Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Letybo 50 units powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 50 units botulinum toxin type A produced by *Clostridium botulinum*.
After reconstitution each 0.1 mL of the solution contains 4 units.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.
White powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Letybo is indicated for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows in adults <75 years old seen at maximum frown (glabellar lines), when the severity of the facial lines has an important psychological impact.

4.2 Posology and method of administration

Letybo should only be administered by physicians with appropriate qualifications and expertise in this treatment and use of the required equipment.

Posology
The recommended dose is a total of 20 units divided into five injections of 4 units (0.1 mL) each: 2 injections in each *corrugator supercilii* muscle and 1 injection in the *procerus* muscle.

Botulinum toxin units are not interchangeable from one product to another.
Doses recommended are different from other botulinum toxin preparations.

Treatment interval should not be more frequent than every three months.
In the absence of any undesirable effects secondary to the previous treatment session, initiation of a further treatment session with at least a three-month interval between the treatment sessions is possible.

In case of treatment failure one month after a previous treatment session, i.e. in the absence of significant improvement from baseline, the following approaches may be considered:
- Analysis of the causes of failure, e.g. incorrect muscles injected, injection technique, formation of toxin neutralising antibodies, insufficient dose.
- Re-evaluation of the relevance of treatment with botulinum toxin type A.

The efficacy and safety of repeat injections of Letybo beyond 12 months has not been evaluated.

Special populations
Elderly population
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 (see section 5.1).

Paediatric population
There is no relevant use of Letybo in the paediatric population. (see section 5.1).

Method of administration

Intramuscular use.

Letybo, after reconstitution, must be used only for one session of injection(s) per patient.

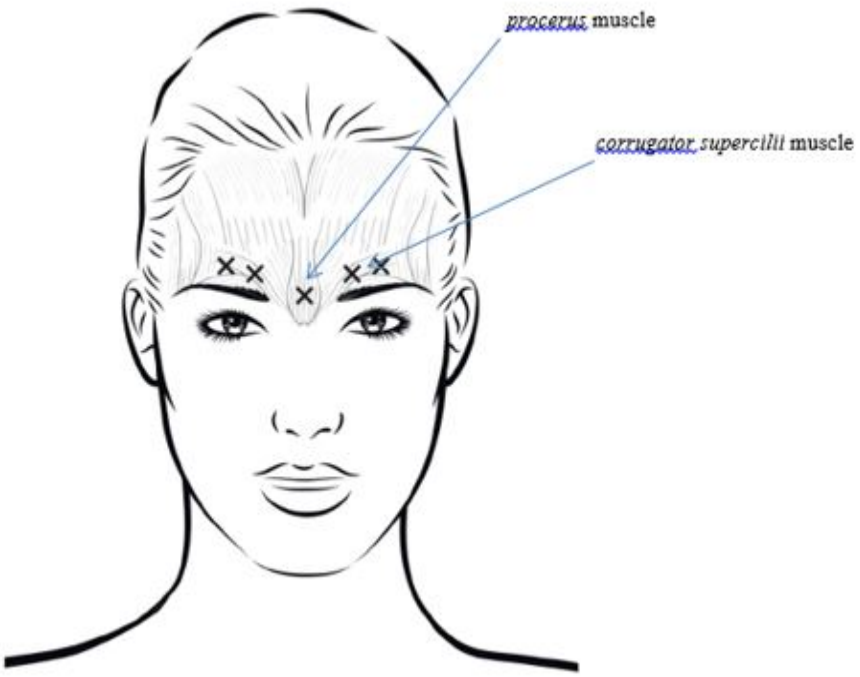
For instructions for dilution, use, handling and disposal of the vials, see section 6.6.

Intramuscular injections should be performed using a sterile insulin or tuberculin-type syringe of 1 mL value with 0.01 mL graduation and a needle with a gauge range of 30 to 31 G.

A volume of 0.5 mL of the properly reconstituted solution should be drawn into the sterile syringe and any air bubbles in the syringe barrel expelled. The needle used to reconstitute the medicinal product should be removed and replaced for administration.

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

In order to reduce the complication of blepharoptosis, injections near the *levator palpebrae superioris* must 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 will 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. When injecting into the medial ends of *corrugator supercilii* muscles and on the midlines of the eyebrows, the injection sites should be at least 1 cm away from the supraorbital ridge (rigid bony boundaries palpable above the upper part of the upper eyelid).



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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis).
Presence of acute infection or inflammation at the proposed injection sites.

4.4 Special warnings and precautions for use

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.

There is a risk of eyelid ptosis following treatment, see section 4.2 for administration instructions on how to minimise this risk.

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. 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 (see section 4.8). 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.

Antibody formation
Too frequent or excessive dosing may enhance the risk of antibody formation. Antibody formation may lead to treatment failure of botulinum toxin type A even for other indications.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium-free".

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No other interactions of clinical significance have been reported in this indication.

Theoretically, the effect of botulinum toxin may be potentiated by aminoglycoside antibiotics,spectinomycin, or other medicinal products that interfere with neuromuscular transmission (e.g. neuromuscular blocking medicinal products).

The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see section 5.3). The potential risk for humans is unknown. Letybo is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether Letybo is excreted in human milk. The use of Letybo during breast-feeding is not recommended.

Fertility
There are no adequate data on the effects on fertility from the use of botulinum toxin type A in women of childbearing potential. Studies in male and female rats have shown fertility reductions (see section 5.3).

4.7 Effects on ability to drive and use 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.

4.8 Undesirable effects

Summary of the safety profile
The safety of Letybo 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.

Adverse reactions may be related to the study medication (Letybo), injection procedure, or both. In general, adverse reactions occur within the first few days following injection and are transient. Most adverse events reported were of mild to moderate severity. The most frequent (reported in at least 2 patients treated with Letybo in cycle 1) adverse drug reactions in the three pivotal studies for Letybo in glabellar lines were headache (1.7% of patients), injection site pain (0.3% of patients), and eyelid ptosis, blepharospasm, head discomfort, and contusion (0.2% of patients each).

Localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Fever and flu syndrome have also been reported after injections of botulinum toxin (see section 4.4).

Tabulated summary of adverse reactions
Based on clinical experience, information on the frequency of undesirable effects is given below. The frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000).

Table 1: Adverse reactions reported in clinical and post-marketing studies after administration of Letybo

System Organ Classification	Frequency	Adverse reaction
Infections and infestations	uncommon	nasopharyngitis
	rare	oral herpes, folliculitis*
Nervous system disorders	common	headache
	uncommon	head discomfort*
	rare	migraine, dizziness, paraesthesia, visual field defect, dysarthria
Eye disorders	uncommon	eyelid ptosis, blepharospasm, periorbital oedema
	rare	conjunctival haemorrhage*, dry eye, blurred vision, eye pain*, eyelid sensory disorder**
Respiratory, thoracic and mediastinal disorders	rare	pharyngeal hypoaesthesia
Gastrointestinal disorders	rare	constipation, nausea
Skin and subcutaneous tissue disorders	rare	brow ptosis, dry skin, urticaria,
Musculoskeletal and connective tissue disorders	uncommon	Mephisto sign (lateral elevation of eyebrows)
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**
	rare	facial pain*, influenza like illness, pyrexia
Investigations	rare	blood potassium increased
Injury, poisoning and procedural complications	uncommon	contusion, periorbital haematoma*

Note: Of the 1162 patients treated with Letybo, rare events occurred in 1 subject only.
A "worse-case approach" was used to assign frequencies when events occurred in clinical and post-marketing studies.
* injection procedure adverse drug reaction. Note, this information was not collected for the Korean post-marketing study.
** post-marketing study only

Description of selected adverse reactions
Application related adverse reactions
Application related undesirable effects that have been reported following administration of Letybo are uncommon events individually, common when added together. Uncommon reactions at the injection site include pain, bruising, swelling, pruritus, mass, and pressure. Rarely occurring injection site events include pain and discomfort.

Risk of spread of toxin distant from the site of administration
Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin (e.g. muscle weakness, dysphagia, constipation or aspiration pneumonia which can be fatal) (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance
Website: www.hpra.ie.

4.9 Overdose

Symptoms of overdose
Overdose of Letybo depends upon dose, site of injection and underlying tissue properties.
No cases of systemic toxicity resulting from accidental injection of botulinum toxin type A have been observed. Excessive doses may produce local, or distant, generalised and profound neuromuscular paralysis. No cases of ingestion of botulinum toxin type A have been reported.

Signs of overdose may not be apparent immediately post-injection.

Management of overdose
Should accidental injection or ingestion occur, the patient should be medically monitored for signs and symptoms of general weakness or muscle paralysis. Admission to hospital should be considered in patients presenting with symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Clostridium botulinum neurotoxin type A blocks the peripheral release of the neurotransmitter acetylcholine at presynaptic cholinergic nerve terminals of neuromuscular junctions by cleaving SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within the nerve endings, thereby leading to denervation of the muscle and a flaccid paralysis.

After injection, there is an initial rapid high-affinity binding of toxin to specific cell surface receptors. This is followed by transfer of the toxin across the plasma membrane by receptor-mediated endocytosis. Finally, the toxin is released into the cytosol with progressive inhibition of acetylcholine release. Clinical signs manifest within 2-3 days, with peak effect seen within 4 weeks of

injection. Recovery occurs usually within 3-4 months after injection when nerve terminals sprout again and reconnect with the endplate.

Clinical data

The safety and efficacy of Letybo was investigated in 3 pivotal, double-blind Phase 3 studies (BLESS I, BLESS II, and BLESS III) in which a total of 955 patients were treated with Letybo and 317 patients were treated with placebo for 1 treatment. In addition, data are 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. Supportive data in glabellar lines comes from the clinical development program in Korea, comprising a Phase 3 study (HG-11-01) in 137 patients and a post-marketing study (HG-13-02) in 815 patients.

Efficacy

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. 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 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 an endpoint requiring 2-point improvement in FWS. High response rates in favour of Letybo were also seen when applying the clinically meaningful response definition of achieving a FWS score of 0 or 1 (no or mild lines) according to the investigator's rating at Week 4 (see Table 2).

Table 2 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

	BLESS I		**BLESS II**		**BLESS III**	
Assessed by:	**Letybo (N = 529)**	**Placebo (N = 175)**	**Letybo (N = 160)**	**Placebo (N = 53)**	**Letybo (N = 266)**	**Placebo (N = 89)**
Response rate (n [%]): Reduction in FWS score from moderate or severe to none or mild (≥ 2-point improvement required)[a]						
Investigator AND Patient	246 (46.5%)*	0 (0%)	78 (48.8%)*	1 (1.9%)	172 (64.7%)*	0 (0.0%)
Investigator	348 (65.8%)*	1 (0.6%)	120 (75.0%)*	1 (1.9%)	209 (78.6%)*	1 (1.1%)
Patient	290 (54.8%)*	0 (0%)	83 (51.9%)*	1 (1.9%)	183 (68.8%)*	0 (0.0%)
Response rate (%): Reduction in FWS score from moderate or severe to none or mild[b]						
Investigator	393 (74.3%)*	3 (1.7%)	136 (85.0)*	2 (3.8%)	218 (82.0%)*	1 (1.1%)

*p-value of <0.001 for Cochran–Mantel–Haenszel test for difference between Letybo and placebo; N: number of patients randomized, n: number of responders

[a] Primary efficacy endpoint

[b] Post-hoc analysis

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 an improvement of ≥ 2 point reduction 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 (see Figure 1).

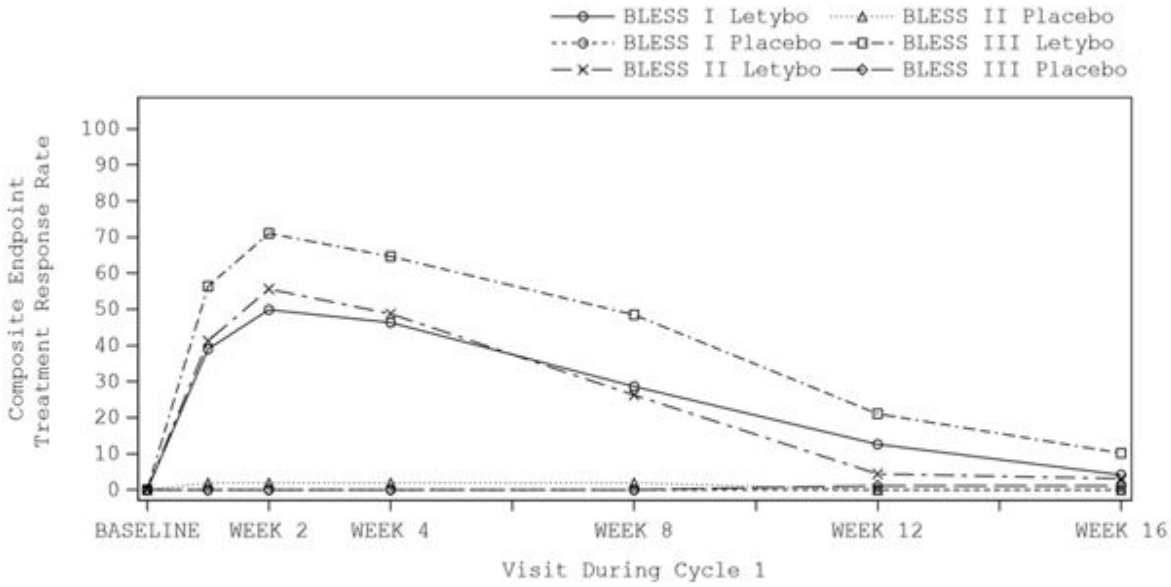


Figure 1 **Time course of responder rate (≥ 2-point improvement in FWS required both according to subject and investigator assessment) during cycle 1 for active versus placebo treatment in pivotal BLESS studies**

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.

Safety

During double-blind treatment in BLESS I, BLESS II, and BLESS III, 33 (3.5%) patients experienced TEAEs considered to be at least possibly related to Letybo and 8 (2.5%) patients experienced TEAEs considered to be at least possibly related to placebo treatment. During open-label treatment, 46 (5.4%) patients experienced TEAEs considered to be at least possibly related to Letybo treatment (including up to 3 treatment cycles). None of these related AEs were considered serious. The results were consistent with the supportive Phase 3 study HG-11-01 in glabellar lines.

In BLESS I, BLESS II, and BLESS III, antibody formation was evaluated before each treatment, at 4 weeks after each treatment, and at the final study visit. No neutralizing antibodies were detected in any patient after administration of Letybo.

Post-marketing data
The post-marketing data, including data from a post-marketing study in glabellar lines (HG-13-02) in 815 patients, are consistent with those observed in clinical studies.

Elderly population
In studies BLESS I, BLESS II and BLESS III, overall, 152/1272 (11.91%) of patients were ≥ 65 years old at screening. No patient was > 75 years of age. The composite responder rate at week 4 (primary endpoint) for patients receiving Letybo was lower in patients ≥ 65 years at 46/118 (39.0%) than in patients < 65 years at 450/839 (53.6%) for studies BLESS I, BLESS II, and BLESS III

combined. There were no large differences in the overall rates of patients with TEAEs considered related to double-blind Letybo treatment in the 3 studies combined (3.7% and 1.7% in patients aged < 65 years and ≥ 65 years, respectively, when medication-related and/or injection procedure-related TEAEs were considered).

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Letybo in all subsets of the paediatric population for treatment of muscle induced wrinkles (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Botulinum toxin type A is not expected to be present in peripheral blood at measurable levels following intramuscular injection of the recommended dose of 20 units.

5.3 Preclinical safety data

Single and repeated-dose toxicity studies with weekly or monthly intramuscular injections of BoNT/A-DP in rats revealed dose-dependent paralysis of the injected muscle leading to reduced locomotion, decreased food consumption, body weights and creatinine due to muscular atrophy, which is considered secondary to the muscular paralysis and reduced agility of the animals. No other severe adverse local or systemic effects which are of toxicological relevance were noted at doses up to 15 U/kg.
In an embryo-foetal development study with daily intramuscular BoNT/A-DP injections up to 8 U/kg from gestation day 5 to 16 in pregnant rats, dose-dependent muscle paralysis resulting in muscular atrophy, reduced body weights and soiled perineal region was evident in the dams. Delayed foetal ossification and reduced foetal body weight (≥20%), but no malformations were detected, which were interpreted as secondary consequences of maternal toxicity in line with experience gained with other botulinum toxin type A containing products. Effects on peri-/postnatal development have not been evaluated.
In rats impairments of male and female fertility have been observed with other botulinum toxin type A containing products at high doses.
No genotoxicity, antigenicity, carcinogenicity or fertility studies have been conducted with BoNT/A-DP.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

human albumin
sodium chloride

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years.

Reconstituted solution
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store and transport refrigerated (2°C - 8°C).
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear 5 ml glass vial (type 1 glass) with a stopper (chlorobutyl rubber) and tamper-proof seal (aluminium).

Packs containing 1 vial or 2 vials.
Multipack containing 2 (2 packs of 1) vials
Multipack containing 6 (6 packs of 1) vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The instructions for use, handling and disposal should be strictly followed.
Reconstitution should be performed in accordance with good practise rules, particularly in the respect of asepsis.

Sodium chloride 9 mg/mL (0.9%) solution for injection must be used as the diluent for reconstitution of Letybo and must be added at a volume of 1.25 mL.

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 denaturation. 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 must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Procedure to follow for a safe disposal of vials, syringes and materials used
For safe disposal, un-reconstituted Letybo should be reconstituted in the vial with a small amount of water and then autoclaved. Any empty vials, vials containing residual solution, syringes or spillage should be autoclaved. Alternatively, the remaining Letybo can be inactivated with diluted sodium hydroxide solution (0.1 N NaOH) or with diluted sodium hypochlorite solution (0.5% or 1% NaOCl).
After inactivation used vials, syringes and materials should not be emptied and must be discarded into appropriate containers and disposed of in accordance with local requirements.

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 a solution of sodium hypochlorite 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 a solution of sodium hypochlorite, 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 medicinal product comes into contact with the skin, wash the affected area with a solution of sodium hypochlorite then rinse abundantly with water.
- If the medicinal product enters into contact with the eyes, rinse thoroughly with plenty of water or with an ophthalmic eyewash solution.
- If the medicinal product enters 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.

7 MARKETING AUTHORISATION HOLDER

Croma-Pharma GmbH
Industriezeile 6
2100 Leobendorf
Austria

8 MARKETING AUTHORISATION NUMBER

PA0846/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th March 2022

10 DATE OF REVISION OF THE TEXT

July 2023