

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125360

LABELING

7 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, 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.

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).
- Blepharospasm in adults previously treated with onabotulinumtoxinA (Botox®) (1.2).

DOSAGE AND ADMINISTRATION

Reconstituted XEOMIN is intended for intramuscular injection. The optimum dose and number of injection sites in the treated muscle(s) should be individualized for each patient and determined by the physician.

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.

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- 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

General

- 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 (5.1).
- Spread of toxin effects may cause swallowing and breathing difficulties that can lead to death (5.2).
- Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties (5.2, 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 (5.6)
- 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.

ADVERSE REACTIONS

Cervical Dystonia: The most commonly observed adverse reactions (≥5% of patients and > placebo) were: 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) were: eyelid ptosis, dry eye, dry mouth, diarrhea, headache, visual impairment, dyspnea, nasopharyngitis, and respiratory tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Merz Pharmaceuticals, LLC at (phone 888-493-6646 and <http://www.merzusa.com>) 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: [m/year]

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FULL PRESCRIBING INFORMATION

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.

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).

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 (5.1) 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 Special Populations

The safety and effectiveness of XEOMIN in the treatment of cervical dystonia and blepharospasm in patients below 18 years of age have not been assessed [see *Warnings and Precautions (5.2)*].

2.4 Preparation and Dilution 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 0.9% saline solution 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	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
2 mL	2.5 Units	5 Units
4 mL	1.25 Units	2.5 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, Storage (16.2)*].

2.5 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. 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 for administration.

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

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.

2.6 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 [See *Dosage and Administration (2.4)*]

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 *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 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)*].

5.2 Spread of Toxin Effect

Post-marketing 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.

5.3 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* (5.2)].

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* (5.2) 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.

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

5.7 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)]

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia [see *Warnings and Precautions* (5.4)]

Spread of Effects from Toxin [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions and for various lengths of time, adverse event rates observed in the clinical trials of a drug cannot be directly compared with rates in other 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 ($\geq 5\%$ 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 Treatment Emergent Adverse Events ($\geq 5\%$) and Greater than Placebo: Double-Blind Phase of Clinical Trial

System Organ Class Preferred Term	XEOMIN 120 Units (N=77)	Double-Blind Phase	
		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%

Double-Blind Phase

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 $\geq 5\%$ 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 Treatment Emergent Adverse Events ($\geq 5\%$) and Greater than Placebo: Double-Blind Phase of Clinical Trial

System Organ Class Preferred Term	Double-Blind Phase	
	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

6.2 Post-Marketing Experience

The following adverse reactions have been reported during post-approval use with XEOMIN: eye swelling, eyelid edema, dysphagia, nausea, 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.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Neutralizing antibody titers were assessed in all clinical studies of XEOMIN, using the hemidiaphragm assay. In the XEOMIN development program, twelve of 1080 subjects (1.1%) who were antibody negative at baseline developed neutralizing antibodies to botulinum toxin during the course of their respective study. Each of these 12 subjects had been treated with another botulinum toxin prior to exposure to XEOMIN. Because the majority of patients had previously been exposed to other botulinum neurotoxins, and because most trials were of short duration with controlled intervals between treatments, the potential for antibody formation has not been fully characterized. The significance of these antibodies is unknown since in the presence of neutralizing antibodies some patients may continue to experience clinical benefit. A single subject with a twenty year history of cervical dystonia who was reported as botulinum toxin-naïve and treated with 240 Units of XEOMIN demonstrated transiently positive neutralizing antibodies which reverted to negative at study termination. This subject was determined to be a primary non-responder.

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.

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 (5.2)].

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.

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 (5.2, 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 0.9% Saline for Injection, USP (without preservative). One vial of XEOMIN contains 50 or 100 Units of incobotulinumtoxinA, 1 mg of human albumin, and 4.7 mg sucrose. One Unit corresponds to the mouse median lethal dose (LD₅₀) when the reconstituted product is injected intraperitoneally into mice under defined conditions. 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 rodents it was shown that degree and duration of hindlimb muscle paralysis is dose-dependent. 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 2 indicates the average XEOMIN dose, and percentage of total dose, injected into specific muscles in the pivotal clinical trial.

Table 4: XEOMIN 120 Units Initial Dose (Units and % of the Total Dose) by Unilateral Muscle Injected During Double Blind Pivotal Phase 3 Study

	Number of Patients Injected Per Muscle	XEOMIN Dose Injected	
		Median XEOMIN Units	75 th 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

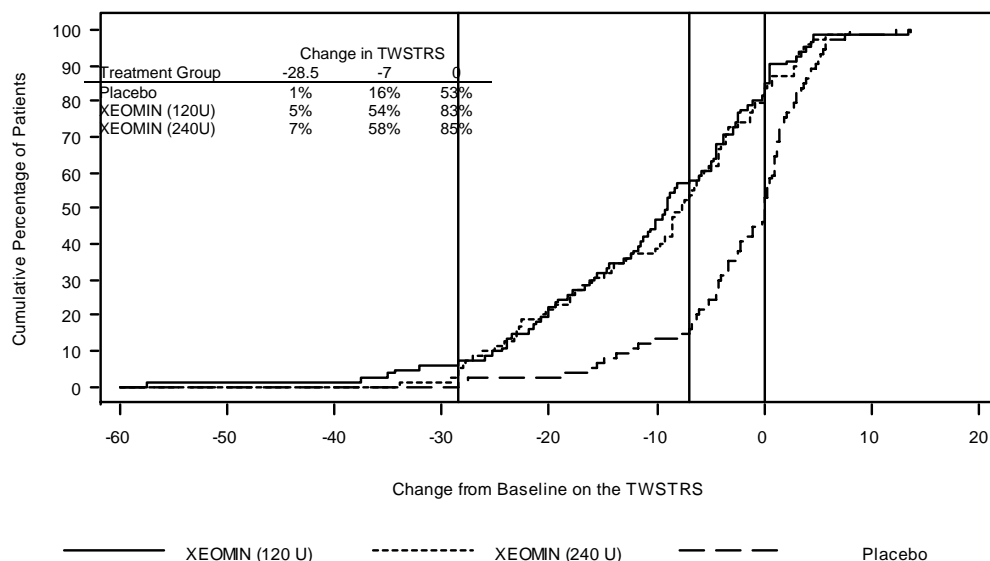
Most patients received a total of 2-10 injections into the selected muscles. Patients were assessed by telephone at one week post-injection, during clinic visits at Weeks 4 and 8, and then by telephone assessments or clinic visits every two weeks up to Week 20.

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 1 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 1: 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 5](#) 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 5: 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)

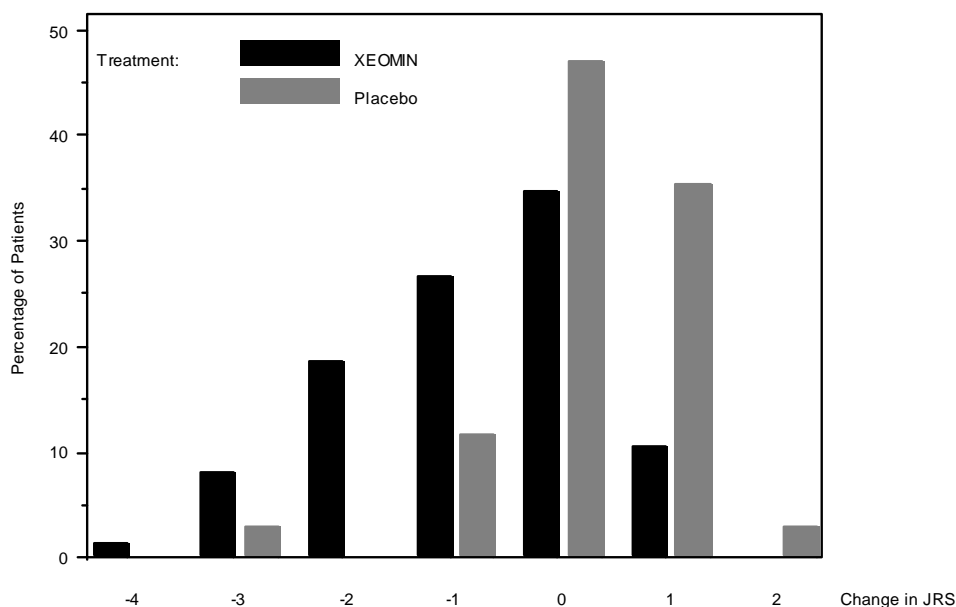
Patients were assessed during clinic visits at Weeks 3 and 6, and then by telephone or at clinic visits every two weeks up to Week 20.

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 2: 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.

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:

Package	XEOMIN 50 Units	XEOMIN 100 Units
single vial pack	NDC 00259-1605-1	NDC 00259-1610-1

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 unpreserved 0.9% sodium chloride solution for injection. Reconstitution and dilution should be performed in accordance with good clinical practice.

See Section 2.4 Dosage and Administration for reconstitution instructions.

XEOMIN should not be used if the reconstituted solution (prepared as above) 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.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully as is done with all medical waste.

17 PATIENT COUNSELING INFORMATION

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.

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 (5.2, 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.

17.2 Blepharospasm

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.

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