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SOLUTIONS

BOTULAX® 100u (Korean) Product Specifications

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Botulax®

Botulinum Toxin Type A

A New Horizon of Botulinum Toxin Type A

hugelpharma

About hugel & hugelpharma

Hugel & Hugel Pharma keep evolution into a top-tier pharmaceutical company that meets the needs of both aesthetic and pharmaceutical market providing botulinum toxin, filler and medical devices with high quality.

2001
- Establishment of Hugel Inc.

2003
- Success in purification of botulinum toxin type A protein

2006
- Completion of non-clinical trial for botulinum toxin type A

2009
- Establishment of Hugel pharma as affiliated company of Hugel Inc.
- Completion of Phase III clinical trial for blepharospasm
- Product launching of Botulax® in Japan

2010
- Product launching of Botulax® in Korea

2011
- Product registration in Thailand

2012
- Completion of Phase III clinical trial for glabellar lines

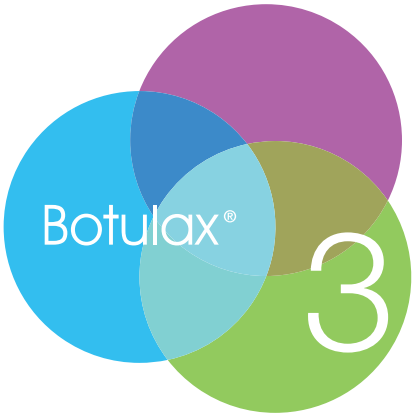
* Botulax® is also registered in 7 countries including Korea, Thailand, Colombia, and Chile, and expected to be registered in more than 4 countries within the year of 2012.

* Botulax® is also being sold worldwide under the names of Regenox®, Zentox® and Reage®.

Product Specifications

	Botulax® 50U	Botulax® 100U	Botulax® 200U
Active Ingredient	*Clostridium Botulinum Toxin* Type A		
Complex Size	900kDa		
Appearance	Freeze-dried		
Potency	KFDA / In-House 40-62 / 45-55	KFDA / In-House 80-125 / 95-115	KFDA / In-House 160-250 / 195-240
Protein (ng/ Vial)	< 2.5	< 5	< 10
Endotoxin Level (EU/ Vial)	KFDA / In-House <0.5 / <0.175	KFDA / In-House <1.0 / 0.175	KFDA / In-House <1.0 / 0.175
PH	6.5±0.5		
Moisture	Less than 3%		
Storage	2~8°C		
Expiration	24 months from the date of manufacture		

Advantages of Botulax®



Better

Potency — Botulax® is controlled more strictly than KFDA specifications.

Price — Botulax® provides reasonable price for its quality.

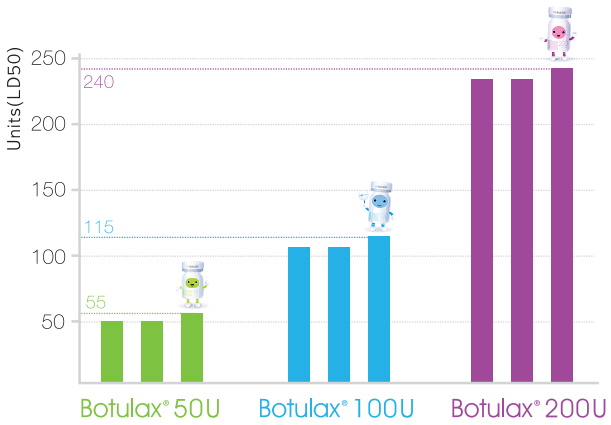
Service — Botulax® provides the customized services to all the users since doctors in aesthetic fields have participated in developing products.

Quality & Stability

Specialized Quality

Botulax® keeps stabilized potency in each product followed by strict quality control.

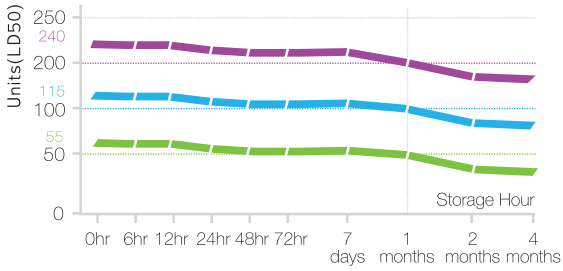
SPECIFICATIONS / TYPE	KFDA	In-House
Botulax® 50U	40-62	45-55
Botulax® 100U	80-125	95-115
Botulax® 200U	160-250	195-240



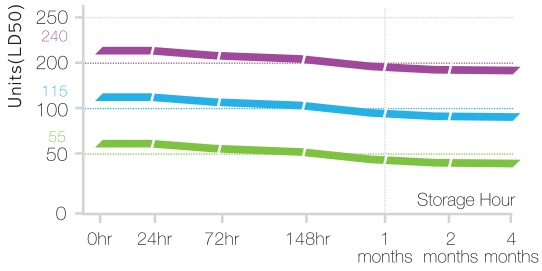
Stability After Reconstitution

Botulax® shows stable potency on the condition of cold storage or freezer after reconstitution.

Cold Storage after Reconstitution



Freezer Storage after Reconstitution



* It is recommended to use Botulax® within 24 hours after reconstitution followed by directions for the use of medicine.

Clinical Study in Blepharospasm

Essential Blepharospasm

This clinical study was conducted to evaluate the safety and efficacy of Botulax® compared to other botulinum toxin type A product (Botox® from Allergan, USA) in essential blepharospasm.

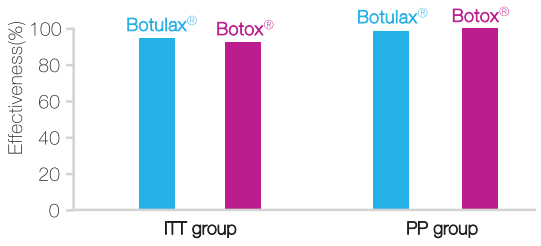
Subjects; 225 patients diagnosed with essential blepharospasm and grade 2 to 4 spasms (Scott Method)

Methodology; A double blinded, randomized assignment, active drug comparative, multi-center, Phase III clinical study

Trial Period; From April 21 2008 to July 24. 2009

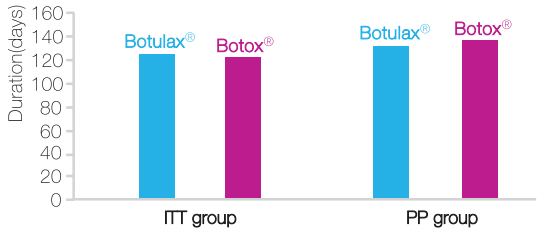
Effectiveness after administration

	Botulax®, n(%)	Botox®, n(%)
ITT group	114/121 (94.2)	97/104 (93.3)
PP group	91/92 (99)	82/82 (100)



Duration after administration

	Botulax®	Botox®	*P-value(>0.05)*
ITT group	122	120	0.36
PP group	131	134	0.65



* ITT: Intention To Treat
* PP: Per- Protocol

Conclusion; Botulax® showed non-inferior efficacy and duration to comparator drug. No serious adverse drug reaction.

* Reference; Clinical study results of Hugel Inc.

Product Information

Composition

50U_Each vial contains

- Active ingredient: Clostridium botulinum toxin type A (Strain: Clostridium botulinum CBFC26) (attached specifications) 50units(U)*
- Stabilizer: Human serum albumin (Korean Minimum Requirements for Biological Products) 0.25mg
- Tonic adjuster: Sodium chloride (KP) 0.45mg

100U_Each vial contains

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

200U_Each vial contains

- Active ingredient: Clostridium botulinum toxin type A (Strain: Clostridium botulinum CBFC26) (attached specifications) 200units(U)*
- Stabilizer: Human serum albumin (Korean Minimum Requirements for Biological Products) 1.0mg
- Tonic adjuster: Sodium chloride (KP) 1.8mg

* One unit (U) of BOTULAX® 50/100/200 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 and should become colorless transparent liquid when the diluent (physiological saline) is added.

Indication

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

Dosage & Administration

For blepharospasm, reconstituted BOTULAX® 50/100/200 (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® 50/100/200 treatment in a 30-day period should not exceed 200U.

Dilution Technique

Prior to injection, reconstitute freeze-dried BOTULAX® 50/100/200 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® 50/100/200 should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTULAX® 50/100/200 should be stored in a refrigerator (2-8°C). Reconstituted BOTULAX® 50/100/200 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® 50/100/200 should be used for a single patient

[Dilution Table]

BOTULAX® 50U		BOTULAX® 100U		BOTULAX® 200U	
Diluent added (0.9% Sodium Chloride Injection)	Resulting dose (U/0.1mL)	Diluent added (0.9% Sodium Chloride Injection)	Resulting dose (U/0.1mL)	Diluent added (0.9% Sodium Chloride Injection)	Resulting dose (U/0.1mL)
0.5mL	10.0U	1.0mL	10.0U	1.0mL	20.0U
1.0mL	5.0U	2.0mL	5.0U	2.0mL	10.0U
2.0mL	2.5U	4.0mL	2.5U	4.0mL	5.0U
4.0mL	1.25U	8.0mL	1.25U	8.0mL	2.5U

Note: These dilutions are calculated for an injection volume of 0.1mL. A decrease or increase in dose is also possible by administering a smaller 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® 50/100/200 should not be administered when; 1) The patients have known hypersensitivity to any ingredient in the formulation of BOTULAX® 50/100/200. 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 patients are pregnant women, women of childbearing potential or nursing mothers.

3. Precautions

BOTULAX® 50/100/200 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.), anti-cholinergic 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) Blepharospasm

Adverse events 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 events were ptosis, lagophthalmos and eye dryness, and most of them were mild or moderate. Regardless of causal relationship, the adverse events per occurrence site are as follows:

Occurrence site	Adverse events (Occurrence 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	Injection site reaction (4.13%), Flushing (0.83%)
Pain	Headache (2.48%), Myalgia (1.65%)
Stomach related	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%)

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%).

Storage: Store at 2-8°C in hermetic container.

How supplied: BOTULAX® 50/100/200 is supplied in a single use vial.

Expiration: The shelf-life of BOTULAX® 50/100/200 is 24 months from the manufacturing date.

Manufactured by hugel bio medical products

Distributed by hugel pharma

Manufactured by hugel bio medical products

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