Vellux

CLOSTRIDIUM BOTULINUM TOXIN TYPE A

[Composition]
Each vial contains:
Active ingredient: Clostridium botulinum toxin type A (In-house) 100units
Stabilizer: Human serum albumin (In-house) 0.5 mg
Tonic adjuster: Sodium chloride (Korean Pharmacopoeia) 0.9 mg

[Description]
A white or slightly yellow dried product in a clear colorless vial and clear transparent solution when dissolved in saline.

[Indications]
Temporary improvement of moderate to severe glabellar wrinkles due to activities of the corrugator and/or procerus muscles in adults between the ages of 19 and 65.

[Dosage and administration]
Glabellar wrinkles
Dilute with preservative-free sterile 0.9 % saline to 100 U/2.5 mL (4 U/0.1 mL).
Using 30-gauge needles, inject 0.1 mL into 2 points for each corrugator muscle and 1 point for the procerus muscle, for a total of 20 U in 5 points. (Refer to figure below)

To reduce the incidence of complications of ptosis, avoid injecting near the levator palpebrae superioris muscle in patients with large brow depressors. When injecting into the medial corrugator and central brow, injection should be performed at least 1 cm from the upper ciliary margin.

Be careful to avoid intravascular injection, and apply firm pressure to the supraorbital rim using the thumb or index finger to prevent inferior migration of the drug. The needle should point centrally and superiorly during the injection, and exact dose must be injected.

The corrugator and orbicularis oculi muscles move the central forehead to create glabellar wrinkles. The procerus and depressor supercilii muscles pull the forehead inferiorly.
These muscles create frown lines or glabellar wrinkles. The location, size, and use of muscles vary between individuals, and the effective dose is determined by overall observation of the movement of surface muscles by each patient.

The effect of this drug for glabellar wrinkles lasts for around 3 to 4 months. The safety and efficacy of this drug for frequent administration has not been clinically evaluated, and is not recommended.

[Dilution method]
To dissolve this dried drug, sterilized saline without preservatives is used.
The recommended diluent is 0.9 % sodium chloride solution. Put an adequate amount of diluent into an adequately sized syringe. Generation of bubbles or any other similar turbulences may result in denaturation of the drug, so the diluent should be injected slowly into the vial.
If the diluent was not injected into the vial in a vacuum state, the vial must be disposed of.
Record the diluted date and time on the label, and use the solution within 24 hours of dissolution.
The diluted solution should be refrigerated (2-8℃). The dissolved solution should be transparent without any visible foreign matters.
Parenteral agents should be checked carefully for any foreign matters or discolorations before administration. Since no preservatives are included in this drug or the diluent, 1 vial should be used or only 1 patient.

[Dilution Table]

Added diluent (0.9% Sodium Chloride injection)	*Resulting dose (U/0.1 mL)*
1.0 mL	*10.0 U*
2.0 mL	*5.0 U*
4.0 mL	*2.5 U*
8.0 mL	*1.25 U*

Note: The diluent is calculated based on 0.1 mL injection dose. The administration dose can also be controlled by increasing the injection dose. 0.05 mL (50 % decrease from the administration dose) ~0.15 mL (50 % increase from the administration)

[Precautions]
1. Beware:
As the active ingredient in this product is the Clostridium botulinum toxin type A produced by the Clostridium botulinum bacteria, precautions during use should be fully comprehended, and the dose and method of use should be strictly followed. The doctor using this product should be fully aware

of neuromuscular structures, periorbital anatomy, any anatomical changes due to past surgeries, and the standard electromyogram techniques. The recommended administration dose and frequency should not be exceeded.

1) Long distance diffusion of the toxin effect:
The botulinum toxin may diffuse to other areas from the injection area to cause botulinum toxicity. Symptoms such as rapid-onset muscle weakness, fatigue, hoarseness, dysphonia, dysarthria, loss of bladder control, dyspnea, dysphagia, diplopia, and ptosis may ensue. Symptoms such as dyspnea and dysphagia may be lethal, and there have been case reports of death from diffusion of toxin.
A particularly high-risk group is the children undergoing treatment for spastic cerebral palsy.
But same symptoms may be also seen in adults undergoing treatment for spastic cerebral palsy or other symptoms. There have been reports of above adverse events occurring at doses for treating cervical dystonia, even at lower doses.

2) Hypersensitivity:
There have been rare reports of severe or immediate hypersensitivity in other botulinum toxin agents.
These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and respiratory distress. In the one case of anaphylaxis, lidocaine was used as the solvent and the causing substance was not reliably identified. If these symptoms ensue after administration of this product, administration should be stopped and appropriate treatment should be performed.

3) In case neuromuscular disorders are present:
In patients with peripheral motor nerve disorders (e.g., amyotrophic lateral sclerosis, motor neuropathies) or neuromuscular junction disorders (e.g., myasthenia gravis, Lambert-Eaton syndrome), conventional doses of botulinum toxin may result in increased risk of marked systemic reactions including severe dysphagia and dyspnea. Clinical literatures have reported rare severe hypersensitivity reactions from systemic effects of conventional dose botulinum toxin administered in patients with diagnosed or undiagnosed neuromuscular disorders. In some of these cases, dysphagia persisted for several months, necessitating the use of nasogastric tubes.

4) Dysphagia:
Dysphagia is a common adverse event reported in patients undergoing treatment for cervical dystonia using botulinum toxin. Rarely in these patients, dysphagia was very severe and necessitated the use of nasogastric tubes. There has been a report of death from aspiration pneumonia due to dysphagia.

5) There have been rare reports of cardiovascular adverse events including arrhythmia and myocardial infarction from the administration of other botulinum toxin agents, and some were lethal.
Some of the patients had risk factors such as pre-existing cardiovascular disorders.

6) Penetration of periorbital structures in treating strabismus using other botulinum toxin agents have resulted in retrobulbar hemorrhages that may risk retinal circulation. Use of appropriate equipment to decompress the easily influenced periorbital pressure is recommended.
Also there have been cases of orbital penetration of a needle. To diagnose situations such as this, ophthalmoscopic examination is necessary. Paralysis of more than one extraocular muscle may be induced to result in spatial disorientation, diplopia, and past-pointing. Closing the affected eye may reduce these symptoms.

7) Blepharospasm:
Injection of other botulinum toxin agents to the orbicularis oculi muscles of facial palsy patients may result in corneal exposure, persistent epithelial defects and corneal ulcers due to decreased blinking.
In an aphakic eye, use of another botulinum toxin agent resulted in corneal perforation in one case, necessitating corneal transplantation. In patient with past surgical history, careful testing on corneal sensation should be performed, and ectropion can be decreased by avoiding injection to the lower eyelids. Any type of corneal epithelial defects should be thoroughly treated. Treatment includes protective eye drops, ointment, therapeutic soft contact lenses, and eye patching.

8) No interchangeability:
Toxin content may differ between botulinum toxin agents, and a unit of one product cannot be converted to another.

9) Injection into or around anatomically vulnerable structures:
When injecting into or around anatomically vulnerable structures, care should be taken.
There have been reports of severe adverse events including death when injecting other botulinum toxin agents into the salivary glands, esophagus, and stomach and around the mouth-tongue-pharynx. Some patients had underlying dysphagia or significant debilities (no safety and efficacy levels have been established for indications including these injection sites). There has been a report of pneumothorax related to the injection procedure during injection of botulinum toxin around the thorax. Care should be taken when injecting near the lungs, especially around the apices.

10) Influences on the pulmonary functions of adults with respiratory disorders undergoing treatment for spasticity of the upper limbs or hyperactivity of the neurogenic bladder. Administration of other botulinum toxin agents in some upper limb spasticity patients with respiratory disorders was reported to have resulted in decreased pulmonary functions (decrease in forced vital capacity [FCV] ≥ 15%).
Upper respiratory tract infections have been reported as more frequent compared to placebo.
(Refer to article 11 below) Administration of other botulinum toxin agents in some hyperactive neurogenic bladder patients with respiratory disorders have resulted in decreased pulmonary functions (decrease in forced vital capacity [FCV] ≥ 15%).

11) Bronchitis and upper respiratory tract infections in patients undergoing treatment for upper limb spasticity. Bronchitis was reported as more frequent in upper limb spasticity patients treated with other botulinum toxin agents compared to placebo. When treating upper limb spasticity in patients with decreased pulmonary functions, upper respiratory tract infection was reported as more frequent in patients treated with other botulinum toxin agents compared to a placebo.

2. Administration is prohibited in the following patients:
1) Patients with hypersensitivity to this product's substance.
2) Patients with systemic neuromuscular junction disorders (e.g., myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, etc.) - may aggravate the disease due to muscle relaxation.
3) When treating cervical dystonia, patients with severe pulmonary function impairments.
4) Pregnant women or women with a possible pregnancy, and lactating women.
5) When injecting into detrusor muscles, patients with urinary tract infections or patients with acute urinary retention who does not perform regular clean intermittent catheterization (CIC).

3. Use cautiously in the following patients:
1) Patients taking muscle relaxants (tubocurarine chloride, dantrolene sodium, etc.) - augmentation of muscle relaxation and increased risk of incidence of dysphagia.
2) Patients taking drugs with muscle relaxing effects such as spectinomycin hydrochloride, aminoglycosides (gentamicin sulfate, neomycin sulfate, etc.), polypeptide antibiotics (polymyxin b sulfate, etc.), tetracyclines, lincosamides, muscle relaxants (baclofen, etc.), anticholinergics (scopolamine butylbromide, trihexyphenidyl hydrochloride), benzodiazepins and other similar agents (diazepam, etizolam, etc.), benzamides (tiapride hydrochloride, sulpiride, etc.) – augmentation of muscle relaxation and increased risk of incidence of dysphagia.

4. Adverse events
1) General details
There have been rare reports of death after botulinum toxin treatment due to dysphagia, pneumonia, and/or severe weakness or anaphylaxis. Also, there have been rare reports of cardiovascular adverse reactions including arrhythmia and myocardial infarction. The causal relationship between these adverse events and botulinum toxin has not been clarified. The following adverse events have been reported in other botulinum toxin agents and its causal relationship with botulinum toxin was unknown: skin rash (including maculopapular rash, urticaria, and psoriatic rash), pruritus, allergic reactions Generally, these adverse events occur within 1 week of injection, and are usually transient, but may persist for several months. Local pain, local infection, inflammation, paresthesia, decreased sensation, pressing pain, contusion, injection site retraction, injection site edema, rash, leeding, injection site burning sensation, and hypertonia of muscles near the injection site may ensue.
Local weakness of the injection site reflects the redicted pharmacologic effect of the botulinum toxin. Weakness of muscles near the injection site may occur due to diffusion of the toxin.
After administration of this product in patients with blepharospasm, and cervical dystonia, there is a possibility that weakness of muscles away from the injection site or electrophysiologic jitters (momentary scattering of waves) unrelated to electrophysiologic abnormalities may occur.

5. General cautions
1) This product contains human albumin derived from human blood. When administering drugs manufactured from human blood or plasma, the possibility of infectious diseases due to transfer of infectious materials cannot be completely excluded. This can also include pathogens unknown until now. To decrease the risk of transfer of such infectious materials, adequate diagnoses are done during the manufacturing process to screen donors and donor sites, and processes to eliminate and/or inactivate these infectious materials are also included.
2) Due to the disease that is being treated, the effect of this product on machine operations and driving skills cannot be predicted.
3) Glabellar wrinkles: Injection of botulinum toxin agents to the orbicularis oculi muscles of facial palsy patients may result in corneal exposure, persistent epithelial defects and corneal ulcers due to decreased blinking. In the case of skin abnormalities at the injection site such as infections, skin diseases, or scars, prior history of face lifting or insertion of permanent implants, prior history of facial palsy or blepharospasms, and if the glabellar wrinkles are not improved by physical force such as smoothing by hand, as these patients have been excluded from the phase 3 safety and efficacy clinical trial, the patients should be warned. Injection of this product should be done at least 3 months apart, and the minimal effective dose should be used.

6. Drug interactions

1) Generally, using botulinum toxin with aminoglycoside antibiotics or drugs that inhibit muscle-nerve transmissions (tubocurarine muscle relaxants) increases the potency of the botulinum toxin agent.
Persistent concomitant use with aminoglycosides or spectinomycin is contraindicated.
Polymyxin, tetracycline, and lincomycin should be used with caution in patients undergoing treatment with this product.
2) The effect of the use of other botulinum neurotoxin serotypes concomitantly or within several months has not been clarified. Administration of other botulinum toxins before the effect of the prior botulinum toxin injection wears off may result in excessive muscle weakness.

7. Administration pregnant and lactating women

There are no adequate controlled studies for this drug on the administration to pregnant women. When other botulinum toxin agents were administered intramuscularly in pregnant mice and rats, the NOEL (No Observed Effect Level) was 4 U/kg, and high doses (8 or 16 U/kg) resulted in decreased fetal weight and/or delayed ossification. In dose-setting studies on rabbits, daily administration of 0.125 U/kg/day (6~18 days of pregnancy) and 2 U/kg/day (6~13 days of pregnancy) resulted in severe reproduction toxicity, abortions, and lethal mutations, and in high doses, fetal death.
Rabbits were confirmed to be a very sensitive species to this drug. If pregnancy is known after administration of this drug, the risk of abortions or lethal mutations observed in rabbits should be informed. It is unknown if botulinum toxin is secreted through breast milk. Many drugs are secreted through breast milk, so close observation is mandatory when administering to lactating women.
Use of this product during pregnancy or lactation is not recommended.

8. Administration in pediatric patients

Other botulinum toxin agents have undergone no studies to evaluate the safety and efficacy on the glabellar wrinkles of children and teenagers under the age of 18.

9. Oncogenicity, mutagenicity, teratogenicity, and animal toxicity

There are no long-term studies evaluating the oncogenicity in animals.

10. Treatment of overdose

Symptoms and signs of overdose do not show clearly immediately after injection.
If administered accidentally or administered orally, symptoms and signs of systemic weakness or muscle palsy should be medically observed for several weeks. If overdose or accidental administration is acknowledged immediately after injection, anti-toxin can be used. The anti-toxin does not reverse the already manifested muscle weakness at the time of anti-toxin injection. If muscles of the oropharynx and esophagus are affected, it can result in aspiration, which in turn may develop into aspiration pneumonia. If respiratory muscles are paralyzed or weakened, endotracheal intubation and assisted ventilation may be necessary until recovery. In addition to general ancillary procedures, tracheostomy and/or long-term mechanical ventilation may be necessary. In these patients, additional medical evaluations and immediate measures including hospitalization must be considered.

11. Cautions for storage and handling

Unopened products should be refrigerated (2~8℃). Dissolved products can be stored in a refrigerator (2~8℃) for 24 hours. Any vials, including ones past the expiration date, and any devices that werein direct contact with the vial or product should be disposed of as medical waste. In the cases where inactivation of the toxin is necessary (e.g., spill), use of diluted hypochlorite (0.5 or 1 %) before disposal as medical waste is recommended.

12. Information for patients

Any concerns on the effects and risks of this product should be consulted with a doctor. Be aware of signs and symptoms of adverse events. If there are muscle weakness, difficulties in swallowing, speaking, and breathing after treatment, seek medical help immediately. Adverse events may appear within a few hours or after several weeks of treatment. This product binds to the receptors at the neuromuscular junction, and enters the nerve terminal to inhibit the secretion of acetylcholine to block the conduction at the neuromuscular junction.
If injected within the treatment dose intramuscularly, this product causes local muscle palsy due to chemical denervation. When a muscle is chemically denervated, the muscle weakens and may develop acetylcholine receptors elsewhere than the neuromuscular junction. The nerve is regenerated and nerve stimulation can regain flow to muscle, proving that the 'washed out' sensation is reversible.

[Storage and Expiry date]
Store at sealed containers, refrigeration (2-8℃), 36 months from the date of manufacture

[How supplied]
100 units/vial (1 vial)