safe or effective in children.

Who should not take XEOMIN®?

Do not take XEOMIN® if you:

- are allergic to XEOMIN® or any of the ingredients in XEOMIN®. **See the end of this Medication Guide for a list of ingredients in XEOMIN®.**
- had an allergic reaction to any other botulinum toxin products such as rimabotulinumtoxinB (MYOBLOC®), onabotulinumtoxinA (BOTOX®, BOTOX® COSMETIC), or abobotulinumtoxinA (DYSPORT®).
- have a skin infection at the planned injection site.

What should I tell my doctor before receiving XEOMIN®?

Before you take XEOMIN® tell your doctor about all your medical conditions, including if you:

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). **See "What is the most important information I should know about XEOMIN®?"**
- have allergies to any botulinum toxin product
- have had any side effect from any other botulinum toxin in the past
- have a breathing problem, such as asthma or emphysema
- have a history of swallowing problems or inhaling food or fluid into your lungs (aspiration)
- have bleeding problems
- have drooping eyelids
- have plans to have surgery
- have had surgery on your face
- are pregnant or plan to become pregnant. It is not known if XEOMIN® can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if XEOMIN® passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Using XEOMIN® with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received XEOMIN® in the past.**

Especially tell your doctor if you:
- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin such as rimabotulinumtoxinB (MYOBLOC®), onabotulinumtoxinA (BOTOX®, BOTOX® COSMETIC) and abobotulinumtoxinA (DYSPORT®) in the past. Be sure your doctor knows exactly which product you received. The dose of XEOMIN® may be different from other botulinum toxin products that you have received.

- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine
- take a blood thinner medicine

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How will I receive XEOMIN®?
- XEOMIN® is a shot (injection) that your doctor will give you.
- XEOMIN® is injected into your affected muscles.
- Your doctor may change your dose of XEOMIN® until you and your doctor find the best dose for you.

What should I avoid while receiving XEOMIN®?

XEOMIN® may cause loss of strength or general muscle weakness, blurred vision, or drooping eyelids within hours to weeks of taking XEOMIN®. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about XEOMIN®?"

What are the possible side effects of XEOMIN®?

XEOMIN® can cause serious side effects. See "What is the most important information I should know about XEOMIN®?"
- **XEOMIN may cause other serious side effects including** allergic reactions. Symptoms of an

allergic reaction to XEOMIN® may include: itching, rash, redness, swelling, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you get wheezing or asthma symptoms, or if you get dizzy or faint.

The most common side effects of XEOMIN® include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- muscle weakness
- eye problems, including: double vision, blurred vision, drooping eyelids, swelling of your eyelids, and dry eyes. Reduced blinking can also occur. Tell your doctor or get medical help right away if you have eye pain or irritation following treatment.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XEOMIN®. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about XEOMIN®

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. XEOMIN® should not be used for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about XEOMIN®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about XEOMIN® that is written for healthcare professionals.

For more information go to www.Xeomin.com or call 888-493-6646.

What are the ingredients in XEOMIN®?

Active ingredient: incobotulinumtoxinA

Inactive ingredients: human albumin and sucrose

Distributed by:
Merz Pharmaceuticals, LLC
4215 Tudor Lane
Greensboro, NC 27410

and

Merz North America, Inc.
4133 Courtney Road, Suite 10
Franksville, WI 53126

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued 07/2011

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Patent pending.

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EM00451-01

PRINCIPAL DISPLAY PANEL - 50 Units/Vial Label

incobotulinumtoxinA

XEOMIN®
for Injection

50 units/vial

For Intramuscular Use.
Single-use vial; Discard unused portion.
Usual dosage: see package insert.

PRINCIPAL DISPLAY PANEL - 50 Units/Vial Carton

Rx Only
NDC 0259-1605-01

incobotulinumtoxinA

XEOMIN®
for Injection

For Intramuscular Use

MERZ

50 units/vial

Dispense the enclosed Medication
Guide to each patient.

PRINCIPAL DISPLAY PANEL - 100 Units/Vial Label

incobotulinumtoxinA

XEOMIN®
for Injection

100 units/vial

For Intramuscular Use.
Single-use vial; Discard unused portion.
Usual dosage: see package insert.

PRINCIPAL DISPLAY PANEL - 100 Units/Vial Carton

Rx Only
NDC 0259-1610-01

incobotulinumtoxinA

XEOMIN®
for Injection

For Intramuscular Use

MERZ

100 units/vial

Dispense the enclosed Medication
Guide to each patient.

PRINCIPAL DISPLAY PANEL - 50 Units/Vial Label - Physician Sample

Physician Sample - not for resale

incobotulinumtoxinA

XEOMIN®
for Injection

50 units/vial

For Intramuscular Use.
Single-use vial; Discard unused portion.
Usual dosage: see package insert.

PRINCIPAL DISPLAY PANEL - 50 Units/Vial Carton - Physician Sample

Rx Only
NDC 0259-4150-01

incobotulinumtoxinA

XEOMIN®
for Injection

MERZ

50 units/vial

PRINCIPAL DISPLAY PANEL - 100 Units/Vial Label - Physician Sample

Physician Sample - not for resale

incobotulinumtoxinA

XEOMIN®
for Injection

100 units/vial

For Intramuscular Use.
Single-use vial; Discard unused portion.
Usual dosage: see package insert.

PRINCIPAL DISPLAY PANEL - 100 Units/Vial Carton - Physician Sample

Rx Only
NDC 0259-4110-01

incobotulinumtoxinA

XEOMIN®
for Injection

MERZ

100 units/vial

XEOMIN

incobotulinumtoxina injection, powder, lyophilized, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0259-1605
Route of Administration	INTRAMUSCULAR	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Botulinum Toxin Type A (UNII: E211KPY694) (Botulinum Toxin Type A - UNII:E211KPY694)	Botulinum Toxin Type A	50 [USP'U]

Inactive Ingredients

Ingredient Name	Strength
Albumin Human (UNII: ZIF514RVZR)	
Sucrose (UNII: C151H8M554)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0259-1605-01	1 in 1 CARTON		
1		1 in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125360	09/01/2010	

XEOMIN

incobotulinumtoxina injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0259-1610
Route of Administration	INTRAMUSCULAR	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Botulinum Toxin Type A (UNII: E211KPY694) (Botulinum Toxin Type A - UNII:E211KPY694)	Botulinum Toxin Type A	100 [USP'U]

Inactive Ingredients

Ingredient Name	Strength
Albumin Human (UNII: ZIF514RVZR)	
Sucrose (UNII: C151H8M554)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0259-1610-01	1 in 1 CARTON		
1		1 in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125360	09/01/2010	

XEOMIN

incobotulinumtoxina injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0259-4150
Route of Administration	INTRAMUSCULAR	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Botulinum Toxin Type A (UNII: E211KPY694) (Botulinum Toxin Type A - UNII:E211KPY694)	Botulinum Toxin Type A	50 [USP'U]

Inactive Ingredients

Ingredient Name	Strength
Albumin Human (UNII: ZIF514RVZR)	
Sucrose (UNII: C151H8M554)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0259-4150-01	1 in 1 CARTON		
1		1 in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125360	09/01/2010	

XEOMIN

incobotulinumtoxina injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0259-4110
Route of Administration	INTRAMUSCULAR	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Botulinum Toxin Type A (UNII: E211KPY694) (Botulinum Toxin Type A - UNII:E211KPY694)	Botulinum Toxin Type A	100 [USP'U]

Inactive Ingredients

Ingredient Name	Strength
Albumin Human (UNII: ZIF514RVZR)	
Sucrose (UNII: C151H8M554)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0259-4110-01	1 in 1 CARTON		
1		1 in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125360	09/01/2010	

Labeler - Merz Pharmaceuticals, LLC (126209282)

Establishment

Name	Address	ID/FEI	Business Operations
Merz Pharmaceuticals GmbH		342235018	ANALYSIS(0259-1605, 0259-1610, 0259-4150, 0259-4110)

Establishment

Name	Address	ID/FEI	Business Operations
Merz Pharma GmbH & Co. KGaA		342543051	MANUFACTURE(0259-1605, 0259-1610, 0259-4150, 0259-4110)