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Botulax® Injection 100 units/vial hugel

RX Only

IS31502

100 Units

Botulax®

Botulinum Toxin Type A

Composition

Each vial contains
Active ingredient : Clostridium botulinum toxin type A 100units(U) * (attached specifications),
Stabilizer : Human serum albumin 0.5mg (attached specifications),
Tonic adjuster : Sodium chloride (KP) 0.9mg
* One unit(U) of BOTULAX® corresponds to the calculated median intraperitoneal lethal dose (LD50) in mice.

Description

It appears as a lyophilized white powder for injection in a colorless transparent vial.

Indication

It is indicated for the treatment of benign essential blepharospasm in patients 18 years of age and above.

Dosage and administration

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 (0.05mL to 0.1mL 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, following which the procedure can be repeated. 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 5.0U per site. Some tolerance may be found when the drug is used in treating blepharospasm if treatments are given any 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 200U.

Dilution Technique

Prior to injection, reconstitute freeze-dried BOTULAX® with sterile normal saline without a preservative. 0.9% Sodium Chloride Injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe. Since the drug 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 on the label. BOTULAX® should be administered within four hours after reconstitution. During this time period, reconstituted BOTULAX® should be stored in a refrigerator (2-8°C). Reconstituted BOTULAX® 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 the drug and diluent do not contain any preservative, one vial of BOTULAX® 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 0.1mL. A decrease or increase in dose is also possible by administering a sma ller or larger injection volume - from 0.05mL (50% decrease in dose) to 0.15mL (50% increase in dose).

Precautions

1. Warnings Since the active constituent in this drug is Clostridium botulinum toxin type A neurotoxin which is derived from Clostridium botulinum, the recommended dosages and frequency of administration should be observed with a full understanding of the precautions in use. Physicians administering the drug must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyographic techniques is also required for the administration of the drug. The recommended dosage and frequency of administration for BOTULAX® 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. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. 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 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 rarely reported with other botulinum toxin injections. These reactions include anaphylaxis, urticaria, soft tissue edema and dyspnea. One fetal case of anaphylaxis has been reported in which lidocaine was used as a diluent but the causal agent cannot be reliably determined. If such a reaction occurs, further injection of the drug 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 laternal sclerosis, or motor neuropathy) or neuromuscular junctional 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 botulinum toxin injection. Published medical literature with other botulinum toxin injection has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

4) Dysphagia : Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.

5) There have also been rare reports of adverse events with other botulinum toxin injection involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

6) Lack of Interchangeability between Botulinum Toxin Products : They are not interchangeable with other preparations of botulinum toxin products. Therefore, units of biological activity of botulinum toxin cannot be compared or converted into units of any other botulinum toxin products assessed with any other specific assay method.

2. Contraindication

BOTULAX® should not be administered when;
1) The patients have known hypersensitivity to any ingredient in the formulation of BOTULAX®.

2) The patients have neuromuscular junctional disorders (e.g., myasthenia gravis, Lambert-Eaton syndrome or amyotrophic laternal sclerosis). (The diseases may be exacerbated due to the muscle relaxation activity of the drug.)

3) The drug is used for the treatment of cervical dystonia in the patients with severe respiratory disorder.

4) The patients are pregnant women, women of childbearing potential, or mothers under lactation.

3. Precautions

BOTULAX® should be administered with caution in ;

1) Patients under treatment by 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 treatments by drugs with muscle relaxing activity, e.g., spectinomycin HCl, aminoglycoside antibiotics (gentamicin sulfate, neomycin sulfate, etc.), polypeptide antibiotics (polymixin B sulfate, etc.), tetracycline antibiotics, lincomycin antibiotics (lincosamides), muscle relaxants (baclofen etc.), anticholinergic agents (scopolamine butylbromide, trihexylphenidil HCl, etc.), benzodiazepine and the similar drugs (diazepam, etizolam, etc.), benzamide drugs (thiapride HCl, sulpiride, etc.). [Muscle relaxation may be potentiated or risks of dysphagia may be increased.]

4. Adverse 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 botulinum toxin. There have also been rare reports of adverse events 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 injection 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 events occur within the first week following injection of the drug and while generally transient may have duration of several months. Local pain, tenderness and/or 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 in patients with blepharospasm or cervical dystonia, some distant muscles from injection site can show increased electrophysiologic jitter (rapid variation in a waveform) which is not associated with clinical weakness or other types of electrophysiologic abnormalities.

2) Strabismus
Extraocular muscles adjacent to the injection site can be affected, causing ptosis or vertical deviations, especially with higher doses of the drug. The incidence rates of these adverse effects with other botulinum toxin injections were as follows ; in 2058 adults who received a total of 3650 injections for horizontal strabismus, ptosis were observed in 15.7% of the patients and vertical deviations were in 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 syndromes. The incidence of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection. Ptosis (0.3%) and vertical deviation greater than two prism diopters (2.1%) were reported to persist for over six months in 5587 injections of horizontal muscles in 3104 patients with other botulinum toxin injection. In these patients, the injection procedure itself caused nine scleral performations. 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). One patient developed anterior segment ischemia after receiving other botulinum toxin injection into the medial rectus muscle under treatment for esotropia.

3) Blepharospasm

In a study of blepharospasm patients who received an average dose per eye of 33U (injected at 3 to 5 sites) of other botulinum toxin injections, the most frequently reported treatment-related adverse reactions were ptosis (20.8%), superficial punctuate keratitis (6.3%) and eye dryness (6.3%). All of these events were mild to moderate except for one case of ptosis which was rated severe. Other events reported in prior 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 other botulinum toxin injections of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, and corneal ulceration. Perforation occurred in the aphakic eye and required corneal grafting. A report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, 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, which required appropriated measures 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 included 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%), eye dryness in 3. Adverse reactions obscure in causality included 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) Cervical dystonia

The most frequently reported adverse events with other botulinum toxin injections in the treatment of spasmodic torticollis included pain and soreness at injection sites, local weakness, symptomatic general weakness and fatigue. However, fatigue was also reported in patients treated with placebo. Dysphagia and local 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 events include; nausea, dizziness, headache, numbness, stiffness, and bruising.

5) Pediatric cerebral palsy

Safety tests of BOTOX® for the treatment of dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients was performed. As is expected for any intramuscular injection procedure, localized pain was associated with the injection in the patients. All treatment-related adverse events were mild-to-moderate in severity. The adverse reactions most frequently reported as related to treatment include recession, leg pain, leg (local) weakness, and general weakness. The percentage of patients who experienced these events at least once during the study are summarized below:

	BOTOX®, n=215
Recession	9.3%
Leg pain	2.3%
Weakness, local	2.3%
Weakness, general	2.3%

Recession may be attributable to a 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.

5. General precautions

1) This drug contains albumin, a derivative of human blood. When a medicinal product derived from human blood or serum is administered in human body, the potential of infectious diseases by transmissible agents cannot be completely excluded. It may include any pathogenic agent that is still unknown. In order to decrease the risks of infection by transmissible agents, particular cares including appropriate assay methods are given to the controls of the donors and donation site, to the manufacturing process and to the virus removal/inactivation process.

2) Due to the nature of the disease being treated, the effects of the drug on the ability to drive or to operate machines cannot be predicted.

3) During the administration of other botulinum toxin injection for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetrations into the orbit. 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.

4) Blepharospasm

Reduced blinking from botulinum toxin injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. One case of other botulinum toxin injection 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, 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.

6. Drug interactions

1) The effect of other botulinum toxin may be potentiated by aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission e.g. tubocurarine-type muscle relaxants. Concomitant use of BOTULAX® with aminoglycosides or spectinomycin is contraindicated. Polymyxins, tetracyclines and lincomycin should be used with caution in the BOTULAX® -treated patient.

2) The effect of administering different botulinum neurotoxin serotypes 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.

7. Pregnancy and lactation

Safety in pregnant women and nursing mothers has not been established in this drug. Other botulinum toxin injection has been shown to produce abortions and effects at daily doses of 0.125U/kg/day and at 2U/kg and higher in rabbits; whereas in rats and mice, no abortions or effects were observed when up to 4U/kg of botulinum toxin were injected. Doses of 8 and 16U/kg in rats and mice have been shown to be associated with reduced fetal body weight and/or delayed ossification of the hyoid bone, which may be reversible. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTULAX® is administered to a nursing woman. BOTULAX® is contraindicated in pregnancy and lactation.

8. Pediatric use

Safety and effectiveness in children below the age of 18 have not been established.

9. Carcinogenesis, mutagenesis, impairment of fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential of botulinum toxin.

10. Overdosage

Signs and symptoms of overdose are not apparent immediately post-injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for up to several weeks for signs or symptoms of systemic weakness or muscle paralysis.

An antitoxin is available in the event of immediate knowledge of an overdose or misinjection. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already appeared by the time of antitoxin administration.

11. Precaution in use

Unopened vials of BOTULAX® should be stored under refrigeration (2-8°C). After reconstitution, BOTULAX® should be stored in a refrigerator (2-8°C) for up to 4 hours prior to use.

For safe disposal, unused vials should be sterilized after melting it with a little amount of water. Equipment used with the drug (such as syringes) should also be sterilized. The residual BOTULAX® should be inactivated using dilute hypochlorite solution(0.5%).

12. Information for patients

BOTULAX® may cause serious side effects that can be life threatening. Call your doctor or get immediate medical help if you experience any negative symptoms after the treatment with BOTULAX®. Problems of swallowing, speaking, breathing, or muscle weakness could happen hours to weeks after the injection of BOTULAX®.

Patients with blepharospasm may have been extremely sedentary for a long time. Such patients should be cautioned to resume activity slowly and carefully after the administration of BOTULAX®. BOTULAX® blocks neuromuscular transmission binding to acceptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, BOTULAX® produces partial chemical denervation of the muscle resulting in a localized muscle activity reduction. 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 BOTULAX®.

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 another botulinum toxin product in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist has not been established or repeated injections may be required for the treatment.

Botulinum toxin is ineffective in chronic paralytic strabismus and only surgical repair is effective to reduce antagonist contracture.

Presence of antibodies to botulinum toxin type A may reduce the effectiveness of botulinum toxin therapy. In clinical studies, reduction in effectiveness due to antibody production has occurred in one patient with blepharospasm receiving 3 doses of botulinum toxin over a 6 week period totaling 92U, and in several patients with torticollis who received multiple doses experimentally, totaling over 300U in a one month period. For this reason, the dose of BOTULAX® for blepharospasm should be kept in any case below 200U in a one month period.

Storage

The unopened lyophilized vial should be stored in a refrigerator (2-8°C).

How supplied

BOTULAX® is supplied in a single use vial.

Expiration

The shelf-life of BOTULAX® is 24 months from the manufacturing date.

Manufacturer: HUGEL, Inc.

941 Yulmun-ri, Sinbuk-eup, Chuncheon-si, Gangwon-do, Korea
www.hugel.co.kr

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