

(RX only)

IS33106

Botulax[®] 50

Clostridium botulinum toxin type A

Composition

| Each Vial contains: | |
|---|-------------|
| Active ingredient : Clostridium botulinum toxin type A (Strain: Clostridium botulinum CBFC26) | |
| (KFDA-approved specifications) | 50units(U)* |
| Stabilizer : Human serum albumin (Korean Minimum Requirements for Biological Products) | 0.25mg |
| Tonic adjuster : Sodium chloride (Korean Pharmacopoeia) | 0.45mg |
| *One unit(U) of BOTULAX® Injection 50 Units/Vial corresponds to the calculated median intraperito | neal lethal |
| dose (LDrs) in mice | |

Description

It appears as a lyophilized white powder for injection in a colorless transparent vial and should become colorless transparent liquid when the diluent (physiological saline) is added.

Indication

1. Benign essential blepharospasm in adult patients, 18 years age or above Temporary improvement of serious glabellar wrinkles ranging from moderate to severe associated with corruga-tors muscle and/or procerus muscle activities in adults aged between 18 and 65

Dosage and administration

1. Blepharospasm

1. Blepharospasm For blepharospasm, reconstituted BOTULAX® 50(see Dilution Table) is injected using a sterile, 27-30 gauge needle without electro-myographic guidance. The initial recommended dose is 1.25-2.5U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient (usually defined as an effect that does not last longer than two months). However, there appears to be little benefit obtainable from injecting more than 5.0 U per site. Some tolerance may be found when this product is used in treating blepharospasm if treatments are given more frequently than every three months, and is rare to have the effect be permanent. The cumulative dose of BOTULAX® 50 treatment in a 30-day period should not exceed 200 U.

2. Glabellar lines

2. Glabellar lines Reconstitute this product with 0.9% preservative-free, sterile saline to make 50 U/1.25 mL (4 U/0.1 mL). Using a 30-gauge needle, inject a dose of 0.1 mL into each of 5 sites, 2 in each corrugators muscle and 1 in procerus muscle, for a total of 20 U. In order to reduce the complication of ptosis, avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes. Injections into inner corrugators muscle and central eyebrow should be placed at least 1 cm above the bony supraorbital ridge. Careful attention should be paid to avoid injection of this product into the blood vessel. In order to prevent exudation below the orbital ridge, be sure to firmly place the thumb or index finger below the orbital ridge, prior to injection. The needle should be toward the upper center during injection and careful attention should be paid to inject accurate volume.



Glabellar facial lines arise from the activity of corrugator muscle and orbicularis oculi muscle. These muscles move the brow medi-ally, and the procerus muscle and depressor supercili muscle pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected. Each treatment lasts approximately three to four months. More frequent injection of this product is not recommended because the safety and efficacy are not established.

Dilution Technique

Prior to injection, reconstitute freeze-dried this product with a preservative-free, sterile saline. 0.9% Sodium Chloride Injection is the recommended diluent. Draw up the proper amount of diluent in the syringe of appropriate size. Since this product is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstituted product should be shored in a refrigerator (2.8°C). Reconstituted product should be used constituted product should be injected gently into the vial. This product should be administered within this product should be used for a single particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Because this product and the diluent do not contain any preservative, one vial of this product should be used for a single patient. this product should be used for a single patient.

[Dilution Table]

| Diluent added | Resulting dose | |
|----------------------------------|----------------|--|
| (0.9% Sodium Chloride Injection) | (U/0.1mL) | |
| 0.5mL | 10.0U | |
| 1.0mL | 5.0U | |
| 2.0mL | 2.5U | |
| 4.0mL | 1.25U | |

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in dose is also possible by administer-ing a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

Precautions

1. Warnings Since the active ingredient of this drug product is Clostridium botulinum toxin type A which is derived from Costridium botulinum, the information in this section should be fully understood and the recommended dosage and administra-tion methods should be strictly followed. Physicians administering this drug product should sufficiently understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. Understanding of standard electromyographic techniques is also required. The recommended dosages and administration frequen-cies should not be exceeded.

- 1) Spread of toxin effect: The effects of botulinum toxin products may spread from the area of injection and produce negative symptoms. The symptoms may include asthenia, generalized muscle weakness, dysphonia, dysarthria, stuttering, urinary incontinence, breathing difficulties, dysphagia (swallowing difficulties), diplopia, blurred vision, and ptosis. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spastic cerebral palsy, but symptoms can also occur in adults treated for spastic cerebral palsy and other conditions. Cases of the above adverse reactions have occurred at doses comparable to those used to treat control dward doses. cervical dystonia and at lower doses.
- cervical dystomia and at lower doses. 2) Hypersensitivity reactions: Serious and/or immediate hypersensitivity reactions have been reported for other botulinum toxin product. These reactions include anaphylaxis, urticaria, soft tissue edema and dyspnea. One fatal case of anaphylaxis has been reported in which lidocaine was used as a diluent, and consequently, the causal agent was not reliably determined. If such a reaction occurs, further injection of this drug product should be discontinued and appropriate medical therapy should be immediately instituted.
- euromuscular disorders: Individuals with peripheral motor peuro The ensuing incomplete and independent indirective income the indirective transmission of the product as the statement of the indirective transmission of the indirective transmission of the indirective transmission of the indirective transmission of a bottlinum toxin to patients with known or unrecognized neuronscular biotective transmission of a bottlinum toxin to patients with known or unrecognized neuronscular biotective transmission of a bottlinum toxin to patients with known or unrecognized neuronscular biotective transmission of a bottlinum toxin to patients with known or unrecognized neuromuscular disorders where patients have shown serious the statement of the statement hypersensitivity to systemic effects of typical clinical doses. In some cases, dysphagia lasted several months and placement of a gastric feeding tube was required.
- JDysphagia: as commonly reported adverse reaction after treatment of cervical dystonia patients with all botulinum toxins. In these patients, rare cases of severe dysphagia requiring the use of a gastric feeding tube were reported. In addi-tion, deaths owing to aspiration pneumonia, as a complication of severe dysphagia, have been reported after treatment with botulinum tend. otulinum toxin
- 5) There have also been reports of adverse reactions with other botulinum toxin product, involving cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascula
- 6) During administration of other botulinum toxin product for treatment of strabismus, retrobulbar hemorrhages sufficient to com-During administration of other botulinum toxin product for treatment of strabismus, retrobulbar hemorrhages sufficient to com-promise retinal circulation have occurred owing to penetration of the needle into areas surrounding eyes. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past-pointing. Covering the affected eye may alleviate these symptoms.

- 7) Blepharospasm: Reduced blinking from injection of botulinum toxin into orbicularis muscle can lead to corneal exposure, persist-ent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of other botulinum toxin product for treatment of blepharospasm, one case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon should be conducted and injection into the lower lid area should be avoided to reduce the risk of ectropion. 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 01 and 61 the torte to the total test in the total test of the eye by patching or 01 and 61 test parts and the total test of the test of the eye by patching or 01 and 61 test parts and the test of the test of the eye by patching or 01 and 61 test parts and the test of the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and the eye by patching or 01 test of test parts and test of test of test of test of test parts and test of test of test parts and test of test o
- 8) Lack of Interchangeability between botulinum toxin products: Since the potency units of botulinum toxin are specific to individual products, they are not interchangeable with other botulinum toxin product. Therefore, units of biological activity of botulinum tox-in cannot be compared or converted into units of any other botulinum toxin product assessed with other specific assay method.
- in cannot be compared or converted into units of any other botulinum toxin product assessed with other specific assay method. 9) Injections in or near vulnerable anatomic structures: Care should be taken when injecting in or near vulnerable anatomic struc-tures. Serious adverse reactions, including fatal outcomes, have been reported in patients who had received other botulinum toxin product injected directly into salivary glands, oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. (Safety and effectiveness have not been established for indications pertaining to these injection sites.) Pneumothorax associated with injection procedure has been reported following the administration of other botulinum toxin near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices. 10) Pulmonary effects in patients with compromised respiratory status treated for upper limb spaticity or for detrusor overactivity associated with a neurologic condition: In patients with upper limb spaticity and respiratory disorder, upper respiratory tract infections and reduced lung function were reported when administered with other botulinum toxin products. Reduced lung functions were also reported in patients treated with other botulinum toxin products for detrusor overactivity a neurologic condition.
- a neurologic condition. 11) Bronchitis and upper respiratory tract infections in patients treated for upper limb spasticity. Bronchitis was reported more
- frequently as an adverse reaction in patients treated with other botulinum toxin for upper limb spasticity, compared to placebo. In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently in patients treated with botulinum toxins, compared to placebo.

2. This drug product should not be administered to the following patients:

- Patients who are hypersensitive to any ingredient in the formulation of this product.
 Patients who have neuromuscular junctional disorders (e.g., myasthenia gravis, Lambert-Eaton syndrome or amyotrophic lateral sclerosis). The diseases may be exacerbated due to the muscle relaxation activity of this drug product.
 Patients with severe respiratory disorders, when used for treatment of cervical dystonia.
 Pregnant women, women of childbearing potential or nursing mothers.

3. This drug product should be carefully administered to the following patients:

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 Patients under treatment with other muscle relaxants (e.g., tubocurarine chloride, dantrolene sodium, etc.) - Muscle relaxation may be potentiated or risks of dysphagia may be increased.
 Patients under treatment with drugs with muscle relaxation activity, e.g., spectinomycin HCI, aminoglycoside antibiotics (gentanticin sulfate, neomycin sulfate, etc.), polypeptide antibiotics (polymyxin B sulfate, etc.), tetracycline antibiotics, lincomycin antibiotics, muscle relaxations (background etc.), anti-cholinergia agents (scopolamine butylphenidil HCI, etc.), benzodiazepine and other similar drugs (diazepam, etizolam, etc.), and benzamide drugs (thiapride HCI, sulpiride, etc.). Muscle relaxation may be potentiated or risks of dysphagia may be increased.

4. Adverse drug reactions

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 Cheeral: There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with other botulinum toxin. There have also been reports of adverse reactions involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. The exact relationship of these events to the botulinum toxin injection has not been established.
 The following events have been reported with other botulinum toxin products and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction. In general, adverse reactions occur within the first week following injection and, while generally transient, may have a duration of several months. Localized pain, tenderness, bruising, traction, swelling, but feeling or hypertonia at nijection stimulition toxin. However, weakness of adjacent muscles may also occur due to spread of toxin. When injected pain, tenderdystonia, osme muscles distant from the injection site can show increased electrophysiological jitter (rapid variation in a waveform) which is not associated with clinical weakness or other types of electrophysiological abnormalities.

2) Strabismus: Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviations, especially with higher doses of this drug product. The incidence rates of these adverse reactions with other botulinum toxin products in 2,058 adults who received a total of 3,650 injections for horizontal strabismus were as follows; Provide 15, 766.

adults who received a total of 3,650 injections for horizontal strabismus were as follows; Ptosis 15.7% Vertical deviation 16.9% Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past-pointing. Cover-ing the affected eye may alleviate these symptoms. The incidence rates of ptosis were 0.9% after inferior rectus injection and 37.7% after superior rectus injection. The incidence rates of adverse reactions observed for 6 months, with other botulinum toxin products in 3,104 patients after a series of 5,587 injections of horizontal muscles, were as follows: Ptosis 0.3% Vertical deviation of greater than 2 prism diopters 2.1% In these patients, the injection procedure itself caused nine scleral perforations. A vitreous hemorrhage occurred in one case and later cleared. No retinal detachment or visual loss occurred in any case. Sixteen retrobulbar hemorrhages occurred without visual loss. Decompression of the orbit after five minutes was done to restore retinal circulation. Five eyes had pupillary change consistent with ciliary qanqlion damage (Adies pupil).

Regardless of causal relationship, adverse reactions per occurrence site are as follows

Anterior segment ischemia after other botulinum toxin injection into the medial rectus muscle for treatment of esotropia was reported.

3) Blepharospasm: Adverse reactions were observed in 39% of those who received this product in clinical study in blepharospasm patients of 18 years of age and above. The most common adverse reactions were ptosis, lagophthalmos and eye dryness, and most of them were mild or moderate.

| Sites | Adverse reactions (Incidence Rates) | |
|-----------------------------|---|--|
| Eye | Ptosis (6.61%), Lagophthalmos (6.61%), Dry eye (6.61%), Watery eye (4.13%), Blepharoedema (1.65%) Photophobia (2.48%), Conjunctivitis (2.48%), Myodesopsia (1.65%), Keratitis (1.65%), Chalasis (0.83%) Chalazion (0.83%), Foreign body sensation (0.83%) | |
| Lymphatic system | Edema (4.96%) | |
| Skin | Reactions at injection sites (4.13%), Flushing (0.83%) | |
| Pain | Headache (2.48%), Myalgia (1.65%) | |
| Gastrointestinal | Hernia (0.83%), Stomach ulcer (0.83%), Stomatitis (0.83%) | |
| Blood system | Hematoma (0.83%) | |
| Metabolism system | Hyperlipemia (0.83%) | |
| Nerve system | Anxiety (0.83%), Depression (0.83%), Dizziness (0.83%), Masked face (0.83%) | |
| Respiratory system | Upper respiratory infection (0.83%) | |
| Heart | Cardiac Arrhythmias (0.83%) | |
| Adverse drug reactions that | at causal relationship with this product cannot be excluded are as follows: | |
| Sites | Adverse drug reactions (Incidence Rates) | |
| Eye | Ptosis (6.61%), Lagophthalmos (6.61%), Dry eye (6.61%), Photophobia (2.48%), Blepharoedema (0.83%), Chalasis (0.83%), Foreign body sensation (0.83%), Watery eye (3.31%) | |
| Lymphatic system | Edema (4.96%) | |
| Skin | Reactions at injection sites (2.48%) | |
| JAIII | | |

Other events reported in clinical studies with other botulinum toxin injections in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia and entropion, diffuse skin rash and local swelling of the eyelid skin lasting for several days following eyelid injection. In two cases of VII nerve disorder (one case of an aphakic eye), reduced blinking from injection of other botulinum toxin into orbicularis muscle led to serious corneal exposure, persistent epithelial defect, and corneal ulceration. Perforation occurred in a patient with aphakic eye, requiring corneal grafting. One case of acute applic closure glaucoma was reported one day after injection of botulinum toxin for blepharospasm, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm. Frequently, anopia or conjunctivitis has been reported and, in such instances, appropriate measures should be taken. In 660 patients with other botulinum toxin injections for 6 years in Korea, a total of 41 patients (6.2%) showed adverse reactions. Adverse reactions include ptosis in 17 patients (2.6%), local swelling in 5 (0.8%), lacimal disorders in 3 (0.5%), bulbar irritation in 3 (0.5%), bulbar irritation sin 3 (0.5%), used evalues in 2 (0.3%), hypertonia in 2 (0.3%), conjunctival congestion in 2 (0.3%), and eye pain in 1 (0.2%).

- 4) Glabellar lines: In Korean clinical studies in subjects with moderate to severe glabellar lines and ≥18 years of age and ≤65 years of age, adverse reactions were observed in 28.4% of subjects who received this product. Most adverse reactions were mild to or dge, burdle reactions are observed in Edward of budgets and burdle the clinical studies. The most request reactions there burdle adverse reactions was reported during the clinical studies. The most frequently reported adverse reactions include infections and infestations in 10 subjects (7.5%), eye disorders in 10 (7.5%), general disorders and administration site condition in 6 (4.5%), and skin and subcutaneous tissue disorders in 6 (4.5%). Adverse reactions for which causal relationship with this drug product could not be eliminated include injection site reaction in 4 subjects (3.0%) and eyelid ptosis in 6 (4.5%).
- 5) Cervical dystonia: In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of other botulinum toxin, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%) and headarde (11%). Other events reported in 2-10% of patients in another study in decreasing order of incidence include: increased cough, flu

Unter events reported in 2-10% or patients in another study in decreasing order or incluence inclueae: increased cough, itu syndrome, lumbago, rhinitis, dizziness, hypertonia, pain at injection sites, asthenia, oral dryness, speech disorder, fever, nausea and drowsiness. Very rare cases of stiffness, numbness, diplopia, ptosis and dyspnea have been reported. The most common severe adverse reaction associated with the use of other bottlinum toxin in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms in rare cases. In addition, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection is the provide the set of the section of the section of the provide the section of the s

of 120 Units of other botulinum toxin products for treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

The most frequently reported adverse reactions with other botulinum toxin injections in the treatment of spasmodic torticollis include: dysphagia, pain and soreness at injection sites, local weakness, symptomatic general weakness and fatigue. However, fatigue was also reported in the placebo group. Dysphagia, local weakness and symptomatic general weakness may be attribut-able to an extension of the pharmacology of botulinum toxin resulting from the spread of the toxin from injected muscles. Since the adverse reactions associated with dosage are more frequently observed in female patients, muscle mass should be taken into consideration when selecting the appropriate dose. Other adverse reactions include nausea, dizziness, headache, numbness, stiffness, and bruising. Post-marketing surveillance in Korea revealed that adverse reactions were observed in 3 patients out of total 68 patients (4.4%), including 2 cases of unknown myalgia (2.9%) and 1 case of muscle stiffness (1.5%).

6) Pediatric cerebral palsy: Safety of other botulinum toxin product for treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients was investigated. As expected for any intramuscular injection procedure, localized pain was associated with the injection in the patients. All treatment-related adverse reactions were mild to moderate in severity. Adverse reactions most frequently reported as related to treatment include recession, leg pain, leg (local) weakness, and general weak-ness. The percentages of patients who experienced these events at least once during the study are as follows:

| Other botulinum toxin product, $n=215$ | | |
|--|-------------------|------|
| | Recession | 9.3% |
| | Leg pain | 2.3% |
| | Weakness, local | 2.3% |
| | Weakness, general | 2.3% |

Recession may be attributable to change in ankle position and gait pattern and/or local weakness. Local weakness represents the expected pharmacological action of botulinum toxin. Other treatment-related adverse reactions reported in 1% of patients

the expected pharmacological action of botulinum toxin. Uther treatment-related adverse reactions reported in 1% of patients were: leg cramps, fever, knee pain, ankle pain, pain at the injection site post-treatment, and lethargy. Adverse reactions reported from clinical experience are as follows; [very frequent (>1/10); frequent (>1/10), <1/10] • Very frequent: viral infections, otitis • Frequent: myalgia, myasthenia, urinary incontinence, delirium, gait disturbance, fatigue, erythema, and feeling of burning. In the post-marketing surveillance study conducted in Korea, adverse reactions were reported from 8 cases (1.4%) out of 572 cases in total as follows: 4 cases of pain at injection sites (0.7%), 3 cases of fever (0.5%) and 1 case of eruption (0.2%). No unknown adverse reaction was reported in this study.

7) Primary axillary hyperhidrosis: Adverse reactions reported in clinical studies of other botulinum toxin in decreasing order of incident are as follows: [frequent (1>100, <1/10); rare (>1/1000, <1/100] Nervous system: headache (frequent); vascular system: flushing (frequent); gastrointestinal system: vomiting (rare); skin and subcutaneous tissue: hyperhidrosis (at sites other than axilla) (frequent), purius (rare); musculoskeletal and connective tissues: muscular weakness, myalgia, arthralgia, and severe pain (rare); general disorders and injection site conditions: reactions and pains at injection sites (frequent), weakness, edema at injection sites, and pain at injection sites (rare). When used for treatment of primary axillary hyperhidrosis, hidrosis at sites other than axilla was reported in 4.5% of patients within one month after injection. However, anatomical pattern for such hidrosis was not identified. This symptom disappeared within forur months in 30% of those patients.

within four months in 30% of those patients.

within four months in 30% of those patients. Arm weakness was reported in rare cases (0.7%). However, it was mild and transient, and did not require medical treatment. Recovery was completed without any aftereffects. This adverse reaction is expected to be associated with treatment or injection skills, or combination of thereof. In rare cases of reported muscular weakness, neurological examination may be considered. In addition, in order to assure correct intradermal injection, it is recommended to re-evaluate the injection skill prior to the second injection. injection

8) Muscular stiffness: Safety in 339 patients treated with other botulinum toxin product for upper limb spasticity associated with cerebral apoplexy was investigated. In general, most reported adverse reactions were mild to moderate. Adverse reactions reported in 1~4% of subjects and considered to have relationship with treatment include arm pain and hypertonia in decreasing order of incidence. Fever and cold symptoms were also reported in about 1% of subjects. Adverse reactions reported in less than 1% of subjects and version of incidence.

Fever and cold symptoms were also reported in about 1% of subjects. Adverse reactions reported in reas than 1% of subjects and considered to have relationship with treatment include in decreasing order of incidence: hyperaphia, arthralgia, asthenia, bursitis, dermatitis, headache, hypersensitivity at injection sites, dysphoria, vomit, paresthesia, postural hypotension, and pruritus. Safety in 82 patients treated with other botulinum toxin product for lower limb spasticity associated with cerebral apoplexy was investigated. Reported adverse reactions considered to have relationship with treatment include injury by accident (1.2%), imbalance (1.2%), and paresthesia (1.2%). Reported adverse reactions were mild or moderate. The second injection was given to 44 subjects in the open-label study among 56 subjects injected with other botulinum toxin products in a double-blind situation. Additionally reported, treatment-related adverse reactions include hypertonia (4.5%), as-thenia (0.2%) and parestave interior (0.2%).

thenia (2.3%), headache (2.3%) and hyperkinesis (2.3%).

9) Chronic migraine: The most frequently reported adverse reactions in double-blind, placebo-controlled study of other botulinum toxin product in 687 patients are summarized in the following table.

<Table> Adverse reactions more frequently (\geq 2%) reported in patients injected with other botulinum toxin product than in placebo-treated patients in two chronic migraine double-blind, placebo-controlled clinical trials

| Adverse reactions by body systems | Other botulinum toxin product 155 U~195 U (n=687) | Placebo (n=692) |
|---|--|---|
| <i>Nervous system disorders</i> Headache Migraine Facial paresis | 32 (5%) 26 (4%) 15 (2%) | 22 (3%) 18 (3%) 0 (0%) |
| <i>Eye disorders</i> Eyelid ptosis | 25 (4%) | 2 (<1%) |
| Musculoskeletal and connective tissue disorders Neck pain Musculoskeletal stiffness Muscular weakness Myalgia Musculoskeletal pain Muscle spasms | 60 (9%) 25 (4%) 24 (4%) 21 (3%) 18 (3%) 13 (2%) | 19 (3%) 6 (1%) 2 (<1%) 6 (1%) 10 (1%) 6 (1%) |
| General disorders and injection site Injection site pain | 23 (3%) | 14 (2%) |
| Vascular disorders Hypertension | 11 (2%) | 7 (1%) |

Discontinuations due to adverse reaction were 4% in the botulinum toxin group and 1% in the placebo group. The most frequent adverse reactions leading to discontinuation in the botulinum toxin group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis. Other adverse reactions that occurred more frequently in the botulinum toxin group compared to the placebo group at a fre-quency of not more than 1% include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% in botulinum toxin group and approximately 0.3% in the placebo group within the first week after treatment.

Detrusor overactivity associated with a neurologic condition: In double-blind, placebo-controlled study of other botulinum toxin product, the following adverse reactions were frequently reported within 12 weeks of injection for detrusor overactivity associ-10) Detr ated with a neurologic condition

<Table> Adverse reactions more frequently (\geq 2%) reported in patients injected with other botulinum toxin product than in placebo-treated patients within the first 12 weeks after intradetrusor injection in double-blind, placebo-controlled clinical trials

| Adverse reactions by body systems | Other botulinum toxin product 200 U (N=262) | Placebo (N=272) |
|---|--|--------------------|
| Infections and infestations Urinary tract infection | 64 (24%) | 47 (17%) |
| Renal and urinary disorders Urinary retention Hematuria | 45 (17%) 10 (4%) | 8 (3%) 8 (3%) |
| General disorders and injection site Fatigue | 10 (4%) | 3 (1%) |
| Psychiatric disorders Insomnia | 4 (2%) | 0 (0%) |

The following adverse reaction rates with other botulinum toxin product 200 U were reported at any time following initial injec-tion and prior to re-injection or study exit (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), fatigue (6%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), insomnia (3%), and muscle spasm (2%)

In the multiple sclerosis patients enrolled in the double-blind, placebo-controlled trials, the multiple sclerosis exacerbation an d rate (i.e. the number of multiple duct and 0.20 for

No change was observed in the overall safety profile with repeat dosing.

11) Post-marketing experience in foreign markets: There have been spontaneous reports of death, sometimes associated with dys-

phagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with other botulinum toxin product. [see 2] and 4) of "1. Warnings" under "Precautions"]. There have also been reports of adverse reactions involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. The exact relationship of these events to the botulinum toxin injection has not been established

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events The exact relationship of these events to the botulinum toxin injection has not been established.

The following adverse reactions have been identified during toxin injection has not been established. The following adverse reactions have been identified during postapproval use of other botulinum toxin product: abdominal pain, anorexia, brachial plexopathy, diarrhea, dyspnea, facial palsy, facial paresis, hyperhidrosis, hypoacusis, hypoaesthesia, localized numbness, malaise, muscle weakness, myalgia, paresthesia, pyrexia, radiculopathy, skin rash (including erythema multiforme and poriasiform eruption), timitus, vertigo, visual disturbances and vomiting. Because these events were 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.

5. General precautions

- 3) To the up product contains albumin, a derivative of human blood. When a drug product derived from human blood or plasma is administered into human body, the potential of infectious diseases by transmissible agents cannot be completely excluded. It may include pathogenic agent that is still unknown. In order to minimize the risks of such infection by transmissible agents, particular cares are given to the albumin manufacturing process, including virus removal and/or inactivation processes, in addition to careful screening of donors and appropriate testing of donation units.
- 2) Due to the nature of the disease being treated, the effects of this drug product on the ability to drive or to operate machines
- Due to the nature of the disease being freated, the energy of this drug product on the dump to the operate matching cannot be predicted.
 Cervical dystonia: Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleido-mastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.
- upper respiratory infection and oxysphagia. 4) Pediatric cerebral palsy: Botulinum toxin product is a drug product developed for treatment of local spasm in connection with standard treatments, but it is not intended to replace such treatment modalities. Botulinum toxin product is not likely to improve the motion at a joint affected by a permanent contracture. 5) Muscular stiffness: Botulinum toxin product is used for treatment of local stiffness investigated in connection with conventional standard treatments. Botulinum toxin product has not been shown to improve the range of motion at a joint affected by a fixed convention.
 - contracture
- Glabellar lines: Patients with facial palsy or ptosis symptoms, patients with infections, skin disorders or scars at proposed injection sites, patients who received facial plastic surgery, such as tissue augmentation, brow lift, and dermal resurfacing and patients who were deemed inappropriate because their glabellar lines were not flattened with fingers and so, their conditions could not be sufficiently improved by physical measures were excluded from the phase 3 study. Injection of this product should not be more frequent than every three months and minimum effective dose should be used.

6. Drug interactions

 The effects of other botulinum toxin products were potentiated by concomitant use of aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission, e.g. tubocurarine-type muscle relaxants. Concomitant use of aminoglycosides or spectriomycin is contraindicated. Polymyxin, tetracycline and lincomycin should be carefully used in patients injected with this product. this product.

Uns product. 2) The effects of administering different botulinum neurotoxin serotypes at the same time or within several months are unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin products before the effects of a previously administered botulinum toxin disappear.

7. Pregnancy and lactation

There are no adequate and well-controlled studies of this product in pregnant women. When pregnant mice and rats were injected There are no adequate and well-controlled studies of this product in pregnant women, when pregnant mice and rats were injected intramuscularly with other botulinum toxin in product during the period of organogenesis, the developmental NDEL (No Observed Effect Level) was 4 U/kg. Higher doses (8 U/kg or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification. In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg/day (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of dams. The rabbit appears to be a very sensitive species to this product. If the patient becomes pregnant after administration of this product, the patient should be apprised of potential risks, including abortion or fetal malformations that have been observed in rabbits. It is not known whether botulinum toxin is excreted in human milk. Because many drugs are excreted in human milk, caution should be excretised when this product is an enviroin woman. Administration of this product is not recommended should be exercised when this product is administered to a nursing woman. Administration of this product is not recommended during pregnancy or lactation.

8. Pediatric use

Safety and effectiveness of this product in patients below the age of 12 years (below the age of 16 years, for cervical dystonia) have not been established for blepharospasm and strabismus.

Safety and effectiveness in children and adolescents below the age of 18 years were not investigated for improvement of glabellar lines or treatment of primary axillary hyperhidrosis and detrusor overactivity associated with a neurologic condition.

9. Carcinogenicity, mutagenicity, teratogenicity and animal toxicity

Long-term studies in animals have not been performed to evaluate carcinogenic potential of this product. Animal toxicity

Animal toxicity In a study of other botulinum toxin product to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 U/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 U/kg (~12X the human dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injection of up to 100 U/kg (~33X the human dose).

10. Overdosage

10. Overdosage Signs and symptoms of overdose are not apparent immediately after injection. Should accidental injection or oral intake occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis. An antitoxin may be used in the event of immediate knowledge of overdose or wrong administration. The antitoxin will not reverse any botulinum toxin-induced muscle weakness effects already appeared by the time of antitoxin administration. The antitoxin will not reverse any botulinum toxin-induced muscle weakness effects already appeared by the time of antitoxin administration. If the muscles of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakneed, intubation and assisted respiration may be required until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

11. Precautions in administration

Prior to injection, this reconstitute freeze-dried product with a preservative-free, sterile saline. 0.9% Sodium Chloride Injection is the Prior to injection, this reconstitute freeze-dried product with a preservative-free, sterile saline. 0.9% sodum Chionde Injection is the recommended diluent. Draw up the proper amount of diluent in the syringe of appropriate size. Since this product is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the space of the label. This product should be administered within 24 hours after reconstitution. During this period, reconstituted product should be stored in a refrigerator (2-8°C). Reconstituted product should be clear, colorless and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Because this product and the diluent do not contain any preservative, one vial of the newly be sured for a prior to administration. this product should be used for a single patient.

12. Precautions in storage and handling

Unopened vials of this drug product should be stored in a refrigerator (2-8°C). Reconstituted product may be stored in a refrigerator (2-8°C) for up to 24 hours after reconstitution. For safe disposal, unused vials should be sterilized after dissolution in a small amount of water. Containers used (such as vials and syringes) should also be sterilized. Any residuals in vials or syringes should be inactivated using dilute hypochlorite solution (0.5%).

13. Information for patients

Patients should be encouraged to consult with their doctor about any and all concerns over effectiveness and/or risks of this product

Patients should be encouraged to consult with their doctor about any and all concerns over effectiveness and/or risks of this product. Careful attention should be paid to potential signs or symptoms of adverse reactions. Call your doctor or get immediate medical help if you experience any unusual symptoms after treatment with this product, including difficulty in swallowing, speaking or breathing, or muscle weakness. Such adverse reactions may happen hours to weeks after injection of this product. Patients with blepharospasm may have been in the extremely sedentary posture for a long time. Such patients should be cautioned to resume activity slowly and carefully after administration of this product. This product blocks neuromuscular transmission by blinding to acceptor sites on motor nerve terminals, entering the nerve termi-nals, and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, this product produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle any atomy, axonal sprouting may occur, and extra junctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by this product. The paralysis activity of botulinum toxin is effective for the relief of excessive abnormal contraction associated with blepharospasm. When injected into neck muscles, other botulinum toxin injection acts to provide relief from boto bicetive signs and subjective symptoms of spasmodic torticollis (cervical dystonia). These improvements may include reduced pain/discomfort, reduced hard rea-troin, reduced shoulder elevation, decreased size and strength of hypertrophic muscles. The efficacy of other botulinum toxin product in deviations of over 50 prism diopters, restrictive strabismus, Duane's syndrome with lateral rectus weakness, and secondary strabis-es to botulinum toxin type A may reduce the effectiveness of botulinum tox

Storage and Expiry date

Store at 2-8°C in hermetic container, 36 months from the date of manufacture

How supplied

50 Units/vial (1 vial)

Manufacturer : HUGEL, Inc.

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* You can get updated information from our web site (www.hugel.co.kr).

