▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – LETYBO®

(letibotulinumtoxinA) powder for injection

1 NAME OF THE MEDICINE

LetibotulinumtoxinA

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of LETYBO powder for injection contains 50 or 100 units (U) of letibotulinumtoxinA, albumin (0.25 or 0.5 mg) and sodium chloride (0.45 or 0.9 mg) in a sterile, freeze-dried form without a preservative.

LetibotulinumtoxinA is a 900 kD molecular weight complex consisting of the *Clostridium botulinum* type A neurotoxin and several accessory proteins.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

LETYBO 50 U or 100 U is a white freeze-dried powder for injection in a clear glass vial.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

LETYBO is indicated for the temporary improvement in the appearance of moderate to severe glabellar frown lines in adults.

4.2 DOSE AND METHOD OF ADMINISTRATION

LETYBO should only be administered by medical practitioners with suitable qualifications and proven experience in the application of botulinum toxin and in the use of the necessary equipment.

Reconstitution

Product is for single use in one patient only. Discard any residue.

LETYBO is reconstituted prior to use with preservative-free sodium chloride 9 mg/mL (0.9%) solution for injection. A suitable sterile needle should be used for administration.

It is good practice to reconstitute the vial content and prepare the syringe over plastic-lined paper towels to catch any spillage. Sodium chloride 9 mg/mL (0.9%) solution for injection is drawn up into a syringe and must be injected gently into the vial (to avoid foam/bubble formation or vigorous agitation which may cause toxin protein denaturation) to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL and a total treatment dose of 20 Units in 0.5 mL (see Table 1). The vial must be discarded if the vacuum does not pull the solvent into the vial. Reconstituted LETYBO is a clear, colourless solution practically free of particulate matter. Prior to use, the vial should be visually inspected to ensure the product is free from foreign particulate matter.

LETYBO must not be used if the reconstituted solution has a cloudy appearance or contains particulate matter.

Any solution for injection that has been stored for more than 24 hours as well as any residual unused solution for injection must be discarded.

LETYBO should be administered within 24 hours after reconstitution. During this time period, unused reconstituted LETYBO should be stored in a refrigerator between 2°C to 8°C in the original carton to protect from light for up to 24 hours until time of use. Do not freeze reconstituted LETYBO.

Table 1: Dilution Instructions for LETBO 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 for Injection

Reconstituted LETYBO is intended for intramuscular injection.

Dosage

The optimum dose and number of injection sites in the treated muscle(s) should be individualised for each patient and determined by the treating doctor.

Dose per injection site: 4 units into each of the 5 injection sites: two injections in each corrugator muscle and one injection in the procerus muscle (Figure 1).

The standard dose is 20 units.

Botulinum toxin units are not interchangeable from one product to another.

The intervals between treatments should be ≥ 12 weeks. The efficacy and safety of repeat injections of LETYBO beyond 48 weeks has not been evaluated.

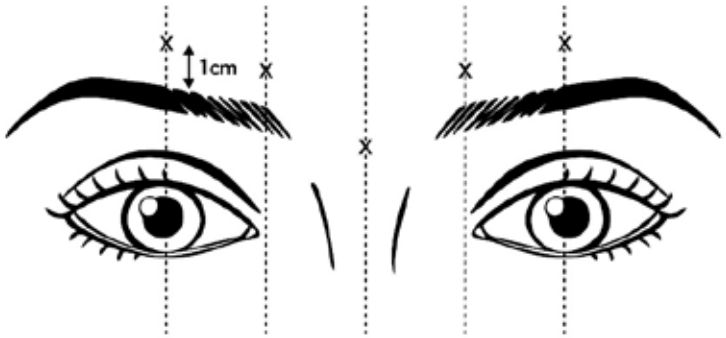

Figure 1: LETYBO Sites (x) for Intramuscular Injection

Method of Administration

To reduce the risk of blepharoptosis, injections near the levator palpebrae superioris and into the cranial portion of the orbicularis oculi should be avoided, particularly in patients with large brow depressor complexes. When injecting into two sites of each corrugator supercilii muscle, the first injection should be made right above the medial margin of eyebrows. The second injection should be made approximately 1 cm above the supraorbital ridge (rigid bony boundaries palpable above the upper part of the upper eyelid) where midlines of the eyebrows meet. The injection site of the procerus muscle is just above the midline of the nasal bridge where horizontal wrinkles are made between the medial ends of the eyebrows. Injections need to be made with caution to avoid intravascular injection. Before injecting, a thumb or an index finger can be placed firmly below the orbital rim to prevent effusion of the medicinal product to this area. The needle needs to be oriented superiorly and medially.

Recommendations should any incident occur during the handling of botulinum toxin

- Any spills of the product must be wiped up: either using absorbent material impregnated with any of the solutions listed in Section 6.6 (SPECIAL PRECAUTIONS FOR DISPOSAL) in case of the powder, or with dry, absorbent material in case of reconstituted product.
- The contaminated surfaces should be cleaned using absorbent material impregnated with any of the solutions listed in Section 6.6 (SPECIAL PRECAUTIONS FOR DISPOSAL), then dried.
- If a vial is broken, proceed as mentioned above by carefully collecting the pieces of broken glass and wiping up the product, avoiding any cuts to the skin.
- If the product comes into contact with the skin, rinse abundantly with water.
- If the product gets into the eyes, rinse thoroughly with plenty of water or with an ophthalmic eyewash solution.
- If product comes into contact with a wound, cut or broken skin, rinse thoroughly with plenty of water and take the appropriate medical steps according to the dose injected.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis).

Infection or inflammation at the proposed injection sites.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lack of interchangeability between botulinum toxin products

The potency units of LETYBO are specific to the preparation and assay method utilised. They are not interchangeable with the 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 Section 4.2 DOSE AND METHOD OF ADMINSTRATION).

General

The anatomy of muscles and the surrounding vascular and nervous structures in the glabellar region, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering LETYBO. Injection into vulnerable anatomic structures must be avoided.

Caution should be taken when LETYBO is used when the targeted muscle shows excessive weakness or atrophy.

Care should be taken to ensure that LETYBO is not injected into a blood vessel.

Procedure-related events

Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope after treatment with other botulinum toxins.

Pre-existing neuromuscular disorders

Patients with unrecognised neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of botulinum toxin type A.

Hypersensitivity reactions

An anaphylactic reaction may occur very rarely after injection of botulinum toxin type A. Epinephrine (adrenaline) or any other anti-anaphylactic measures should therefore be available.

Local or distant spread of toxin effects

Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin type A (see Section 4.8 ADVERSE

EFFECTS). Patients treated with therapeutic doses may experience exaggerated muscle weakness.

Swallowing and breathing difficulties are serious and can result in death. Injection of LETYBO is not recommended in patients with a history of dysphagia and aspiration.

Patients should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

There is a risk of eyelid ptosis following treatment. See Section 4.2 DOSE AND METHOD OF ADMINISTRATIION for instructions on how to minimise this risk.

Antibody formation

As with all therapeutic proteins, there is a potential for immunogenicity. The formation of neutralising antibodies to botulinum toxin type A may reduce the effectiveness of treatment by inactivating the biological activity of the toxin. The critical factors for neutralising antibody formation have not been well characterised. Too frequent doses may increase the risk of antibody formation, which can result in treatment failure. The potential for antibody formation may be minimised by injecting with the lowest effective dose given at the longest feasible intervals between injections.

No neutralising anti-drug antibodies were detected in subjects receiving up to 4 treatments with LETYBO in the phase 3 clinical studies.

Bleeding disorders

Caution should be exercised when LETYBO is used in patients with bleeding disorders as injection may lead to bruising.

Human albumin and transmission of viral diseases

This product contains a small amount of human albumin. The risk of transmission of viral infection or prion-related infection such as Creutzfeldt-Jakob Disease (CJD) cannot be excluded with absolute certainty following the use of human blood or blood products.

Use in the elderly

There are no clinical data with LETYBO in patients older than 75 years. No specific dose adjustment is required for use in the elderly older than 65 years of age.

Paediatric use

LETYBO has not been studied in the paediatric population and is therefore not recommended for use in the paediatric age group.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Coadministration of LETYBO and aminoglycoside antibiotics or other agents interfering with neuromuscular transmission, e.g., tubocurarine-type muscle relaxants, should only be used with caution in patients treated with botulinum toxin type A.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no adequate data on the effects on fertility from the use of letibotulinumtoxinA in women of childbearing potential.

No animal fertility studies have been conducted with letibotulinumtoxinA. Intramuscular doses of 4 U/kg (males) and 8 U/kg (females) of a similar drug did not affect rat fertility. Decreased fertility occurred with higher doses, which also resulted in signs of toxicity. The relevance of these findings to human fertility is not known.

Use in pregnancy – Pregnancy Category B3

There are no adequate data from the use of letibotulinumtoxinA in pregnant women. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. LETYBO should not be used during pregnancy.

Following daily IM exposure to pregnant rats at doses ≥1.18 U/kg/day (266-fold the clinical dose) during the period of organogenesis, small fetuses, lower fetal weights and minor skeletal and visceral variations were seen. These effects were likely due to maternal toxicity.

Use in lactation

It is not known whether letibotulinumtoxinA is excreted in human milk. The use of LETYBO during lactation is not recommended.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

LETYBO can have an effect on the ability to use and drive machines.

No studies have been performed on the effects on the ability to drive and use machines. However, botulinum toxin type A has been associated with asthenia, muscle weakness, dizziness and visual disturbance, which could affect driving and the operation of machinery.

Patients should be counselled that they should avoid driving, operating machinery or engage in other potentially hazardous activities, if any of the above symptoms develop.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Events

The safety of LETYBO for the treatment of glabellar frown lines was evaluated in three pivotal Phase 3 clinical studies that all included a placebo-controlled part (cycle 1) and a long-term extension part (cycles 2-4) covering a period of up to a year and including 1162 patients

receiving LETYBO. In addition, supportive data are available from a Phase 3 study in glabellar lines carried out in Korea as well as post-marketing data.

Most adverse events reported were of mild to moderate severity. Table 2 summarises the frequency of adverse events in greater than 2% of patients for LETYBO and placebo during clinical trials.

Table 2: Number (%) of Patients with Adverse Events (> 2% of Patients)

Adverse events	**LETYBO** (N = 955); n (%)	**Placebo** (N = 317); n (%)
Infections and infestations	84 (8.8)	27 (8.5)
Nasopharyngitis	25 (2.6)	9 (2.8)
Nervous system disorders	34 (3.6)	8 (2.5)
Headache	28 (2.9)	4 (1.3)
Injury, poisoning and procedural complications	25 (2.6)	7 (2.2)
Musculoskeletal and connective tissue disorders	20 (2.1)	7 (2.2)
Gastrointestinal disorders	20 (2.1)	4 (1.3)
General disorders and administration site conditions	15 (1.6)	7 (2.2)

Note: Based on pooled placebo-controlled clinical studies

Adverse Reactions

Table 3 summarises the clinical experience information on the frequency of adverse reactions. The frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Of the 1162 patients treated with LETYBO, rare events occurred in 1 subject only.

Table 3: Adverse Reactions

Body System	**Adverse Reactions**	
Infections and infestations	*Uncommon:*	nasopharyngitis
	Rare:	oral herpes, bronchitis, folliculitis, pharyngitis streptococcal, pneumonia, sinusitis
Nervous system disorders	*Common:*	headache
	Uncommon:	head discomfort
	Rare:	migraine, dizziness, paraesthesia, visual field defect
Eye disorders	*Uncommon:*	eyelid ptosis, blepharospasm, periorbital oedema
	Rare:	conjunctival haemorrhage, dry eye, eye pain
Respiratory, thoracic and mediastinal disorders	*Rare:*	pharyngeal hypoaesthesia

Body System	Adverse Reactions	
Gastrointestinal disorders	*Rare:*	constipation, nausea
Skin and subcutaneous tissue disorders	*Rare:*	brow ptosis, dry skin, urticaria
General disorders and administration site conditions	*Common:*	injection site reaction
	Uncommon:	injection site pain, injection site bruising, administration site swelling, injection site pruritus, injection site mass, injection site pressure
Investigations	*Rare:*	blood potassium increased
Injury, poisoning and procedural complications	*Rare:*	contusion, periorbital haematoma

Note: Based on placebo-controlled and uncontrolled studies

In general, 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.

Administration related adverse effects

As expected for any injection procedure, localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, itching, localised infection, haematoma, bleeding and/or bruising may be associated with the injection.

Needle related pain and/or anxiety may result in vasovagal responses, including transient symptomatic hypotension, nausea, tinnitus and syncope.

Adverse effects related to pharmacological class

Localised muscle weakness is one expected pharmacological effect of botulinum toxin.

Post-market experience

There is currently no post-marketing experience in Australia with LETYBO.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Contact the Poisons Information Centre on telephone in Australia on 13 11 26.

Symptoms of Overdose

Increased doses of letibotulinumtoxinA may result in pronounced neuromuscular paralysis distant from the injection site with a variety of symptoms (symptoms may include general weakness, ptosis, diplopia, breathing difficulties, speech difficulties, paralysis of the respiratory muscles or swallowing difficulties which may result in an aspiration pneumonia). Signs of overdose may not be apparent immediately post-injection.

Measures in Case of Overdose

In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary. Respiratory support may be required if paralysis of the respiratory muscles occurs.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: other muscle relaxants, peripherally acting agents [ATC code: M03AX01].

LetibotulinumtoxinA blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine from peripheral cholinergic nerve terminals. This inhibition occurs according to the following sequence:

- heavy chain of toxin binding to cholinergic nerve terminals
- internalisation of the toxin within vesicles into the nerve terminal
- translocation of the light-chain of the toxin molecule into the cytosol of the nerve terminal
- enzymatic cleavage of SNAP25, the presynaptic target protein essential for the release of acetylcholine.

Complete recovery of endplate function/impulse transmission after intramuscular injection normally occurs within 3-4 months as nerve terminals sprout and reconnect with the muscle endplate and the presynaptic neurotransmitter release mechanism becomes functional again.

Clinical trials

Three identically designed randomised, double-blind, multi-centre, placebo-controlled Phase 3 clinical trials (BLESS I, BLESS II, and BLESS III) were conducted to evaluate LETYBO for use in the temporary improvement of moderate to severe glabellar lines. The studies included a total of 955 subjects treated with LETYBO and 317 subjects treated with placebo for a single double-blind treatment. The study patients received either 20 units (0.5 mL) LETYBO or an equal volume of placebo. The total dose was delivered in 5 equally divided aliquots of 4 units each to specific injection sites.

In studies BLESS I, BLESS II and BLESS III, all patients had moderate (27% of patients) or severe (73% of patients) glabellar lines at maximum frown at baseline.

Overall, 152/1272 (11.9%) of patients were ≥ 65 years old at screening. No patient was > 75 years of age.

At week 4 of treatment period, LETYBO at the dose of 20 units significantly reduced the severity of glabellar lines seen at maximum frown, as measured by the investigator's and patient's composite assessment of glabellar line severity on a 4-point facial wrinkle scale (FWS). Statistically significant response rates in favour of LETYBO were seen when using a composite endpoint requiring an FWS score of 0 or 1 and a 2-point improvement in FWS. High response rates in favour of LETYBO were also see when considering the investigator and subject individual rating at Week 4 (see Table 4).

Table 4: Response rate from baseline to week 4 at maximum frown based on facial wrinkle scale (FWS) in BLESS I, BLESS II, and BLESS III studies – Full analysis set

Endpoint	BLESS I		BLESS II		BLESS III	
	LETYBO (N = 529)	Placebo (N = 175)	LETYBO (N = 160)	Placebo (N = 53)	LETYBO (N = 266)	Placebo (N = 89)
Composite Investigator and Subject Assessment	246 (46.5%)	0 (0%)	78 (48.8%)	1 (1.9%)	172 (64.7%)	0 (0.0%)
Investigator Assessment	348 (65.8%)	1 (0.6%)	120 (75.0%)	1 (1.9%)	209 (78.6%)	1 (1.1%)
Subject Assessment	290 (54.8%)	0 (0%)	83 (51.9%)	1 (1.9%)	183 (68.8%)	0 (0.0%)

A total of 38.3% of LETYBO-treated subjects showed a 3-point improvement in line severity from a baseline value of severe lines (FWS grade 3) to no lines (FWS grade 0) at Week 4 according to investigator's assessment

The improvement in glabellar lines (based on ≥ 2 point improvement in FWS score at maximum frown based on both subject and investigator assessment) started within one week after the injection and reached a maximal effect during the second week following the injection. The duration of the effect can be considered to be between 12 and 16 weeks.

It could be demonstrated that the responder rate of ≥ 1-point reduction in FWS score at rest was statistically significantly higher in the LETYBO group compared with the placebo group: Four weeks after injection, investigators judged 63.1%, 59.4%, and 61.3% of LETYBO treated patients and 15.4%, 5.7%, and 9.0% of placebo treated patients to have experienced a ≥ 1-point improvement on FWS at rest in studies BLESS I, BLESS II, and BLESS III, respectively (p-value for between treatment differences was <0.001 for all studies).

Long-term repeat dose open-label data confirmed that response rates after the second, third, and fourth treatments with LETYBO over the one-year study period remained high even though, based on study design, the re-treatment cycles included some bias towards non-response.

According to the newly developed Modified Skindex-16 Glabellar Line Quality of Life Scale, more than 85% of the patients entering the studies experienced a moderate or severe negative psychological impact from their glabellar lines at baseline, while about 15% of patients reported a mild impact.

A distinct improvement in psychological impact was observed in patients with LETYBO compared to placebo treatment as measured by the Modified Skindex-16 Glabellar Line Quality of Life Scale.

Broadly favourable patient reported cosmetic outcomes were recorded as well as high rates of satisfaction with outcome.

Data were available for 854 patients treated with LETYBO in an unblinded extension part of Studies BLESS I and II for a further 1 to 3 treatments. Long-term repeat dose open-label data confirmed that the therapeutic effect was maintained for up to 4 treatments with LETYBO over a one-year study period.

In the clinical development program, no neutralizing antibodies were detected in any patient after administration of LETYBO.

5.2 PHARMACOKINETIC PROPERTIES

Botulinum toxin type A is not expected to be present in peripheral blood at measurable levels following intramuscular injection owing to the extremely small quantities administered and rapid irreversible binding to cholinergic nerve terminals.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with letibotulinumtoxinA.

Carcinogenicity

No long term carcinogenicity studies in animals have been conducted with letibotulinumtoxinA.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Albumin

Sodium chloride

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Unopened vial

36 months

Reconstituted solution

24 hours

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vial

Store at 2 to 8°C (Refrigerate. Do not freeze).

Reconstituted solution

To reduce microbiological hazard, use as soon as practicable after reconstitution. lf storage is necessary, hold at 2-8°C for not more than 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Clear glass vial (type 1 glass) with a stopper (chlorobutyl rubber) and tamper-proof seal (aluminium).

LETYBO is availble in 2 strengths: 50 Units per vial and 100 Units per vial.

Each carton contains 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused vials, residual reconstituted solution in the vial and/or syringe should be autoclaved or inactivated by adding one of the following solutions: 70% ethanol, 50% isopropanol, diluted sodium hydroxide solution (0.1 N NaOH), or diluted sodium hypochlorite solution (at least 0.1% NaOCl).

Used vials, syringes, and materials should not be emptied and should be discarded into appropriate containers and disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

LETYBO neurotoxin complex is produced from the fermentation of *Clostridium botulinum* type A and is purified from the culture solution as an approximately 900 kD molecular weight complex consisting of the neurotoxin and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing human serum albumin and is sterile filtered prior to filling and freeze-drying.

One unit (U) of LETYBO corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice, performed in a mouse potency assay. This assay method is specific to LETYBO. Due to specific method details such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, units of biological activity of LETYBO cannot be compared to or converted into units of any other botulinum toxin activity.

CAS number

1800016-51-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Croma Australia Pty Ltd
Level 26, 1 Bligh Street
Sydney NSW 2000 Australia

Phone: 1800 276 622

9 DATE OF FIRST APPROVAL

28 November 2022

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	First version.