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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LETYBO safely and effectively. See full prescribing information for LETYBO.

LETYBO (letibotulinumtoxinA-wlbg) for injection, for intramuscular use
Initial U.S. Approval: 2024

WARNING: DISTANT SPREAD OF TOXIN EFFECT
See full prescribing information for complete boxed warning.

The effects of all botulinum toxin products, including LETYBO, may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. LETYBO is not approved for the treatment of spasticity or any conditions other than glabellar lines. (5.1)

----------INDICATIONS AND USAGE----------

LETYBO is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. (1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dose is 0.1 mL (4 Units) by intramuscular injection into each of five sites, for a total dose of 20 Units (2.2, 2.3)

----------DOSAGE FORMS AND STRENGTHS----------

For Injection: 50 Units or 100 Units freeze-dried powder in a single-dose vial (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to any botulinum toxin preparation or to any of the components in the LETYBO formulation (4)
- Infection at the injection site (4)

----------WARNINGS AND PRECAUTIONS----------

- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur. (5.1, 5.3, 5.7)
- Potency Units of LETYBO are not interchangeable with other preparations of botulinum toxin products. (5.2, 11)
- Potential serious adverse reactions after LETYBO injections for unapproved uses. (5.3)
- If a hypersensitivity reaction occurs, discontinue LETYBO and immediately initiate appropriate therapy. (5.4)
- Adverse event reports have been received involving the cardiovascular system, some with fatal outcomes. Use caution when administering to patients with pre-existing cardiovascular disease. (5.5)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment. (5.6)
- Use with caution in patients with compromised respiratory function or dysphagia (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reaction is headache (2%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact HUGEL at 1-888-674-5355 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Aminoglycoside antibiotics, anticholinergic agents, or any other agents that interfere with neuromuscular transmission may potentiate the effect of LETYBO; co-administer only with caution and close observation. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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FULL PRESCRIBING INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT

The effects of all botulinum toxin products, including LETYBO, may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. LETYBO is not approved for the treatment of spasticity or any conditions other than glabellar lines *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

LETYBO is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

The potency Units of LETYBO (letibotulinumtoxinA-wlbg) for injection are specific to the preparation and assay utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of LETYBO cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay *[see Warnings and Precautions (5.2) and Description (11)]*.

LETYBO should be administered no more frequently than every three months. Consideration of the cumulative dose is necessary when treating adult patients with LETYBO for glabellar lines if other botulinum toxin products are or have been used to treat other indications approved for those products.

The safe and effective use of LETYBO depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques.LETYBO

After reconstitution, only use each LETYBO vial for one injection session and for only one patient. Discard any remaining solution in vial immediately after administration.

Reconstitution instructions are provided specifically for the 50 Unit and the 100 Unit vials (Table 1)

2.2 Recommended Dosage

The total recommended dose is 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each (two injections in each corrugator muscle and one injection in the procerus muscle).

2.3 Preparation and Dilution Technique

LETYBO is supplied in a single-dose 50 or 100-Unit vial. Prior to intramuscular injection, reconstitute each freeze-dried vial of LETYBO with the required amount of sterile, preservative-free 0.9% Sodium Chloride Injection, USP to achieve a reconstituted solution at a concentration of 4 Units/0.1 mL (see Table 1).

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Table 1: Dilution Instructions for LETYBO Vials (50 and 100 Units)

Vial	Amount of Diluent* Added	Resulting Dose Units per 0.1 mL
50 Units	1.25 mL	4 Units
100 Units	2.5 mL	4 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP

Slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Dispose of any unused diluent. Gently mix LETYBO with 0.9% sodium chloride injection, USP by rotating the vial.

Reconstituted LETYBO is clear and colorless, and free of particulate matter. Inspect visually the reconstituted LETYBO for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or discolored or contains flakes or particles.

Administer LETYBO within 24 hours after reconstitution. During this time period, store unused reconstituted LETYBO in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze reconstituted LETYBO.

2.4 Administraton

The upper eyelid margin position should be carefully examined for separation or weakness of the levator palpebrae superioris muscle. Evaluate the range of upper eyelid excursion while manually immobilizing the frontalis to assess degree of levator function and frontalis compensation.

In order to reduce the complication of eyelid ptosis the following steps should be taken:

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Ensure the injected volume/dose is accurate and administer in a steady, controlled manner.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
- Avoid injecting toxin closer than 1 centimeter above the central eyebrow.

Draw at least 0.5 mL of the properly reconstituted toxin into a sterile syringe and expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30-31 gauge needle. Confirm the patency of the needle. Inject a dose of 0.1 mL (4 Units) intramuscularly into each of 5 sites, the inferomedial and superior middle of each corrugator and one in the mid-line of the procerus muscle for a total dose of 20 Units (see Figure 1).

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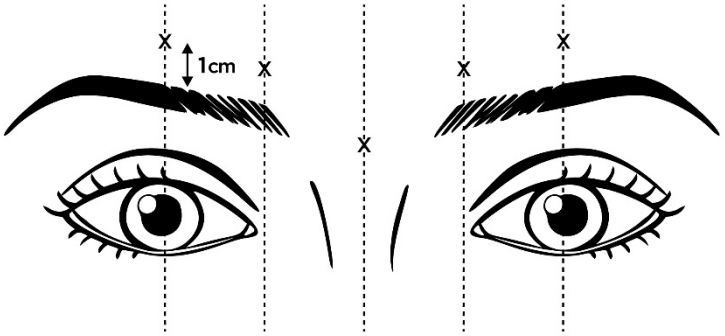
Figure 1: LETYBO Sites (x) for Intramuscular Injection



3 DOSAGE FORMS AND STRENGTHS

For injection: 50 Units or 100 Units of white, freeze-dried powder in a single-dose vial for reconstitution with sterile, preservative-free 0.9% Sodium Chloride Injection, USP.

4 CONTRAINDICATIONS

LETYBO is contraindicated in:

- Patients with known hypersensitivity to any botulinum toxin preparation or to any of the components in the LETYBO formulation *[see Warnings and Precautions (5.4)]*.
- The presence of infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Toxin Effects

Postmarketing safety data from other approved botulinum toxins suggest that botulinum toxin effects may be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, blurred vision and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. In unapproved uses and approved indications, symptoms consistent with spread of toxin effects have been reported at doses comparable to or lower than the maximum recommended total dose *[see Use in Specific Populations (8.4)]*. LETYBO is not approved for any conditions other than glabellar lines. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory difficulties occur.

5.2 Lack of Interchangeability between Botulinum Toxin Products

The potency units of LETYBO are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of LETYBO cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description (11)]*.

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5.3 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received botulinum toxin injections for unapproved uses. In these cases, the adverse reactions may have resulted from the administration of botulinum toxin products to the site of injection and/or adjacent structures. In several of the cases, patients had preexisting dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of botulinum toxin products.

5.4 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported for botulinum toxin products. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, discontinue further injection of LETYBO and immediately institute appropriate medical therapy. LETYBO*[see Contraindications (4)]*.

5.5 Cardiovascular System Adverse Reactions

There have been reports following administration of botulinum toxins of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

5.6 Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders

Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from typical doses of LETYBO. Monitor patients with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) for increased neuromuscular compromise following botulinum toxin treatment.

5.7 Dysphagia and Dyspnea

Treatment with botulinum toxin products, including LETYBO, can result in dysphagia and dyspnea including respiratory failure. These reactions can occur within hours to weeks after injection with botulinum toxin. Patients with preexisting dysphagia and dyspnea may be more susceptible to these complications. In most cases, this has been a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin products. Dysphagia may persist for several months. Patients treated with botulinum toxin products, including LETYBO, may require immediate medical attention should they develop problems with swallowing, speech, or breathing. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions (5.1)]*.

5.8 Pre-existing Conditions at the Injection Site

Use caution when LETYBO treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

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Use caution when LETYBO treatment is used in patients who have marked facial asymmetry, with surgical alterations to the facial anatomy, pre-existing eyelid or eyebrow ptosis, when excessive weakness or atrophy is present in the target muscles, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin (e.g., the inability to substantially lessen glabellar lines even by physically spreading them apart).

5.9 Ophthalmic Adverse Reactions in Patients Treated with Botulinum Toxin Products

Dry eye has been reported with the use of botulinum toxin products in the treatment of glabellar lines. Reduced tear production, reduced blinking, and corneal disorders may occur with use of botulinum toxins, including LETYBO. If symptoms of dry eye (e.g., eye irritation, photophobia or visual changes) persist, consider referring patient to an ophthalmologist *[see Warnings and Precautions (5.1)]*.

5.10 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (CJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), which would also be considered remote. No cases of transmission of viral diseases or CJD or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Contraindications (4) and Warnings and Precautions (5.4)]*
- Cardiovascular System Adverse Reactions *[see Warnings and Precautions (5.5)]*
- Increased Neuromuscular Compromise in Patients with Pre-Existing Neuromuscular Disorders *[see Warnings and Precautions (5.6)]*
- Dysphagia and Dyspnea *[see Warnings and Precautions (5.7)]*
- Ophthalmic Adverse Reactions in Patients Treated for Glabellar Lines *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the three randomized, placebo-controlled, Phase 3 clinical trials that assess the use of LETYBO for the temporary improvement in the appearance of moderate to severe glabellar lines (BLESS I, II and III), 911 out of the 955 subjects who received a single dose treatment of 20 Units LETYBO and 310 out of the 317 subjects who received a single dose of placebo were included in safety analyses *[see Clinical Studies (14)]*.

Table 2 lists the adverse reactions reported in more than one subject in the LETYBO group compared to the placebo in the placebo-controlled trials. Most adverse reactions occur within the first week following injection of LETYBO and while generally transient, may have a duration of several months or longer.

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Table 2: Adverse Reactions Reported in More Than One Subject in the LETYBO Group Compared to the Placebo Group in BLESS I, II and III

Adverse Reaction	Treatment	
	LETYBO BLESS I, II, III N=911 n (%)	PLACEBO BLESS I, II, III N=310 n (%)
Headache*	17 (2%)	2 (1%)
Brow ptosis**	3 (<1%)	0
Eyelid ptosis	3 (<1%)	0
Blepharospasm	2 (<1%)	0

* Includes headache, head discomfort, migraine, and procedural headache.
** Includes brow ptosis and brow heaviness.

The most frequently reported injection site reactions included administrative site swelling, facial pain, folliculitis, periorbital hematoma; and injection site bruising, reaction, pain, hematoma, nodule, pruritus, and mass.

BLESS I, II and III also included an open label, extension part with LETYBO. The extension allowed subjects who had completed the double-blind portion of the trials to receive up to 3 additional elective LETYBO 20-Unit treatments for moderate to severe glabellar lines over a 48-week period. Treatments were separated by at least a 3-month period. Of the 1,129 subjects enrolled in the open label extension part of the trials, the median number of treatments was 3. The adverse reaction profile was comparable to that reported in the randomized, single dose, double blind part of the trials.

Headache was the most common adverse reaction, reported in 2% of subjects, followed by injection site reactions (1%) [including contusion/bruising, administration site swelling, facial pain, periorbital hematoma, skin swelling; and injection site reaction, bruising, hematoma, mass, and nodule] and eyelid ptosis in 0.5% of subjects. The incidence of these adverse reactions did not increase with multiple re-treatments.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to letibotulinumtoxinA-wlbg in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Treatment with botulinum toxins may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin. Among 1,195 subjects treated with letibotulinumtoxinA-wlbg, four subjects (0.3%) developed antibodies to letibotulinumtoxinA-wlbg following treatment with LETYBO. In the selected anti-drug antibodies positive samples that were further tested, there were no neutralizing anti-drug antibodies detected.

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7 DRUG INTERACTIONS

No drug interaction studies have been conducted with LETYBO. Certain drugs may potentiate the effects of LETYBO which may result in excessive neuromuscular weakness and heighten systemic anticholinergic effects. Use caution with concurrent use of LETYBO with the following products and monitor closely for excessive neuromuscular weakness:

- Aminoglycosides or other agents interfering with neuromuscular transmission
- Anticholinergic drugs
- Botulinum neurotoxin products administered as the same time or within several months of LETYBO
- Muscle relaxants administered before or after administration of LETYBO

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with LETYBO use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Systemic exposure following intramuscular injection of letibotulinumtoxinA-wlbg was not assessed *[see Clinical Pharmacology (12.3)]*. In an animal reproduction study, intramuscular administration of letibotulinumtoxinA-wlbg to rats during pregnancy resulted in adverse effects on fetal growth (decreased fetal body weight and skeletal ossification) at maternally toxic doses 3 times the maximum recommended human dose (MRHD) (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

An embryofetal development study was conducted in rats with letibotulinumtoxinA-wlbg. For comparison of animal to human doses based on a body weight comparison, the MRHD is set at 20 Units/subject (0.34 Units/kg for an average 60 kg subject). Administration to pregnant rats once daily during organogenesis (gestation days 5 to 16) caused decreased fetal body weight and decreased fetal skeletal ossification at doses ≥1 Unit/kg (3 times the MRHD. These treatment related effects were associated with maternal toxicity.

8.2 Lactation

Risk Summary

There are no data regarding the presence of letibotulinumtoxinA-wlbg in human or animal milk, its effects on the breastfed infant, or the effects on milk production. Systemic exposure following intramuscular injection of letibotulinumtoxinA-wlbg was not assessed *[see Clinical Pharmacology (12.3)]*.The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LETYBO and any potential adverse effects on the breastfed infant from LETYBO or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of LETYBO in pediatric patients have not been established.

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8.5 Geriatric Use

The 3 clinical trials of LETYBO included 148 subjects age 65 and greater. Although no clinically meaningful differences in safety or efficacy were observed between older and younger subjects, clinical studies of LETYBO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

Excessive doses of LETYBO may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of the respiratory muscles. Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness or paralysis.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100.

11 DESCRIPTION

LetibotulinumtoxinA-wlbg is an acetylcholine release inhibitor and a neuromuscular blocking agent. LetibotulinumtoxinA-wlbg is a 900 kDa botulinum toxin typeA, produced from fermentation of *Clostridium botulinum*.

LETYBO (letibotulinumtoxinA-wlbg) for injection is supplied as a sterile, preservative-free, white, freeze-dried powder in a single-dose vial for intramuscular use after reconstitution. Each vial contains either 50 Units of letibotulinumtoxinA-wlbg, albumin human (0.25 mg) and sodium chloride (0.45 mg); or 100 Units of letibotulinumtoxinA-wlbg, albumin human (0.5 mg) and sodium chloride (0.9 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

LETYBO blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, LETYBO is internalized into the nerve terminal, translocates into the neuronal cytosol where it cleaves SNAP25, a protein necessary for synaptic membrane docking and subsequent release of acetylcholine which produces a dose dependent decrease of muscle function. Recovery of muscle function is gradual due to degradation of the neurotoxin and formation of axonal sprouts. Muscle reinnervation occurs, leading to a slow reversal of the pharmacological effects of LETYBO.

12.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with LETYBO.

12.3 Pharmacokinetics

Using currently available analytical technology, it is not possible to detect LETYBO in the peripheral blood following intramuscular injection at the recommended doses.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic, mutagenic, or impairment of fertility potential of letibotulinumtoxinA-wlbg.

14 CLINICAL STUDIES

Three randomized, multi-center, double-blind, placebo-controlled trials (BLESS I [NCT02677298], BLESS II [NCT02677805] and BLESS III [NCT03985982]) of identical design were conducted to evaluate LETYBO for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. These trials enrolled 1,276 subjects, randomized 3 to 1 to a single treatment with LETYBO (n=957) or placebo (n=319). Of the 1,276 enrolled subjects, 1,271 were included in the full analysis set (FAS) evaluable for efficacy with LETYBO (n=954) and placebo (n=317).

The trials enrolled healthy adults (ranging in age from 19 to 75) with glabellar lines of at least moderate severity at maximum frown and excluded subjects who had ptosis, deep dermal scarring or an inability to substantially lessen glabellar lines even by physically spreading the glabellar lines apart. The mean age was 50 years with 152 subjects (12%) ≥65 years of age. Most of the subjects were women (91%) and White (91%). Injection volume was 0.1 mL/injection site, for a dose/injection site in the active treatment groups of 4 Units. Subjects were injected intramuscularly at 5 sites, 1 in the procerus muscle and 2 in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 Units.

The primary efficacy endpoint was measured at Week 4 and was defined as the proportion of subjects achieving a score of 0 or 1 and an improvement of at least 2 points from baseline at maximum frown, as assessed independently by both the investigator and the subject using the Glabellar Line Scale (GLS). The GLS is a 4-point grading scale (0=none, 1=mild, 2=moderate, 3=severe). The results of these 3 efficacy trials are presented in Table 3.

Table 3: Percentage of Subjects with Moderate to Severe Glabellar Lines Achieving a Score of 0 or 1 and an Improvement of At Least 2 Points from Baseline to Week 4 at Maximum Frown on the Investigator and Subject Assessment of Glabellar Line Severity (Full Analysis Set) in Trials BLESS I, II, and III

	BLESS I		**BLESS II**		**BLESS III**	
	LETYBO (N = 528)	Placebo (N = 175)	LETYBO (N = 160)	Placebo (N = 53)	LETYBO (N = 266)	Placebo (N = 89)
Treatment Success*						
Multi-component Assessment n (%)	246 (47%)	0 (0%)	78 (49%)	1 (2%)	172 (65%)	0 (0%)
Treatment Difference and 95% Confidence Interval**	47% (43%, 51%)		45% (36%, 54%)		65% (59%, 71%)	
Individual Components						
Investigator Assessment n (%)	348 (66%)	1 (1%)	120 (75%)	1 (2%)	209 (79%)	1 (1%)
Subject Assessment n (%)	290 (55%)	0 (0%)	83 (52%)	1 (2%)	183 (69%)	0 (0%)

* A score of 0 or 1 (none or mild) and an improvement of at least 2 points from baseline at maximum frown concurrently on both the investigator's and subject's assessments

** Based on the Mantel-Haenszel method

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LETYBO (letibotulinumtoxinA-wlbg) for injection is a sterile, white, freeze-dried powder supplied in a single-dose vial in the following sizes:
Carton containing one 50 Units/vial (NDC 81165-050-01)
Carton containing one 100 Units/vial (NDC 81165-100-01)

Storage and Handling

Unopened LETYBO vials should be stored in a refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.
Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Swallowing, Speaking or Breathing Difficulties, or other Unusual Symptoms

Advise patients or caregivers to seek immediate medical care if swallowing, speech, or respiratory disorders arise or existing symptoms worsen *[see Warnings and Precautions (5.1, 5.6)]*.

Ability to Operate Machinery or Vehicles

Advise patients that if loss of strength, muscle weakness, blurred vision or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities *[see Warnings and Precautions (5.1)]*.

Ophthalmic Adverse Reaction

Inform patients that LETYBO injection may cause eye dryness. Advise patients to report symptoms of eye dryness (e.g., eye pain, eye irritation, photosensitivity or changes in vision) to their healthcare provider *[see Warnings and Precautions (5.9)]*.

Manufactured by:
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MEDICATION GUIDE
LETYBO (le tye boe)
(letibotulinumtoxinA-wlbg)
for injection, for intramuscular use

What is the most important information I should know about LETYBO?

LETYBO may cause serious side effects that can be life threatening. Call your healthcare provider or get medical help right away if you have any of these problems after treatment with LETYBO:

- **Problems swallowing, speaking, or breathing. These problems can happen hours, days, or weeks after an injection of LETYBO** if the muscles that you use to breathe and swallow become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with LETYBO.
  - People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with LETYBO.
  - Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving LETYBO have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
  - loss of strength and muscle weakness all over the body
  - double vision, blurred vision, and drooping eyelids
  - hoarseness or change or loss of voice
  - trouble saying words clearly
  - loss of bladder control
  - trouble breathing
  - trouble swallowing

These symptoms can happen hours, days, or weeks after you receive an injection of LETYBO.
These problems could make it unsafe for you to drive a car or do other dangerous activities. See "**What should I avoid while receiving LETYBO**?"

What is LETYBO?

LETYBO is a prescription medicine for adults that is injected into muscles to temporarily improve the look of moderate to severe frown lines between the eyebrows (glabellar lines).
It is not known if LETYBO is safe and effective for use in children.

Do not receive LETYBO if you:

- are allergic to LETYBO or any of the ingredients in LETYBO. See the end of this Medication Guide for a list of ingredients in LETYBO.
- had an allergic reaction to any other botulinum toxin product such as rimabotulinumtoxinB (MYOBLOC), onabotulinumtoxinA (BOTOX, BOTOX COSMETIC), abobotulinumtoxinA (DYSPORT), incobotulinumtoxinA (XEOMIN), prabotulinumtoxinA-xvfs (JEUVEAU), or daxibotulinumtoxinA-lanm (DAXXIFY).
- have a skin infection at the planned injection site.

Before receiving LETYBO, tell your healthcare provider about all of your medical conditions, including if you:

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Easton syndrome). See "**What is the most important information I should know about LETYBO?**"
- had any side effect from any botulinum toxin product in the past
- have or have had a breathing problem, such as asthma or emphysema
- have or have had swallowing problems
- have or have had bleeding problems
- have or have had heart problems
- plan to have surgery
- have weakness of your forehead muscles, such as trouble raising your eyebrows
- have drooping eyelids
- have had surgery on your face
- have had dry eyes with the use of botulinum toxin products in the past
- are pregnant or plan to become pregnant. It is not known if LETYBO can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LETYBO passes into breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with LETYBO.

This label may not be the latest approved by FDA.
For current labeling information, please visit https://www.fda.gov/drugsatfda

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Using LETYBO with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your healthcare provider that you have received LETYBO in the past.**

Especially tell your healthcare provider if you:

- have received any other botulinum toxin product in the last several months.
- have received injections of botulinum toxin, such as prabotulinumtoxinA-xvfs (JEUVEAU), onabotulinumtoxinA (BOTOX, BOTOX COSMETIC), rimabotulinumtoxinB (MYOBLOC), abobotulinumtoxinA (DYSPORT), incobotulinumtoxinA (XEOMIN), or daxibotulinumtoxinA-lanm (DAXXIFY) in the past. Be sure your healthcare provider knows exactly which product you received.

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.

How will I receive LETYBO?

- LETYBO is an injection that your healthcare provider will give you.
- LETYBO is injected into your affected muscles.
- LETYBO should not be received more than 1 time every 3 months.
- Your healthcare provider may change your dose of LETYBO, until you and your healthcare provider find the best dose for you.
- Your healthcare provider will tell you how often you will receive your dose of LETYBO injections.

What should I avoid while receiving LETYBO?

LETYBO may cause loss of strength or general muscle weakness, blurred vision, or drooping eyelids within hours to weeks of receiving LETYBO. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "**What is the most important information I should know about LETYBO?**"

What are the possible side effects of LETYBO?

LETYBO may cause serious side effects, including:

- See "**What is the most important information I should know about LETYBO?**
- **Allergic reactions.** Symptoms of an allergic reaction to LETYBO may include: itching, rash, hives, wheezing, trouble breathing, or you may become dizzy or faint. Tell your healthcare provider or get emergency medical help right away if you develop wheezing or trouble breathing, or if you feel dizzy or faint.
- **Heart problems.** Irregular heartbeat and heart attack that have caused death, have happened in some people who received botulinum toxin products.
- **Eye problems.** Dry eye, reduced blinking, and corneal problems have happened in some people who receive LETYBO. Tell your healthcare provider if you develop eye pain or irritation, sensitivity to light, or changes in your vision.

The most common side effect of LETYBO was headache.

These are not all of the possible side effects of LETYBO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effect to Hugel, Inc. at 1-877-390-2906.

General information about the safe and effective use of LETYBO.

Medicines are sometime prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider or pharmacist for information about LETYBO that is written for healthcare professionals.

What are the ingredients in LETYBO?

Active ingredient: letibotulinumtoxinA-wlbg

Inactive ingredients: albumin human and sodium chloride

Manufactured by: Hugel, Inc., 61-20 Sinbuk-ro, Sinbuk-eup, Chuncheon, 24206 Korea

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