Botulax® Injection 100 UNITS/Vial

hugel

IS31507

RX only

100 Units

Botulax®

Clostridium botulinum toxin type A

Composition

Each vial contains:

Active ingredient : Clostridium botulinum toxin type A (Strain: Clostridium botulinum CBFC26) (KFDA-approved specifications)	100units(U)*
Stabilizer : Human serum albumin (Korean Minimum Requirements for Biological Products)	0.5mg
Tonic adjuster : Sodium chloride (Korean Pharmacopoeia)	0.9mg

*One unit(U) of BOTULAX® Injection 100 Units/Vial corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) 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
2. Temporary improvement of serious glabellar wrinkles ranging from moderate to severe associated with corrugators muscle and/or procerus muscle activities in adults aged between 18 and 65

Dosage and administration

1. Blepharospasm

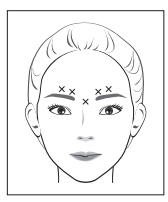
For blepharospasm, reconstituted BOTULAX® (see Dilution Table) is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25-2.5U (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the 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® treatment in a 30-day period should not exceed 200 U.

2. Glabellar lines

Reconstitute this product with 0.9% preservative-free, sterile saline to make 100 U/2.5 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 medially, and the procerus muscle and depressor supercilii 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 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 this product should be used for a single patient.

[Dilution Table]

Diluent added (0.9% Sodium Chloride Injection)	Resulting dose (U/0.1mL)
1.0mL	10.0U
2.0mL	5.0U
4.0mL	2.5U
8.0mL	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 administering 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 *Clostridium botulinum*, the information in this section should be fully understood and the recommended dosage and administration 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 frequencies 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 cervical dystonia 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.
3) Pre-existing neuromuscular disorders: Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy) or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) may be at increased risk of clinically significant systemic effects, including severe dysphagia and respiratory compromise from typical doses of this product. Published medical literatures with other botulinum toxin product have reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where patients have shown serious hypersensitivity to systemic effects of typical clinical doses. In some cases, dysphagia lasted several months and placement of a gastric feeding tube was required.
4) Dysphagia: Dysphagia is a 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 addition, deaths owing to aspiration pneumonia, as a complication of severe dysphagia, have been reported after treatment with botulinum 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 cardiovascular disease.
6) During administration of other botulinum toxin product for treatment of strabismus, retrobulbar hemorrhages sufficient to compromise 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, persistent 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 other means.
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 toxin 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 structures. 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 spasticity or for detrusor overactivity associated with a neurologic condition: In patients with upper limb spasticity 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 associated with 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:

1) Patients who are hypersensitive to any ingredient in the formulation of this product.
2) 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.
3) Patients with severe respiratory disorders, when used for treatment of cervical dystonia.
4) Pregnant women, women of childbearing potential or nursing mothers.

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

1) 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.
2) Patients under treatment with drugs with muscle relaxation activity, e.g., spectinomycin HCl, aminoglycoside antibiotics (gentamicin sulfate, neomycin sulfate, etc.), polypeptide antibiotics (polymyxin B sulfate, etc.), tetracycline antibiotics, lincomycin antibiotics (lincosamides), muscle relaxants (baclofen etc.), anti-cholinergic agents (scopolamine butylbromide, trihexylphenidil HCl, etc.), benzodiazepine and other similar drugs (diazepam, etizolam, etc.), and benzamide drugs (thiapride HCl, sulpiride, etc.). Muscle relaxation may be potentiated or risks of dysphagia may be increased.

4. Adverse drug reactions

1) General : 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, hot feeling or hypertonia at injection site or adjacent muscles may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin. When injected to patients with blepharospasm or cervical dystonia, some 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;
Ptosis 15.7%
Vertical deviation 16.9%
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.
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 ganglion damage (Adies pupil).
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.

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

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 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%)
Pain	Myalgia (1.65%)

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 angle 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%), lacrimal disorders in 3 (0.5%), bulbar irritation in 3 (0.5%), logophthalmos in 3 (0.5%), muscle weakness in 3 (0.5%), and eye dryness in 3 (0.5%). Unknown adverse reactions include traction at injection site in 2 patient (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 moderate and no serious adverse reaction 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 headache (11%).
Other events reported in 2-10% of patients in another study in decreasing order of incidence include: increased cough, flu 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 botulinum 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 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 attributable 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 weakness. 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 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 (>1/100, <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 products 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), pruitus (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 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.

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 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%), asthenia (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 (≥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)
Nervous system disorders		
Headache	32 (5%)	22 (3%)
Migraine	26 (4%)	18 (3%)
Facial paresis	15 (2%)	0 (0%)
Eye disorders		
Eyelid ptosis	25 (4%)	2 (<1%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (9%)	19 (3%)
Musculoskeletal stiffness	25 (4%)	6 (1%)
Muscular weakness	24 (4%)	2 (<1%)
Myalgia	21 (3%)	6 (1%)
Musculoskeletal pain	18 (3%)	10 (1%)
Muscle spasms	13 (2%)	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 frequency 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.

10) 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 associated with a neurologic condition.

<Table> Adverse reactions more frequently (≥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	45 (17%)	8 (3%)
Hematuria	10 (4%)	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 injection 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 annualized rate (i.e., the number of multiple sclerosis exacerbation events per patient-year) was 0.23 for other botulinum toxin product and 0.20 for placebo.
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 dysphagia, 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 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 psoriasiform eruption), tinnitus, 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

1) This drug 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 cannot be predicted.
3) Cervical dystonia: Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid 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 upper respiratory infection and dysphagia.
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 contracture.
6) 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

1) 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 spectinomycin is contraindicated. Polymyxin, tetracycline and lincomycin should be carefully used in patients injected with this 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 product 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 intramuscularly with other botulinum toxin product during the period of organogenesis, the developmental NOEL (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 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
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

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.
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 weakened, 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 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 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. 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 binding to acceptor sites on motor nerve terminals, entering the nerve terminals, 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 may atrophy, 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 both objective signs and subjective symptoms of spasmodic torticollis (cervical dystonia). These improvements may include reduced pain/discomfort, reduced head rotation, 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 strabismus caused by prior surgical over-recession of the antagonist has not been clearly established or repeated injections may be required for treatment of such conditions. For other botulinum toxin product, it was reported that botulinum toxin is ineffective in chronic paralytic strabismus and only surgical procedure is effective in reducing conjunctiva antagonist contracture. The presence of antibodies to botulinum toxin type A may reduce the effectiveness of botulinum toxin therapy. In clinical studies, reduced effectiveness due to antibody production was observed in one patient with blepharospasm receiving 3 doses of botulinum toxin (92 U in total) over a 6-week period and in several patients with torticollis who received multiple doses experimentally (over 300 U) in one month. For this reason, the dose of this product for blepharospasm and strabismus should be kept in any case below 200 U in one month.

Storage and Expiry date

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

How supplied

100 Units/vial (1 vial)

Manufacturer : HUGEL, Inc.

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www.hugel.co.kr ☎ 82-33-255-3882

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

Botulax® Injection 100 UNITS/Vial hugel IS31507

208 X 360mm