swissmedic

Date: 7 December 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Letybo

International non-proprietary name: botulinum toxin type A (strain CBFC26)
Pharmaceutical form: powder for solution for injection
Dosage strength(s): 50 units
Route(s) of administration: intramuscular use
Marketing authorisation holder: Medius AG
Marketing authorisation no.: 68864
Decision and decision date: approved on 12 October 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BoNT/A	Botulinum neurotoxin type A
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
kDa	Kilodalton
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for botulinum toxin type A (strain CBFC26) in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose is a total of 20 units divided into 5 injections of 4 units (0.1 mL) each:
2 injections in each corrugator supercilii muscle and 1 injection in the procerus muscle.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	31 August 2022
Formal objection	23 September 2022
Response to formal objection	27 September 2022
Formal control completed	6 October 2022
List of Questions (LoQ)	24 January 2023
Response to LoQ	21 March 2023
Preliminary decision	13 June 2023
Response to preliminary decision	17 July 2023
Final decision	12 October 2023
Decision	approval

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3 Medical context

Botulinum neurotoxin type A (BoNT/A) was first used clinically in ophthalmology in 1983. Since then, the use of BoNT/A has extended to various medical indications.
The effect of BoNT/A on facial lines was first reported in the early 90s. Studies on facial lines showed that BoNT/A weakens the overactive underlying muscle contraction, causing a flattening of the facial skin and improved appearance due to reduction of e.g. glabellar lines.

4 Quality aspects

4.1 Drug substance

INN: none
Botulinum toxin type A for injection is described in monograph 2113 of the European Pharmacopoeia.

Molecular mass: approximately 900,000 Dalton

Molecular structure:
The protein complex is composed of a 150 kDa neurotoxin, 4 non-toxic haemagglutinins, and 1 non-haemagglutinating protein.

Manufacture:
A two-tiered cell bank system has been established. The origin of the cell banks can be traced back to a bacterial culture derived from canned soy bean food contaminated with *C. botulinum* type A. The upstream process comprises expansion of cells and fermentation under anaerobic conditions. The downstream process includes harvest of the culture medium followed by several precipitations, buffer exchanges and chromatography steps for purification of the drug substance.
The drug substance manufacturing process is validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.
Several changes were implemented during development of the drug substance manufacturing process, including changes to manufacturing site and production scale. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability between processes.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

Specification:
The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g., for identity, purity and impurities, quantity, and potency. Specifications are in conformance with current compendial or regulatory guidelines.
Batch analysis data for numerous batches of drug substance were provided. All specific analytical methods are described and are fully validated.

Stability:
The drug substance is stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

4.2 Drug product

Description and composition:
The drug product is supplied as a sterile, single-use powder for solution for intramuscular injection to be reconstituted with 1.25 mL sterile 0.9% (w/v) sodium chloride solution. Each vial contains 50 units

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of botulinum toxin type A (from *Clostridium botulinum*), and human serum albumin and sodium chloride as excipients. One unit of toxin corresponds to the LD_{50} after intraperitoneal injection of mice under defined conditions.

Pharmaceutical development:
The formulation composition and dosage form were not the subject of an extensive formulation development effort as these are well known from other approved botulinum toxin type A products.
The excipients, human serum albumin, sodium chloride, and water for injection (removed upon lyophilisation) are of compendial grade.

Manufacture:
The drug product manufacturing process consists of the following steps: formulation, sterile filtration, filling and half-stoppering, lyophilisation and stoppering, cap sealing, visual inspection, labelling, and secondary packaging.
The drug product manufacturing process is validated with several consecutive batches, and the data demonstrated a consistent production.
Several changes were implemented during development of the drug product manufacturing process, including changes to manufacturing site and production scale. However, comparability studies demonstrated comparability between processes.

Specification:
The specifications for release and stability of the drug product include relevant tests and acceptance criteria, e.g., for identity, purity and impurities, quantity, potency, water, appearance, pH, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.
Batch analysis data for numerous batches of drug product were provided. All specific analytical methods are described and are fully validated.

Container closure system:
The container closure system consists of a borosilicate glass vial with a rubber stopper and an aluminium cap with a flip off button. The materials of the type I glass vial and rubber stopper meet compendial requirements.

Stability:
The vials are stored at 2°C to 8°C protected from light. The stability data support a shelf life of 36 months.

4.3 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.
Safety of the product with regard to non-viral contaminants is adequately addressed.

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5 Nonclinical aspects

Regarding the marketing authorisation application of Letybo, the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the EU-Assessment Report (decentralised procedure, DE/H/6379/001/DC) that was provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Letybo in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered sufficient. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals and in the RMP.

There are no safety concerns regarding impurities and excipients.

Based on the ERA, the risk for the environment is low.

From the nonclinical perspective, approval may be granted in the proposed indication.

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6 Clinical aspects

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions (DE/H/6379/001/DC). The available assessment report issued by the German authority on 25. January 2022 (*RMS Final Assessment Report DE/H/6379/001/DC Letybo 50 units powder for solution for injection, Clostridium botulinum neurotoxin type A (900 KD)* and the according product information were used as a basis for the clinical evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see Chapter 8 of this report.

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7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Letybo was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Letybo®

Composition

Active substances

Botulinum toxin type A*.
* from *Clostridium botulinum* (strain CBFC26).

Excipients

Human albumin, sodium chloride.
One vial contains 0.18 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Powder for solution for injection.
50 units per vial.
After reconstitution, each 0.1 ml of the solution contains 4 units.
Botulinum toxin units are not transferable from one preparation to another.
One unit corresponds to LD_{50} following intraperitoneal injection in mice under defined conditions.
For intramuscular use.
White powder.

Indications/Uses

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

Dosage/Administration

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

Usual dosage

The recommended dose is a total of 20 units divided into 5 injections of 4 units (0.1 ml): 2 injections in each *corrugator supercilii* muscle and 1 injection in the *procerus* muscle.
Botulinum toxin units from different medicinal products are not interchangeable from one product to another.
Recommended doses are different from other botulinum toxin preparations.

The treatment intervals should not be more frequent than every three months.
If no adverse reactions occur after a treatment session, the treatment may be repeated after no earlier than three months.
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, wrong injection technique, formation of toxin-neutralising antibodies, underdose.
- Re-evaluation of the relevance of treatment with botulinum toxin type A.

The efficacy and safety of repeat injections of Letybo beyond 12 months have not been investigated.

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Special dosage instructions

Elderly patients

There are no clinical data on the use of Letybo in patients older than 75 years. The use of Letybo in persons older than 75 years is not recommended. No specific dose adjustment is required for use in the elderly older than 65 years of age (see "Properties/Effects").

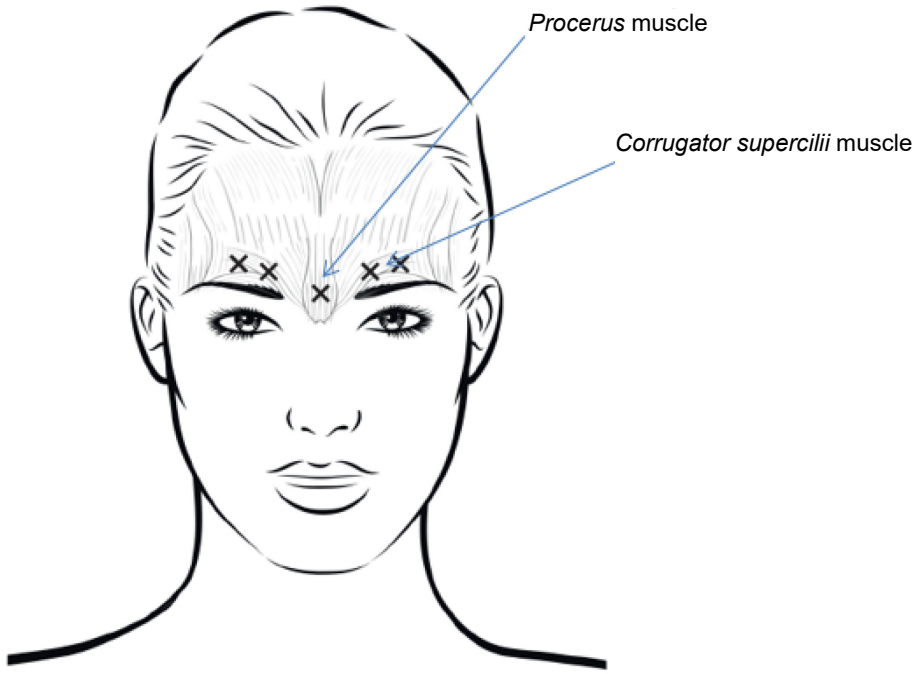
Children and adolescents

There is no relevant use of Letybo in the paediatric population. The safety and efficacy of Letybo in persons under 18 years have not been investigated. The use of Letybo in persons under 18 years is not recommended.

Method of administration

Intramuscular use.
After reconstitution, Letybo must be used only for one session of injections per patient.
For instructions for dilution, use, handling and disposal of the vials, see "Other information".
Intramuscular injections should be performed using a sterile insulin or tuberculin-type syringe with a volume of 1 ml and a 0.01 ml graduation, as well as a needle with a gauge range of 30 to 31 G.
A volume of 0.5 ml of the properly reconstituted Letybo solution should be drawn into the sterile syringe. Any air bubbles in the syringe barrel should be expelled. The needle used to reconstitute the medicinal product should be removed and replaced prior to the injection.
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* muscle 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 the eyebrows. The second injection is made approximately 1 cm above the supraorbital ridge (rigid bony boundaries palpable above the upper part of the upper eyelid) where the midlines of the eyebrows meet. The injection site into the *procerus* muscle is just above the midline of the nasal bridge where horizontal wrinkles develop between the medial ends of the eyebrows. When injecting into the medial end of the *corrugator supercilii* muscle and in 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.

Contraindications

Letybo must not be used in the case of:

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

Warnings and precautions

General

The anatomy of the muscles and 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 "Dosage/Administration" for instructions on how to minimise this risk.
The use of Letybo is not recommended in persons who are under 18 or over 75 years of age.

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 therapeutic 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 injection site have been reported very rarely with botulinum toxin (see "Undesirable effects"). Patients treated with therapeutic doses may experience exaggerated muscle weakness.
Swallowing and breathing difficulties are serious and can result in death. The 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.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free".

Interactions

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.

Pregnancy, lactation

Pregnancy

Up to now, there has been no adequate experience with the use of botulinum toxin type A in pregnant women. Studies in animals have shown reproductive toxicity at high doses (see "Preclinical data"). The potential risk for humans is unknown. Letybo is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation

It is unknown whether botulinum toxin type A is excreted in human milk. Letybo should not be used during lactation.

Fertility

No clinical data are available on the effects on fertility from the use of botulinum toxin type A. Studies in animals with botulinum toxin type A have shown a reduction in fertility (see "Preclinical data").

Effects on ability to drive and use machines

No corresponding studies have been performed. However, botulinum toxin type A has been associated with asthenia, muscle weakness, dizziness and visual disturbance, which could negatively affect driving and the operation of machinery.

Undesirable effects

Summary of the safety profile

The safety of Letybo was evaluated in three pivotal Phase III 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 1 year and including 1 162 patients receiving Letybo. In addition, supportive data are available from a Phase III study in glabellar frown 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 reactions reported were of mild to moderate severity. The most frequent (reported in at least 2 patients treated with Letybo in Cycle 1) adverse reactions in the three pivotal studies for Letybo in glabellar frown 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, haemorrhage and/or bruising have been associated with the injection. Fever and flu syndrome have also been reported after injections of botulinum toxin (see "Warnings and precautions").

List of adverse reactions

The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies 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*
Blood and lymphatic system disorders	rare	blood potassium increased
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, blurry vision, eye pain*, eyelid sensory disorder**
Respiratory, thoracic and mediastinal disorders	rare	pharyngeal hypoaesthesia
Gastrointestinal disorders	rare	constipation, nausea

System organ classification	Frequency	Adverse reaction
Skin and subcutaneous tissue disorders	rare	brow ptosis, dry skin, urticaria
Musculoskeletal and connective tissue disorders	uncommon	Mephisto sign (lateral lift 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
Injury, poisoning and procedural complications	uncommon	contusion, periorbital haematoma*

Note: Of the 1 162 patients treated with Letybo, rare events occurred in 1 subject only.

A “worst-case approach” was used to assign frequencies when events occurred in clinical and post-marketing studies.

* Injection procedure adverse reaction. Note, this information was not collected for the Korean post-marketing study.

** Post-marketing study only

Description of specific adverse reactions and additional information

Application-related adverse reactions

Application-related adverse reactions that have been reported following administration of Letybo are uncommon events individually, common when added together. Uncommon injection site reactions 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 injection site have been reported very rarely with botulinum toxin (e.g. muscle weakness, dysphagia, constipation or aspiration pneumonia which can be fatal) (see "Warnings and precautions").

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

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 cause local, or distant, generalised and profound neuromuscular paralysis. No cases of an oral ingestion of botulinum toxin A have been reported.
Symptoms of an overdose may not be apparent immediately post-injection.

Treatment

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).

Properties/Effects

ATC code

M03AX01

Mechanism of action / Pharmacodynamics

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. The effect usually subsides within 3-4 months after injection when nerve terminals resprout and reconnect with the endplate.

Clinical efficacy

The safety and efficacy of Letybo were investigated in 3 pivotal, double-blind Phase III 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 one treatment. In addition, data are available for 854 patients treated with Letybo in an unblinded extension phase of the studies BLESS I and II for a further 1 to 3 treatments. Supportive data in glabellar frown lines comes from the clinical development program in Korea, comprising a Phase III study (HG-11-01) in 137 patients and a post-marketing study (HG-13-02) in 815 patients.
In studies BLESS I, BLESS II and BLESS III, all patients had moderate (27% of patients) or severe (73% of patients) glabellar frown lines at maximum frown at baseline. Letybo at the dose of 20 units significantly reduced the severity of glabellar frown lines seen at maximum frown, as measured by the investigator's and patient's assessment of glabellar frown 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 a 2-point improvement on the FWS. High response rates in favour of Letybo were also seen when applying the clinically meaningful response definition (achieving a FWS score of 0 or 1, or no lines 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 the facial wrinkle scale (FWS) in the 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 (improvement by ≥ 2 points 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 randomised, 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 wrinkle severity from a baseline value of severe wrinkles (FWS grade 3) to no wrinkles (FWS grade 0) at Week 4 according to investigator's assessment.

The improvement in glabellar frown 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 is between 12 and 16 weeks (see Figure 1).

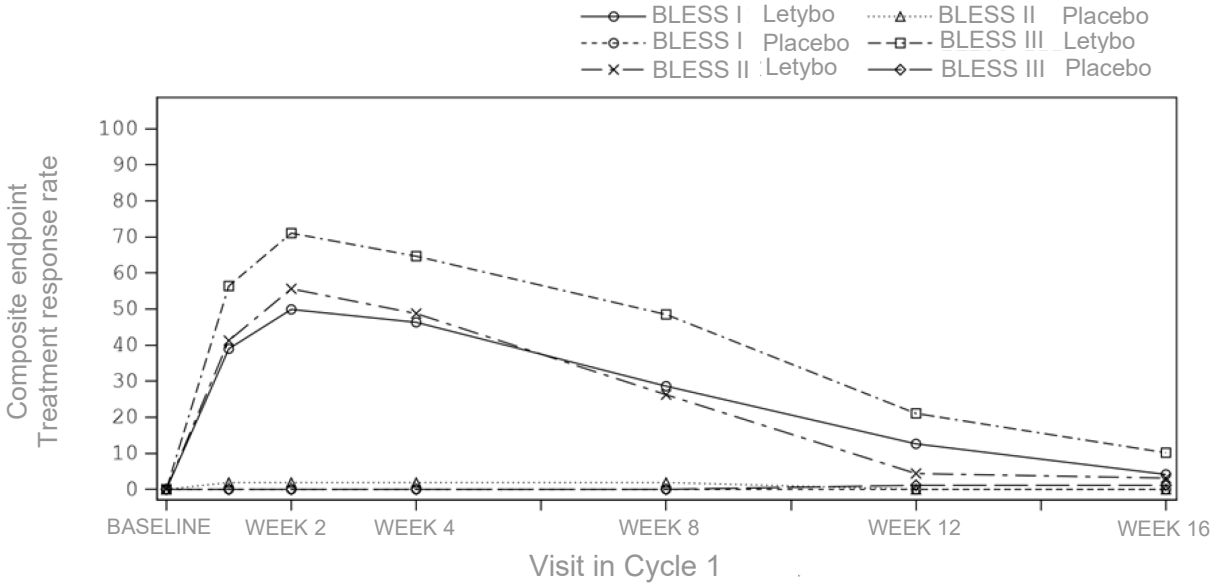


Figure 1: Time course of responder rate (≥ 2-point improvement in FWS required both according to subject and investigator assessment) during Cycle 1 for active versus placebo treatment in pivotal BLESS studies

It could be demonstrated that the responder rate with reduction of the FWS score at rest of ≥ 1 point(s) was statistically significantly higher in the Letybo group compared to 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 1-year study period remained high even though, based on study design, the re-treatment cycles included some tendency 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 frown 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.
The patients reported overall favourable cosmetic results as well as high rates of satisfaction with the outcome.

Post-marketing data

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

Elderly patients

In studies BLESS I, BLESS II and BLESS III, overall, 152/1 272 (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).

Pharmacokinetics

Absorption

Not applicable.

Distribution

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.

Metabolism

Not applicable.

Elimination

Not applicable.

Preclinical data

Single and repeated dose toxicity

Single and repeated-dose toxicity studies with weekly or monthly intramuscular injections of Letybo in rats revealed dose-dependent paralysis of the injected muscle leading to reduced locomotion, decreased food consumption, body weights and creatinine due to muscle 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.

Mutagenicity and carcinogenicity

No studies on the genotoxic or carcinogenic potential of Letybo have been conducted.

Reproductive toxicity

No studies on fertility have been performed with Letybo. However, impairments of male and female fertility in rats have been observed with other botulinum toxin type A-containing products at high doses.

In an embryo-foetal development study with daily intramuscular Letybo injections up to 8 U/kg from gestation day 5 to 16 in pregnant rats, dose-dependent muscle paralysis resulting in muscle 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.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under "Instructions for handling".

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

The reconstituted preparation for injection is not preserved. Chemical and physical in-use stability has been demonstrated for a period of 48 hours at 2 – 8 °C. From a microbiological point of view, the reconstituted solution should be used immediately. If the solution is not used immediately, storage conditions and duration of storage are the responsibility of the user and should normally be no longer than 24 hours at 2 – 8 °C, unless the dilution/reconstitution has taken place under controlled and validated aseptic conditions.

Special precautions for storage

Store in a refrigerator (2 – 8 °C).
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

Instructions for handling

The instructions for use, handling and disposal should be strictly followed.
Reconstitution should be performed in accordance with good practise rules, particularly with regard to 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 recommended to reconstitute the vial contents 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

that 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 national 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 national requirements.

Recommendations in the event of incidents during the handling of botulinum toxin

- Any spills of the medicinal product must be wiped up: either using absorbent material impregnated with a solution of sodium hypochlorite (in case the powder was spilled), or with dry, absorbent material (in case the reconstituted product was spilled).
- 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. In doing so, be careful to avoid 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 and 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.
- If the medicinal product enters into contact with a wound, cut wound or skin injury, rinse thoroughly with abundant water and take the appropriate medical steps according to the dose injected.

Authorisation number

68864 (Swissmedic)

Packs

Packs with 1 vial [A].
Bundle pack with 2 vials (2 packs with 1 vial each) [A].
Bundle pack with 6 vials (6 packs with 1 vial each) [A].

Marketing authorisation holder

Medius AG, 4132 Muttenz

Date of revision of the text

June 2023