1. NAME OF THE MEDICINAL PRODUCT

Letybo 100 Units

2. COMPOSITION

Each vial contains:
Active ingredient: Clostridium botulinum toxin type A 100 units (U) *
Stabilizer: Human serum albumin 0.50 mg
Tonic adjuster: Sodium chloride 0.90 mg

* One unit (U) of Letybo corresponds to the calculated median lethal dose (LD_{50}) when the reconstituted product is injected intraperitoneally into mice.

3. PHARMACEUTICAL FORM

A lyophilized white powder for injection in a colorless transparent vial. The product should be colorless and transparent liquid after reconstitution with saline solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

1) Temporary improvement of benign essential blepharospasm in adult patients.
2) Temporary improvement of serious glabellar wrinkles ranging from moderate to severe associated with corrugators muscle and/or procerus muscle activities in adults.
3) Muscle spasticity: for adult patients aged 20 or above with post stroke upper limb spasticity.
4) Temporary improvement of lateral canthal lines (crow's feet lines) ranging from moderate to severe associated with orbicularis oculi muscles activity in adults.

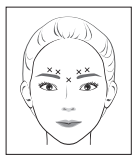
4.2 Posology and method of administration

4.2.1 Blepharospasm

For blepharospasm, reconstituted Letybo (see Dilution Table) is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25-2.5 units (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 units 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 Letybo treatment in a 30-day period should not exceed 200 units.

4.2.2 Glabellar lines

Reconstitute this product with 0.9 % preservative-free, sterile saline to make 100 units/2.5 mL (4 units/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 units.



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.

4.2.3 Muscle spasticity

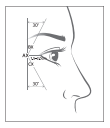
Accurate dosage and number of injecting site may vary depending on the size, number, and location of relevant muscles, degree of stiffness, weakening of local muscle, and response of patient from previous treatment. Muscle stress showed clinical improvement between 3-5 weeks after injection. The amount administered in the clinical trial is shown below.
In the clinical trial, the administered amount did not exceed maximum dose 360 units, and it was injected in each muscle. A 24-30 gauge sterile syringe and a proper length needle were used for dosing, depending on the depth of the muscular tissues. The location of muscle as an injection site were selected by using electric stimulation, needle electromyography or ultrasound, and administration was performed based on the dosage and the injection site presented in table below.

Injection site	Dosage	No. of sites
Flexed wrist		
Flexor carpi radialis	15 - 60 U	1-2 sites
Flexor carpi ulnaris	10 - 50 U	1-2 sites
Clenched fist		
Flexor digitorum superficial	15 - 50 U	1-2 sites
Flexor digitorum profundus	15 - 50 U	1-2 sites
Flexed elbow		
Biceps	100 - 200 U	Up to 4 sites

The duration of beneficial effect reported in clinical trials is approximately 12 weeks.

4.2.4 Lateral Canthal Lines (crow's feet lines)

Lateral canthal lines arise from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. The strong contraction of orbicularis oculi causes lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients.
Inject 0.1 ml (4U) into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscles.



As shown in the figure, the first injection site should be at least 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim (marked as AX). The next injection site (marked as BX and CX) is 1.0-1.5 cm above and below from the first injection site at an approximately 30° angle medially. The safety and efficacy of improvement of lateral canthal lines (crow's feet lines) were evaluated for 16 weeks with single dose.

4.2.5 Precautions for administration

Prior to injection, reconstitute this 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.

[Dilution Table]

Diluent added (0.9% Sodium Chloride Injection)	Resulting dose (U/0.1 mL)
1.0 mL	10.0U
2.0 mL	5.0U
4.0 mL	2.5U
8.0 mL	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).

4.3 Contraindications

Letybo should not be administered when:

- The patients have known hypersensitivity to any ingredient in the formulation of Letybo.
- 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.
- The patients are pregnant women, women of childbearing potential, or mothers under lactation.

4.4 Special warnings and precautions for use

4.4.1 Special 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. Understanding of standard electromyographic techniques is also required for the administration of the drug. The recommended dosage and frequency of administration for Letybo 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, language disorder, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. Swallowing and breathing difficulties can be life threatening and there have been reports of death.
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 drug reaction 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) 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.
7) 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.
8) Injections in or near vulnerable anatomic structures: Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events, 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 preexisting 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.
9) 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 (decreased forced vital capacity [FVC] ≥ 15 %) have been reported more frequently compared with placebo. Reduced lung functions (decreased forced vital capacity [FVC] ≥ 15 %) have been also reported in patients with detrusor overactivity associated with a neurologic condition, having disturbances of respiratory tracts following the administration of other botulinum toxin.
10) Bronchitis and upper respiratory tract infections in patients treated for upper limb spasticity: Bronchitis was reported more frequently 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.

4.4.2 Letybo should be carefully administered to the following patients:

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 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].

4.4.3 General Precautions

1) This drug 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 any 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 process, in addition to careful screening of donors and appropriate testing of donation units.
2) Glabellar lines/Lateral Canthal Lines (crow's feet lines): The following conditions were excluded from the phase 3 study: 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, a dermal resurfacing and patients who were deemed inappropriate because their glabellar lines/lateral canthal lines (crow's feet lines), were not flattened with fingers and so, their conditions could not be sufficiently improved by physical measures.
3) Muscle Spasticity: Botulinum toxin product is only used for the treatment of localized stiffness studied in association with general standard therapeutic method. Botulinum toxin product is not effective for improving the motor range of joint being affected by a fixed rigidity.
4) Too frequent or excessive dosing can result in antibody formation, which may lead to resistance to treatment.

4.5 Interaction with other medicinal products and other forms of interaction

1) The effect of 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 Letybo with aminoglycosides or spectinomycin is contraindicated. Polymyxins, tetracyclines and lincomycin should be used with caution in the Letybo -treated patient.
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 before the effects of a previously administered botulinum toxin disappear.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate and well-controlled studies of this product in pregnant women, Letybo should not be used during pregnancy. See preclinical safety data.

Lactation

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 this product is administered to nursing women.
Administration of this product is not recommended during pregnancy or lactation.

4.7 Effects on ability to drive and use machines

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.

4.8 Undesirable effects

4.8.1 Adverse Event

4.8.1.1 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 on pressure 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.
* Incident rate is defined as follows: Very rare (<0.01%), Rare (≥0.01% and <0.1%), Uncommon (≥0.1% and <1%), Common (≥1% and <10%), Very Common (≥10%)

4.8.1.2 Blepharospasm

The safety of Letybo was evaluated in a double blind, randomized, comparative trial for treatment of blepharospasm in 225 adult patients aged 18 years or above. Adverse events per occurrence site are as follows and most of these adverse events were classified as mild to moderate in severity.

Body site	Incident rate	Letybo treatment group (121 subjects)	Control group (104 subjects)
Eyes	Common (≥1% and <10%)	Ptosis (6.61%, 8 cases) Lagophthalmos (6.61%, 8 cases) Dry eyes (6.61%, 8 cases) Watery eyes (3.31%, 6 cases) Photophobia (2.48%, 3 cases)	Ptosis (2.88%, 3 cases) Lagophthalmos (5.77%, 6 cases) Dry eyes (9.62%, 10 cases) Watery eyes (4.81%, 5 cases) Photophobia (2.88%, 3 cases)
	Uncommon (≥0.1% and <1%)	Palpebral edema (0.83%, 1 case) Chalasis (0.83%, 1 case) Foreign body sensation (0.83%, 1 case)	Palpebral edema (0.96%, 1 case) Foreign body sensation (0.96%, 1 case) Diplopia (0.96%, 1 case) Entropion (0.96%, 1 case) Sleep (0.96%, 1 case) Keratitis (1.92%, 2 cases)
Lymphatic system	Common (≥1% and <10%)	Edema (4.96%, 6 cases)	Edema (2.88%, 3 cases)
Skin	Common (≥1% and <10%)	Reaction at injection sites (2.48%, 3 cases)	Reaction at injection sites (2.88%, 3 cases)
	Uncommon (≥0.1% and <1%)	-	Flushing (0.96%, 1 case) Itch (0.96%, 1 case)
Pain	Common (≥1% and <10%)	Myalgia (1.65%, 2 cases)	-
	Uncommon (≥0.1% and <1%)	-	Myalgia (0.96%, 1 case)
Nerve system	Uncommon (≥0.1% and <1%)	Masked face (0.83%, 1 case)	-

Letybo®

SOHO Global Health

Botulinum Toxin Type A 100 Units Lyophilized Powder for Injection

[SM56501] 565

Letybo®

Results of Post-Marketing Surveillance in Korea (Blepharospasm)
In the post-marketing surveillance conducted with 695 patients with benign essential blepharospasm for 6 years (2010.3.17.~2016.3.16.) in Korea, the incidence of adverse events was 21.2% (147/695, 215 cases).

Incident rate	Adverse Drug Reaction	Serious Adverse Events	Unexpected Adverse Events	Unexpected Adverse Events with Causal Relationship	Serious Unexpected Adverse Events
Common (≥ 1% and < 10%)	eye dryness, ptosis, ophthalmalgia, blepharoedema	-	cold, ophthalmalgia	ocular pain	-
Uncommon (≥ 0.1% and < 1%)	blurred vision, epiphora, diplopia, lagophthalmos, increased lacrimation, dysesthesia, lacrimal disorder, ocular irritation, lacrimation, red eye, eye strain, keratopathy, keratitis, corneal abrasion, conjunctivitis, reduced eyesight, headache, dizziness, ophthalmoplegia, palpebral pruritus, skin erosion, palpebral skin disease, wrinkle, bruise, facial edema, ectropion	spine fracture, tendon rupture, hypothyroidism, hematosepsis, metrofibroma, gastritis, insomnia, pulmonary embolism	blurred vision, diplopia, blepharitis, gastritis, eye strain, osteoarthritis, arthralgia, spine fracture, skin erosion, dyslipidemia, bruise, back pain, insomnia, conjunctival disease, photopsia, blepharitis, macular edema, sore throat, phlegm, tonsillitis, dyspepsia, gastroesophageal reflux, atrophic gastritis, gastric polyp, gingivitis, hemorrhoid, reduced bone mass, dysarthrosis, leg fracture, crepitation, ligament disorder, tendon rupture, pruritus, urticaria, onycholysis, dermatitis, dystonia, paralysis, Meigs' syndrome, Bell's palsy, facial pain, spinal stenosis, diabetes mellitus, dystrophic calcification, unindicated herpes, hematosepsis, pulmonary embolism, neoplasm of female breast, metrofibroma, conjunctival hemorrhage, atherosclerosis, tinnitus, hypothyroidism, anemia, burning sensation, injection site pain, joint dislocation, cataract extraction, food poisoning, laceration	blurred vision, diplopia, ocular dysesthesia, facial edema, eye strain, corneal abrasion, reduced eye sight, palpebral pruritus, skin erosion, palpebral skin disease, wrinkle, ophthalmoplegia ectropion, bruise	spine fracture, tendon rupture, hypothyroidism, hematosepsis, metrofibroma, gastritis, insomnia, pulmonary embolism

4.8.1.3 Glabellar lines

The safety of Letybo was evaluated in a double blind, randomized, comparative trial for treatment of moderate to severe glabellar lines in 271 adult patients between 18 and 65 years of age. Adverse events per occurrence site are as follows and most of these adverse events were classified as mild to moderate in severity.

Body site	Incident rate	Letybo treatment group (134 subjects)	Control group (137 subjects)
General disorder and condition of injection site	Common (≥1% and <10%)	Reaction at injection sites (3.0%, 4 cases)	Reaction at injection sites (8.0%, 11 cases)
	Uncommon (≥0.1% and <1%)	Injection site swelling (0.7%, 1 case)	-
Eye disorder	Common (≥1% and <10%)	Ptosis (4.5%, 6 cases)	Ptosis (2.2%, 3 cases)
	Uncommon (≥0.1% and <1%)	Keratitis (0.7%, 1 case) Chalasis (0.7%, 1 case) Sensory disorder of eyelid (0.7%, 1 case)	-
Nerve system disorder	Uncommon (≥0.1% and <1%)	Headache (0.7%, 1 case)	Headache (0.7%, 1 case) Dizziness (0.7%, 1 case)
Gastrointestinal tract disorder	Uncommon (≥0.1% and <1%)	-	Vomiting (0.7%, 1 case)
Skin and subcutaneous tissue disorder	Uncommon (≥0.1% and <1%)	Contact dermatitis (0.7%, 1 case)	-

312 x 360 mm

Results of Post-Marketing Surveillance in Korea (Glabellar lines)
In the post-marketing surveillance conducted on 815 patients with moderate or severe glabellar line wrinkles in Korea for 4 years, 6.38% (52/815, 64 cases) of adverse events occurred.

Incident rate	Adverse Drug Reaction	Serious Adverse Events	Unexpected Adverse Events	Unexpected Adverse Events with Causal Relationship	Serious Unexpected Adverse Events
Common (≥ 1% and < 10%)	reaction at injection site	-	-	-	-
Uncommon (≥ 0.1% and < 1%)	bruise in injection site, eye sensory disorder, pruritus in injection site, headache, swelling around eyes, pressure in injection site, rash in injection site, swelling in injection site, ptosis	-	bruise in injection site, swelling around eyes, cold, rash in injection site, pressure in injection site, allergic dermatitis, flushing, dermatitis, chest pain, nausea, reaction in surgery site, vaginitis	bruise in injection site, swelling around eye, pressure in injection site, rash in injection site	-

4.8.1.4 Upper Limb Spasticity
The safety of Letybo was evaluated in a randomized, comparative trial for treatment of post stroke upper limb spasticity in 187 adult patients aged 20 years or above. Adverse events per occurrence site are as follows and most of these adverse events were classified as mild in severity.

Body site	Incident rate	Letybo treatment group (95 subjects)	Control group (92 subjects)
Infection	Common (≥1% and <10%)	Rhinopharyngitis (1.05%, 1 case)	-
Renal and urological disorder	Common (≥1% and <10%)	Urinary frequency (1.05%, 1 case)	-
Skin and subcutaneous tissue disorder	Common (≥1% and <10%)	-	Hyperhidrosis (1.09%, 1 case)

4.8.1.5 Lateral Canthal Lines (crow's feet lines)
The safety of Letybo was evaluated in a randomized, comparative trial for treatment of moderate to several lateral canthal lines in 240 adult patients between 19 and 65 years of age.

Body site	Incident rate	Letybo treatment group (119 subjects)	Control group (121 subjects)
General disorder and condition of injection site	Uncommon (≥0.1% and <1%)	Pain at the injection site (0.84%, 1 case) Discomfort at the injection site (0.84%, 1 case)	-

4.8.2 Pediatric use
Safety and effectiveness of this product in children and adolescent below the age of 18 years for blepharospasm and glabellar lines, below the age of 19 years for lateral canthal lines (crow's feet lines), and below the age of 20 years for muscle spasticity (post stroke upper limb spasticity) have not been established.

4.8.3 Carcinogenesis, mutagenesis, impairment of fertility
No clinical studies have been performed to evaluate carcinogenesis, mutagenesis and impairment of fertility.

4.9 Overdose
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Botulinum toxin blocks the release of neurotransmitter, acetylcholine, at peripheral cholinergic nerve terminals to induce muscle paralysis. When botulinum toxin is administered excessively, it may bind to the nerve terminals of cholinergic ganglia that can affect the autonomic nervous system, however this effect is not observed when the product is administered correctly. Botulinum toxin molecules cannot pass through the blood-brain barrier, so they do not affect the central nervous system.

5.1.1 **Action mechanism**
Botulinum toxin's neurotoxicity process consists of the following 3 steps.

a) Binding
Different types of botulinum toxins have different binding sites on neurons, which are not well identified.

b) Internalization
After binding to the cell membrane, botulinum toxins enter the neurons through an endocytic process. Since endosomes have an acidic pH, the structure of toxin protein is altered, leading to separation of heavy chain and light chain. Subsequently, the light chain goes to cytoplasm through the endosome's channel.

c) Neuromuscular blockage
The light chain has the activity of metal-dependent metalloendopeptidase. It hydrolyses the SNAP-25 protein that is essential for the release of the acetylcholine neurotransmitter vesicle, resulting in blocking the release of acetylcholine and muscular paralysis. Clinical signs are manifest within 2-3 days, with peak effect seen within 5-6 weeks of injection. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

5.1.2 **Reversibility of Inhibition of Acetylcholine Release**
The neuromuscular junction (NMJ) is temporarily inactivated by the toxin in a manner similar to a chemical denervation. However, this denervation is not permanent and the NMJ is eventually reestablished, after a period of two to six or more months. The re-establishment of the NMJ was originally thought to be the result of nerve sprouting and formation of new nerve-muscle contacts (Alderson et al. 1991; Borodic et al. 1994).
de Paiva et al. (1999) reported that after a single botulinum toxin type A injection in mice, the NMJ responded with the anticipated sprouting. However, the original endplate eventually regained exocytotic function to re-establish a stable NMJ. Thus, re-establishment of the pre-existing NMJ is probably an important mechanism for the long duration of action observed with botulinum toxin type A therapy.

5.2 Pharmacokinetic properties
Due to the very small amount of product that is administered, pharmacokinetic studies are very difficult to perform and, due to the well-characterised nature of the product, are not expected to be informative. Therefore, pharmacokinetic studies have not been conducted for Letybo.
Pharmacokinetic studies have been performed using other botulinum toxins: distribution studies in rats indicate slow muscular diffusion of ^{125}I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabeled material in the muscle declined with a half-life of approximately 10 hours.
At the injection site, the radioactivity was bound to large protein molecules, whereas in the plasma it was bound to small molecules, suggesting rapid systemic metabolism of the substrate.
Within 24 hours of dosing, 60 % of the radioactivity was excreted in the urine. The toxin is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways. Classical absorption, distribution, biotransformation and elimination (ADME) studies on the active substance have not been performed due to the nature of this product.
It is believed that at therapeutic doses, low systemic distribution of botulinum toxin occurs in patients. Clinical studies using single fibre electromyographic techniques have shown increased electrophysiologic neuromuscular activity in muscles distant to the injection site, with no associated clinical signs or symptoms.

5.3 Preclinical safety data
To evaluate the single-dose toxicity of Letybo in Sprague-Dawley (SD) rats, Letybo was administered intramuscularly to male and female rats at dose levels of 6, 30, and 150 units/kg. In conclusion, a single intramuscular administration of Letybo in male and female rats induced the paralysis of muscle, adrenergic nerve blocking syndromes, suppression of body weight gain, dark-red discharge around eyes and nose, soiled perineal region, and atrophy of thymus in an animal in female 150 units/kg group. The LD_{50} value was calculated to be 129.5 units/kg (95 % confidence limits; not determined). In case of the acute toxicity of Letybo in Beagle dogs, no change was found in Beagle dogs following single intramuscular administration of Letybo up to 200 units/kg group, which was equivalent to 600 times of the estimated clinical dose. Therefore, the minimum lethal dose of Letybo in Beagle dogs was higher than 200 units/kg. The No Observed Adverse Effect Level (NOAEL) in rats administered Letybo once a week for 4 weeks (5 times in total) in repeated intramuscular dose was estimated at 1.5 unit/kg unaccompanied by histological changes of muscles at the administration site. No significant toxicological change appeared in the Beagle dogs receiving Letybo once a week for 4 weeks under the test conditions. The NOAEL for Beagle dogs was 30 units/kg.
Repeated intramuscular injection of Letybo to pregnant rats in the organogenetic period resulted in an increase of paralytic gait, continuous suppression of weight gain, a decrease of body weight gain, and chronic mysitis followed by muscular atrophy in dams in groups at higher than 1 unit/kg/day dose. It induced decreases of food consumption and of organ weights of thymus, spleen, kidney, heart, lung and liver in groups at higher than 4 units/kg/day dose. In fetuses, it caused dwarfism and a decrease of fetal body weight in males at higher than 1 unit/kg/day doses, and it produced decreases of fetal body and placental weight in females, and retarded ossification characterized by a retardation of meta-tarsal ossification at higher than 4 units/kg/day/doses. Thus, under this experimental condition, the NOAEL of Letybo is considered to be less than 1 unit/kg/day for both dam and embryo-fetus, and it is concluded that Letybo is not teratogenic. The impacts on embryo-fetuses are considered as secondary effects resulted by maternal toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal.

6.2 Shelf life
The shelf-life of Letybo is 36 months from the manufacturing date. After reconstitution, an immediate use of the solution is recommended; however, stability has been demonstrated for 24 hours at 2 – 8°C. The vial which is expired or kept more than 24 hours after reconstitution should be abandoned.

6.3 Special precautions for storage
The unopened lyophilized vial 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.

6.4 Nature and contents of container
Powder in a vial (Ph. Eur. type I borosilicate glass) fitted with a stopper (rubber) and a cap (aluminium), Letybo is supplied in a single use vial.

6.5 Special precautions for disposal
This unopened medicinal product should be stored in cold condition (2 - 8°C). The reconstituted one can be stored for 24 hours in cold condition (2 - 8°C). All vials including expired ones or any materials which have been in direct contact with the product should be disposed of as medical waste. If inactivation of toxin is required (i.e. leakage), it is recommended to use a diluted hypochlorite solution (0.5 or 1 %) before disposal as medical waste.

Manufactured by:
HUGEL, Inc.
23, Geodudanji 1-gil, Dongnae-myeon, Chuncheon-si,
Gangwon-do, Korea

Imported and Marketed by:
PT. SOHO Industri Pharmasi
a SOHO Global Health Company
Jakarta, Indonesia

Reg. No. LETYBO 100 Units: DKI2264600144B1

ON MEDICAL PRESCRIPTION ONLY

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

INFORMASI PRODUK UNTUK PASIEN

Baca seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini mengandung informasi penting untuk Anda.

- Simpan leaflet ini. Anda mungkin perlu untuk membacanya lagi di suatu saat.
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker Anda.
- Obat ini diresepkan hanya untuk Anda. Jangan berikan obat ini kepada orang lain. Hal ini dapat membahayakan mereka, meskipun mereka memiliki gejala penyakit yang sama seperti Anda.
- Apabila Anda mengalami efek samping, bicarakan dengan dokter, apoteker, atau perawat Anda. Hal ini termasuk efek samping yang tidak tercantum dalam leaflet ini. Lihat bagian 4.

Yang terkandung dalam leaflet ini:

1. Apa itu Letybo dan apa kegunaannya

Letybo adalah relaksan otot yang digunakan untuk mengatasi beberapa kondisi tubuh. Letybo mengandung substansi aktif berupa toksin Botulinum tipe A dan disuntikkan pada otot atau ke bagian dalam kulit. Letybo bekerja dengan cara menyekat parsial impuls saraf pada otot yang telah disuntik dan mengurangi kontraksi berlebih pada otot-otot tersebut.

Letybo dapat disuntikkan langsung pada otot dan dapat digunakan untuk:
- Perbaikan sementara untuk kontraksi otot kelopak mata yang tidak normal (blefarospasme/*Benign essential blepharospasm*) pada pasien dewasa.
- Perbaikan sementara untuk kerutan di antara kedua alis (garis glabelar/*glabellar wrinkles*) mulai dari derajat sedang sampai parah yang dihubungkan dengan aktivitas otot korugator dan/atau otot procerus pada orang dewasa.
- Kekakuan otot (*muscle spasticity*): untuk pasien dewasa usia 20 tahun atau lebih dengan spastisitas tungkai atas paska stroke (*post stroke upper limb spasticity*).
- Perbaikan sementara pada garis-garis seperti kipas di sudut mata (garis yang menyerupai kaki burung gagak/*crow's feet lines*) dari derajat sedang sampai parah yang dihubungkan dengan aktivitas otot orbikularis okuli pada orang dewasa.

2. Apa yang perlu Anda ketahui sebelum menggunakan Letybo

Jangan gunakan Letybo
- Apabila Anda alergi (hipersensitif) terhadap toksin botulinum tipe A atau bahan-bahan lain yang terkandung pada obat ini (tertera pada bagian 6).

Peringatan dan pencegahan
Bicarakan dengan dokter atau apoteker Anda sebelum menggunakan Letybo:
- Apabila Anda pernah mengalami masalah bernafas, menelan, atau berbicara. Masalah-masalah ini dapat terjadi dalam hitungan jam, hari, atau minggu setelah suntikan Letybo, biasanya terjadi karena otot yang Anda gunakan untuk bernafas atau menelan dapat menjadi lemah setelah suntikan. Kematian dapat terjadi karena komplikasi apabila Anda memiliki masalah serius pada menelan atau bernafas setelah pengobatan dengan Letybo;
- Apabila Anda **berusia lebih dari 65 tahun** dan memiliki penyakit serius;
- Apabila Anda menderita **penyakit otot lain** atau penyakit kronis yang menyerang otot (seperti miastenia gravis atau Sindrom Lambert-Eaton);
- Menderita **penyakit** tertentu yang menyerang **sistem saraf** (seperti *amyotropic lateral sclerosis* atau neuropati motoris);
- Apabila Anda memiliki **kelemahan** atau **penyusutan otot** yang signifikan di tempat yang disuntik dokter;
- Apabila Anda pernah menjalani **operasi** yang mengubah otot yang akan disuntik;
- Apabila Anda sebelumnya pernah memiliki **masalah dengan penyuntikan** (seperti pingsan);
- Apabila Anda memiliki **peradangan pada otot atau kulit** di tempat yang akan disuntik dokter;
- Apabila Anda pernah memiliki masalah dengan penyuntikan toksin botulinum sebelumnya;
- Apabila Anda menderita penyakit kardiovaskuler (penyakit jantung dan pembuluh darah).

Setelah Anda mendapatkan suntikan Letybo

Anda atau perawat Anda sebaiknya menghubungi dokter dan mencari pertolongan medis segera apabila Anda mengalami hal-hal berikut:
- Kesulitan **bernafas, menelan, atau berbicara**;
- **Gatal-gatal, bengkak** termasuk bengkak pada wajah atau tenggorokan, **mengi, rasa lemah dan nafas pendek** (kemungkinan gejala reaksi alergi berat).

Pencegahan umum
Sama seperti suntikan lainnya, prosedur ini dapat menyebabkan infeksi nyeri, bengkak, rasa terbakar dan tersengat, peningkatan sensitifitas, kelembutan, kemerahan, dan/atau perdarahan/memar pada lokasi penyuntikan.

Efek samping yang mungkin terkait dengan penyebaran toksin pada tempat yang jauh dan lokasi penyuntikan pernah dilaporkan (sebagai contoh kelemahan otot, kesulitan menelan atau ditemukannya makanan atau cairan yang tidak diinginkan pada jalan nafas). Hal ini kadang-kadang merupakan risiko pada pasien dengan penyakit dasar yang membuat mereka lebih rentan terkena gejala-gejala diatas.

Apabila Anda diberikan Letybo terlalu sering atau dengan dosis yang terlalu tinggi, kemungkinan Anda dapat mengalami kelemahan otot atau efek samping terkait dengan penyebaran toksin, atau tubuh Anda mungkin mulai memproduksi antibodi yang dapat menurunkan efek dari Letybo. Untuk menurunkan risiko ini, interval dari dua pengobatan tidak boleh kurang dari tiga bulan, sesuai indikasi pengobatan.

Apabila Letybo digunakan dalam pengobatan penyakit yang tidak tertera pada leaflet ini, Letybo dapat menyebabkan reaksi serius, terutama pada pasien yang tengah mengalami kesulitan bernafas atau kelemahan tubuh yang signifikan.

Apabila Anda belum melakukan olahraga dalam waktu yang lama sebelum menerima pengobatan Letybo, Anda sebaiknya mulai berolahraga secara bertahap setelah mendapat suntikan.

Saat Letybo digunakan pada pengobatan spasme otot kelopak mata yang persisten, hal ini dapat menyebabkan berkurangnya frekuensi kedipan mata yang berbahaya bagi permukaan bola mata Anda. Untuk mencegah hal ini, Anda mungkin memerlukan pengobatan dengan tetes mata atau salep mata, lensa kontak lembut, atau penutup mata agar mata Anda dalam keadaan tertutup. Dokter Anda akan memberitahukan Anda apabila hal-hal ini diperlukan.

Saat Letybo digunakan pada pengobatan garis-garis vertikal dan garis berbentuk kipas pada sudut mata, penurunan kelopak mata dapat terjadi setelah pengobatan.

Obat-obatan lain dengan Letybo
Beritahukan dokter atau apoteker apabila:
- Anda menggunakan **antibiotik** (digunakan untuk mengobati infeksi), atau obat-obatan lain yang mempengaruhi saraf yang mengontrol otot (contohnya obat-obatan **antikolinesterase** atau **relaksan otot**). Beberapa obat-obatan ini dapat meningkatkan efek Letybo;
- Anda baru-baru ini disuntik dengan obat yang mengandung toksin botulinum (substansi aktif Letybo) karena hal ini dapat meningkatkan efek Letybo secara berlebihan;
- Anda menggunakan produk anti-platelet (mirip aspirin) dan/atau antikoagulan (pengencer darah).

Beritahukan dokter atau apoteker Anda apabila Anda sedang atau baru-baru ini atau kemungkinan menggunakan obat-obatan lain.

Kehamilan dan menyusui
Penggunaan Letybo tidak direkomendasikan selama kehamilan. Tidak diketahui apakah Letybo akan dikeluarkan melalui air susu ibu. Apabila Anda sedang hamil atau menyusui, atau merasa Anda mungkin hamil atau berencana untuk hamil, tanyakan pada dokter atau apoteker Anda untuk nasihat sebelum menggunakan obat ini.

Mengemudi dan menggunakan alat berat
Letybo dapat menyebabkan pusing, rasa kantuk, lelah, dan masalah penglihatan. Apabila Anda mengalami efek samping ini, jangan mengemudi atau mengoperasikan alat-alat berat. Apabila Anda tidak yakin, konsultasikan dengan dokter Anda.

3. Cara penggunaan Letybo

Letybo hanya dapat disuntikkan oleh dokter dengan keterampilan khusus dan pengalaman dalam menggunakan obat ini.

Metode dan rute administrasi
Letybo disuntikkan pada otot Anda (intramuskular). Letybo disuntikkan langsung pada area yang dimaksud; dokter Anda biasanya akan menyuntikkan **Letybo pada beberapa titik dalam area yang dimaksud**.

Informasi umum tentang dosis
- Jumlah suntikan untuk setiap otot dan dosis berbeda-beda tergantung indikasi. Untuk itu, dokter Anda akan menentukan berapa banyak, seberapa sering, dan pada otot mana Letybo akan diberikan. Direkomendasikan agar dokter Anda menggunakan dosis efektif terendah.
- Dosis untuk orang usia lanjut sama dengan dosis orang dewasa.

Dosis Letybo dan durasi dan efeknya akan berbeda-beda tergantung pada kondisi pengobatan. Di bawah ini adalah detail dan kondisi-kondisi tersebut.

Keamanan dan efektivitas Letybo belum dapat ditentukan untuk anak-anak/remaja di bawah usia berikut:

Spasme kelopak mata abnormal (blefarospasme)	12 tahun
Garis kerut di antara alis (garis glabelar) dan garis-garis berbentuk kipas pada sudut mata (*crow's feet lines*)	18 tahun

Sebagai tambahan, terdapat sangat sedikit pengalaman dalam penggunaan Letybo untuk mengobati garis kerut pada pasien berusia lebih dari 65 tahun.

Untuk spasme kelopak mata abnormal (blefarospasme), perbaikan akan terlihat dalam waktu 3 hari setelah penyuntikan dan efek maksimum dapat dilihat setelah 1 sampai 2 minggu.

Untuk **garis vertikal di antara** alis, Anda dapat melihat perbaikan dalam 1 minggu setelah pengobatan. Efek pengobatan dapat terlihat sampai 4 bulan setelah penyuntikan.

Apabila Anda menerima Letybo lebih dari jumlah yang seharusnya

Tanda-tanda penggunaan Letybo yang berlebih kemungkinan tidak muncul sampai beberapa hari setelah penyuntikan. Apabila Anda menelan Letybo atau tidak sengaja menyuntikkan Letybo, Anda harus segera menemui dokter Anda yang dapat memantau kondisi Anda selama beberapa minggu.
Apabila Anda menerima terlalu banyak Letybo, Anda dapat mengalami gejala-gejala di bawah ini dan Anda harus menghubungi dokter Anda segera. Dokter Anda akan menentukan apakah Anda perlu pergi ke rumah sakit:
- Kelemahan otot yang bersifat lokal atau jauh dari lokasi penyuntikan;
- Kesulitan bernafas, menelan, atau berbicara karena kelumpuhan otot;
- Makanan atau cairan yang secara tidak sengaja masuk ke paru-paru yang dapat menyebabkan pneumonia (infeksi paru) akibat kelumpuhan otot.

Apabila Anda memiliki pertanyaan lebih lanjut mengenai penggunaan produk ini, tanyakan pada dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi

Apabila Anda memiliki kesulitan bernafas, menelan, atau berbicara setelah menerima suntikan Letybo, hubungi dokter Anda segera.
Apabila Anda mengalami gatal-gatal, bengkak termasuk bengkak pada wajah atau tenggorokan, mengi, pandangan ganda, lemas, dan kesulitan bernafas, hubungi dokter Anda segera.

Seperti semua obat-obatan, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya. Secara umum, efek samping terjadi dalam beberapa hari pertama setelah penyuntikan.
Efek samping ini biasanya bertahan dalam jangka waktu pendek, namun efek samping dapat bertahan hingga beberapa bulan dan bahkan lebih lama lagi pada kasus-kasus tertentu.

Seperti yang diperkirakan pada prosedur penyuntikan lainnya, rasa nyeri/terbakar/tersengat, bengkak, kelemahan otot, kelelahan, dan atau memar dapat diasosiasikan dengan penyuntikan.

Efek samping dapat diklasifikasikan menjadi kategori-kategori berikut, tergantung seberapa sering efek samping ini terjadi:

Sangat sering	≥10%
Sering	≥1% dan <10%
Tidak sering	≥0.1% dan <1%
Jarang	≥0.01% dan <0.1%
Sangat jarang	<0.01%

Di bawah ini adalah daftar efek samping yang bervariasi tergantung pada bagian tubuh dimana Letybo disuntikkan. Apabila efek samping ini menjadi serius, atau apabila Anda merasakan efek samping yang tidak tertera dalam leaflet ini, beritahukan pada dokter atau apoteker Anda.

Injeksi (suntikan) untuk kontraksi otot kelopak mata yang tidak normal (blefarospasme/*Benign essential blepharospasm*)

Sering	• Kelopak mata terkulai • Kelopak mata tidak dapat menutup sepenuhnya • Mata kering • Air mata berlebihan • Sensitif terhadap cahaya • Pembengkakan • Reaksi pada lokasi injeksi • Nyeri otot
Tidak sering	• Kelopak mata bengkak • *Chalasis* • Sensasi benda asing • Wajah tanpa ekspresi

Injeksi (suntikan) untuk kerutan di antara kedua alis (garis glabelar/*glabellar wrinkles*)

Sering	• Reaksi pada lokasi injeksi • Kelopak mata terkulai
Tidak sering	• Bengkak pada lokasi injeksi • Radang kornea mata • *Chalasis* • Gangguan sensorik pada kelopak mata • Sakit kepala • Dermatitis kontak

Injeksi (suntikan) pada spastisitas / kekakuan otot tungkai atas

Sering	• Radang hidung & tenggorokan • Frekuensi urinasi

Injeksi (suntikan) pada garis-garis seperti kipas di sudut mata (garis yang menyerupai kaki burung gagak/*crow's feet lines*)

Tidak Sering	• Nyeri pada lokasi injeksi • Rasa tidak nyaman pada lokasi injeksi

5. Bagaimana penyimpanan Letybo

Jauhkan dari jangkauan anak-anak. Simpan vial yang belum dibuka pada lemari pendingin (2 – 8°C). Setelah larutan dibuat, gunakan larutan segera; namun demikian larutan dapat disimpan sampai 24 jam dalam lemari pendingin (2 – 8°C).

Dokter Anda tidak disarankan menggunakan Letybo setelah lewat tanggal kedaluarsa yang tertera pada label `ED'. Tanggal kedaluarsa mengacu pada hari terakhir pada bulan tersebut.

6. Isi kemasan dan informasi lainnya

Apa yang dikandung Letybo
- Substansi aktif: Toksin Botulinum tipe A dari *Clostridium botulinum*.
- Komposisi lainnya adalah albumin manusia dan natrium klorida.

Seperti apa bentuk Letybo serta isi kemasan obat
Letybo disajikan sebagai bubuk berwarna putih dalam vial kaca transparan. Sebelum penyuntikan, produksi ini harus dilarutkan dalam larutan salin steril. Setiap vial mengandung 100 Unit Toksin Botulinum tipe A.

Diproduksi oleh:
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HARUS DENGAN RESEP DOKTER

Pada proses pembuatannya bersinggungan dengan bahan bersumber babi.

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