swissmedic

Date: 17 April 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Relfydess

International non-proprietary name:	botulinum toxin type A (strain l01)
Pharmaceutical form:	solution for injection
Dosage strength(s):	150 units / 1.5 mL
Route(s) of administration:	intramuscular use
Marketing authorisation holder:	IPSEN Pharma Schweiz GmbH
Marketing authorisation no.:	69620
Decision and decision date:	approved on 10 March 2025

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.

Table of contents

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
IM	intramuscular
INN	International non-proprietary name
ITT	Intention-to-treat
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
Ph. Eur.	European Pharmacopoeia
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)
USP	Unites States Pharmacopeia

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 I01) in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Relfydess is indicated for the temporary improvement in the appearance of:
- moderate to severe glabellar lines at maximum frown
- moderate to severe lateral canthal lines at maximum smile,

alone or in combination, in adult patients aged 18 years and older, when the severity of the facial lines has an important psychological impact.

2.2.2 Approved indication

Relfydess is used for temporary improvement in the appearance of:
- moderate to severe glabellar lines at maximum frown
- moderate to severe lateral canthal lines at maximum smile,

alone or in combination, in adult patients under 65 years, when the severity of these lines has a significant psychological impact on the patient.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended dose for the treatment of the glabellar lines is a total of 50 units divided into five injections of 10 units (0.1 mL) each: 2 injections in each corrugator muscle and 1 injection in the procerus muscle.
The recommended dose for the treatment of the lateral canthal lines is a total of 60 units divided into six injections of 10 units (0.1 mL) each: 3 injections in each orbicularis oculi muscle.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	30 October 2023
Formal objection	16 November 2023
Response to formal objection	15 December 2023
Formal control completed	12 January 2024
List of Questions (LoQ)	29 April 2024
Response to LoQ	26 July 2024
Preliminary decision	23 October 2024

Response to preliminary decision	13 December 2024
Labelling corrections and other aspects	20 February 2025
Response to labelling corrections and other aspects	25 February 2025
Final decision	10 March 2025
Decision	approval

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

The botulinum toxin type A drug substance (QM1114-DS, BoNT/A) consists of two protein subunits; a 100 kDa heavy chain and a 50 kDa light chain that are connected by a disulfide bond between two cysteine residues.
The manufacturing process for QM1114-DS consists of fermentation of botulinum toxin, type A in Clostridium botulinum bacteria. The original Clostridium botulinum bacterial cell line was isolated from a soil sample. After the fermentation under anaerobic conditions, the cell culture fluid is harvested and the neurotoxin product is purified by several filtration and chromatographic steps. The drug substance manufacturing process is performed by Q-Med AB, Uppsala, Sweden. The manufacturing process was validated, and the validation demonstrated a consistent manufacturing process that effectively reduces process-related impurities. The physicochemical and biological properties of the drug substance and its impurities were characterised using state-of-the-art methods.
The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for appearance, identity, several purity and impurity tests, protein concentration and a specific activity test. Specifications are in conformance with current compendial (including Ph. Eur. 2113) or regulatory guidelines. All the analytical methods are described, and non-compendial methods were validated in accordance with ICH guidelines. Batch analysis data for several batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release.
The drug substance is stored frozen. No significant changes were observed within the proposed storage conditions. A shelf-life of 36 months at long-term (<- 70°C) storage has been accepted.

4.2 Drug product

Relfydess is available as 100 units / mL drug product solution for injection, which is supplied as a sterile solution with no preservatives in a single-use vial. It is intended for intramuscular injection. All excipients used comply with the European Pharmacopoeia.
The finished product manufacturing process consists of sterile filtration, aseptic filling, capping, visual inspection, labelling, and secondary packaging. The whole process is conducted at Q-Med AB, Uppsala, Sweden. Process validation studies were executed at commercial scale using three validation batches.
The specifications for the drug product were based on compendial requirements, including Ph. Eur. 2113. They include relevant tests and limits, e.g. for appearance, identity, potency, pH, visible and subvisible particles, bacterial endotoxins and sterility. All specific methods are validated in accordance with ICH guidelines. Batch analysis data from development, clinical, and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.
The drug product is stored in 2R Type I clear glass vials at 2 - 8°C, protected from light. Each vial is closed with a butyl rubber stopper. The stoppered vial is sealed with an aluminium closure with a flip-off button. All components are Ph. Eur. and USP compliant. A shelf-life of 18 months has been accepted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated studies.

5 Nonclinical aspects

5.1 Pharmacology

No in vitro pharmacology studies were conducted, which is accepted given that the primary pharmacodynamic profile of botulinum toxin type A (BoNT/A) is already well-established. In vivo data showed that botulinum neurotoxin type A1 (QM1114-DP) produces dose-dependent local paralysis of the injected muscle comparable with other BoNT/A marketed products. Secondary and safety pharmacology studies were not conducted, which is accepted due to the local effect of QM1114-DP, its lack of systemic distribution, and the well-established safety profile in clinical settings.

5.2 Pharmacokinetics

Preclinical pharmacokinetics or ADME studies were not conducted for QM1114-DP, which is deemed acceptable. The product is highly specific to cholinergic terminals and is intended solely for local treatment. In case of an unintended systemic exposure at detectable levels, toxicity would be expected.

5.3 Toxicology

Findings in the toxicity studies were consistent with the well-known pharmacological effects and toxicological profile of botulinum toxin A products, including paralysis of the injected muscle accompanied by atrophy, reduced muscle fibres, and interstitial fibrosis. Effects seen in the haematological examinations were secondary to the pharmacological effect. Genotoxicity and carcinogenicity studies were not conducted. The drug product exhibited good local tolerance. The absence of fertility, embryofoetal and pre- and postnatal developmental toxicity studies is accepted, as the impact of BoNT/A on reproductive and developmental toxicity is already well documented in animals.

5.4 Nonclinical conclusions

The pharmaco-toxicological profile of QM1114-DP is sufficiently well characterised. The submitted nonclinical data support the approval of QM1114-DP in the proposed indication. Relevant information has been included in the Information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

No pharmacokinetic or drug metabolism studies were conducted with the product. It is intended for local intramuscular (IM) injections into the facial muscles, and no systemic exposure is expected due to the small volume of the injections.

6.2 Final clinical benefit risk assessment

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority in Sweden. The clinical aspects in this SwissPAR refer to the publicly available assessment report Relfydess, SE/H/2438/01/DC issued by the Swedish Medical Products Agency.

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

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.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Relfydess 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.

▼ 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.

Relfydess®

Composition

Active substances

Botulinum toxin type A (150 kD) from *Clostridium botulinum* (Strain I01)

Excipients

Disodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate dihydrate, potassium chloride, sodium chloride, polysorbate 80, L-tryptophan, water for injections
One vial contains 5.4 mg sodium, 0.18 mg potassium and 1.6 mg polysorbate 80.

Pharmaceutical form and active substance quantity per unit

Clear, colourless to pale yellow solution for injection for intramuscular use
150 units of botulinum toxin type A (150 kD) per vial (= 1.5 mL solution).
Botulinum toxin units are not interchangeable from one medicinal product to another. The recommended dosages differ from those of other medicinal products of botulinum toxin.
One unit corresponds to the LD_{50} after intraperitoneal use in mice under defined conditions.

Indications/Uses

Relfydess is used for temporary improvement in the appearance of:

- moderate to severe glabellar lines at maximum frown
- moderate to severe lateral canthal lines at maximum smile,

alone or in combination, in adult patients under 65 years, when the severity of these lines has a significant psychological impact on the patient.

Dosage/Administration

Relfydess may only be used by suitably qualified physicians with appropriate experience in this treatment and having the required equipment.

Botulinum toxin units vary depending on the medicinal product. The units of Relfydess are specific to this medicinal product and are not transferable to other botulinum toxin preparations.
Each vial of Relfydess may only be used for one single patient during a single treatment session. Any residual product remaining after treatment should be discarded.
The dosage and treatment interval depend on the individual response determined in each patient. The treatment interval with Relfydess should be no more frequent than every 12 weeks.
When treating adult patients with Relfydess for glabellar lines and lateral canthal lines, alone or in combination, the cumulative dose should be taken into account when other botulinum toxin products are or have been used to treat other indications approved for these products.
The recommended injection sites for glabellar lines are described in Figure 1; the recommended injection site for lateral canthal lines are described in Figure 2.

Usual dosage

Relfydess is ready to use with a concentration of 10 units per 0.1 mL and does not require reconstitution.

Table 1: Dosing instructions for Relfydess

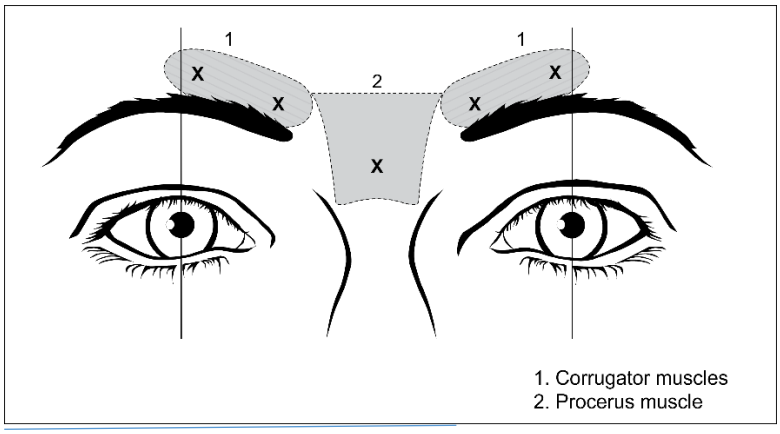
Treatment(s)	**Total recommended dose**	**Dose per injection**
Glabellar lines (GL)	50 units/0.5 mL	5 injections of 10 units/0.1 mL: 2 injections on each side into the corrugator muscle and 1 injection into the procerus muscle near the nasofrontal angle (see **Figure 1**)
Lateral canthal lines (LCL)	60 units/0.6 mL	6 injections of 10 units/0.1 mL: 3 injections on each side into the orbicularis oculi muscle (see **Figure 2**)
Combined treatment of glabellar lines and lateral canthal lines	110 units/1.1 mL	11 injections totalling 10 units/0.1 mL for combined GL and LCL

Glabellar lines

The recommended dose for the treatment of glabellar lines in adults is a total of 50 units/0.5 mL, which are administered in equal parts (10 units/0.1 mL per injection) by intramuscular injection into each of the 5 intramuscular injection sites (see **Figure 1**): 2 injections on each side into the corrugator muscle and 1 injection into the procerus muscle near the nasofrontal angle.
In order to reduce the risk of eyelid ptosis, the following measures should be taken:

- Avoid injections near the *levator palpebrae superioris* muscle, particularly in patients with larger brow-depressor complexes.
- Lateral *corrugator* injections should be placed at least 1 centimetre above the bony supraorbital ridge.
- Ensure that the injected dose (volume) is accurate.
- The injection should be given no closer than 1 centimetre above the middle eyebrow.

Figure 1: Injection site locations for glabellar lines

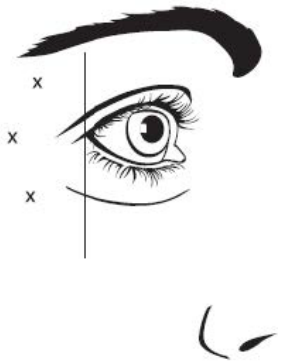


Lateral canthal lines

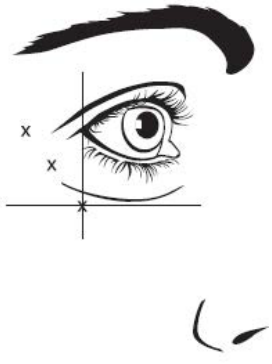
The recommended dose for the treatment of lateral canthal lines in adults is a total of 60 units/0.6 mL administered by intramuscular injection, which are divided into equal parts of 10 units/0.1 mL and given into each of the 6 intramuscular injection sites (see **Figure 2**: Option 1 and Option 2):
3 injections (30 units/0.3 mL) on each side into the *orbicularis oculi* muscle. The injections should be given with the needle pointing obliquely upwards and away from the eye into the lateral *orbicularis oculi* muscle. When lines in the lateral canthal region appear both above and below the lateral *canthus*, inject as per Option 1. When lines in the lateral canthal region appear mainly below the lateral *canthus*, *inject as per* Option 2.

Figure 2: Injection site locations for lateral canthal lines

Option 1: Above and below the lateral *canthus*



Option 2: Below the lateral *canthus*



The anatomical landmarks of lateral canthal lines can be more readily identified if observed and palpated at maximal smile. Care must be taken not to inject the *zygomaticus major/minor* muscles, in order to avoid lateral mouth drop and an asymmetrical smile.

Combined treatment of glabellar lines / lateral canthal lines

For combination treatment of glabellar lines and lateral canthal lines, the respective individual dosage and administration should be followed for a total dose of 110 units/1.1 mL of Relfydess.

The recommended dose for the treatment of glabellar lines is 50 units/0.5 mL (10 units/0.1 mL per injection) into each of 5 intramuscular injection sites and - for the treatment of lateral canthal lines - 60 units/0.6 mL (10 units/0.1 mL into each of 6 intramuscular injection sites).

General information

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

If treatment fails or the effect diminishes after repeat injections, alternative therapeutic methods should be used. In case of treatment failure after the first administration, the following measures may be considered:

- Analysis of the reasons for treatment failure, e.g. incorrect muscles injected, or inappropriate injection technique, formation of toxin-neutralising antibodies
- Re-evaluation of the relevance of treatment with botulinum toxin A

Treatment duration

The safety and efficacy of repeat injections with Relfydess has been studied for up to 12 months and for up to 7 repeat treatment cycles.

Elderly patients

There are limited clinical data on the use of Relfydess in patients over 65 years. The use of Relfydess in individuals over 65 years is not recommended.

Children and adolescents

The safety and efficacy of Relfydess have not been established in individuals under 18 years. The use of Relfydess in individuals under 18 years is not recommended.

Contraindications

Relfydess must not be used in the following cases:

- Hypersensitivity to the active substance or to any of the excipients listed in the composition.
- Infections at the intended injection sites.
- Presence of myasthenia gravis, Eaton-Lambert syndrome or amyotrophic lateral sclerosis.

Warnings and precautions

General

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

The use of Relfydess is not recommended in individuals under 18 or over 65 years.

As with all intramuscular injections, the use of Relfydess in patients with prolonged bleeding time is not recommended.

Hypersensitivity reactions

Serious and/or immediate hypersensitivity reactions have been reported for botulinum toxin products. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue oedema and dyspnoea. If such a reaction occurs, further injection of Relfydess should be discontinued and appropriate medical therapy immediately instituted, provided that the required equipment and medicinal products are available.

Local and distant spread of the toxin effect

Post-marketing safety data from other approved botulinum toxin products suggest that the effects of botulinum toxin may be observed beyond the site of local injection. Symptoms are consistent with the mechanism of action for botulinum toxins and may include asthenia, generalised muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have occurred hours to weeks after injection.

Swallowing and breathing difficulties may be life-threatening and there are reports of fatalities associated with the spread of the toxin effect. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In particular, very rare cases of fatalities have been reported following treatment with botulinum toxin in patients with dysphagia, pneumopathy or significant asthenia. Therefore, treatment in such patients must be carried out under the supervision of a specialist and only if the benefit of treatment outweighs the risk.

Patients or caregivers should be instructed to consult a physician immediately in the event of swallowing, speaking or breathing difficulties.

No subjects in the Relfydess clinical development programme experienced distant spread of the toxin effect.

Existing neuromuscular disorders

Relfydess should be used with caution in patients at risk for marked neuromuscular transmission defects. These patients may have increased sensitivity to active substances such as botulinum toxin and may experience excessive muscle weakness (including systemic effects of severe dysphagia and impaired breathing) following treatment. In some of these cases, dysphagia persisted for several months and required the placement of a nasogastric tube.

Pre-existing conditions at the injection site

Caution is advised when Relfydess is used in the presence of inflammation at the proposed injection site(s), or excessive weakness or atrophy of the targeted muscle(s).
Caution is advised when Relfydess treatment is used in patients with marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring or thick sebaceous skin.
Adverse ophthalmic reactions
Dry eyes, reduced tear production, reduced blinking and corneal disorders may occur with the use of botulinum toxins. If dry eye symptoms (e.g. eye irritation, photophobia or visual changes) persist, the patient should be referred to an ophthalmologist.
Muscular atrophy
After repeated botulinum toxin treatment, muscle atrophy can be expected due to flaccid paralysis of the treated muscles.

Antibody formation
Injections at shorter intervals or at higher doses may increase the risk for the formation of neutralising antibodies against botulinum toxin. Clinically speaking, the formation of neutralising antibodies may compromise the effectiveness of subsequent treatments.

Excipients
This medicine contains potassium, but less than 1 mmol (39 mg) per vial, that is to say essentially ‘potassium-free’. This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.
This medicine contains 1.6 mg polysorbate 80 per vial, equivalent to 1.1 mg/mL. Polysorbates may cause allergic reactions.

Interactions

No interaction studies have been conducted.
Concomitant treatment with Relfydess and other botulinum toxin products, aminoglycosides or other medicinal products that affect neuromuscular conduction (e.g. curare-like agents), anticholinergics and muscle relaxants should only proceed with caution, as the effect of Relfydess may be potentiated.

Pregnancy, lactation

Pregnancy
There are no adequate data on the use of botulinum toxin type A in pregnant women. There are no sufficient animal studies with respect to reproductive toxicity (see “Preclinical data”). The potential risk for the patient is unknown. Relfydess should not be used during pregnancy or in women of childbearing potential who are not using contraception.

Lactation

It is unknown whether Relfydess is excreted in human milk. The excretion of Relfydess in milk has not been studied in animals. Relfydess must not be used during breast-feeding.

Fertility

No clinical data are available on the effect of Relfydess on fertility. No animal studies on fertility have been conducted. Animal studies with other preparations containing botulinum toxin type A have shown a reduction in fertility (see “Preclinical data”).

Effects on ability to drive and use machines

Other botulinum toxin products have been reported to have minor or moderate influence on the ability to drive and/or use machines. There is a potential risk of localised muscle weakness or visual disturbances associated with the use of Relfydess, which may temporarily affect the ability to drive or use machines.

Undesirable effects

Summary of the safety profile

The majority of adverse reactions reported after treatment in the pivotal placebo-controlled phase III studies with Relfydess were mild to moderate in intensity. The most commonly reported adverse reactions were injection site bruising and headache, which occurred in approximately 2% of subjects. In general, treatment/injection technique-related reactions occurred within the first month after injection and were transient.

The adverse reactions are from pivotal placebo-controlled clinical phase III studies with Relfydess and are arranged by primary system organ class (SOC) for each preferred term in MedDRA.

In the combined treatment of glabellar and lateral canthal lines, the type and frequency of adverse reactions were comparable to those observed with treatment of the individual indications.

List of adverse reactions

The frequency of adverse reactions is classified as follows:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 2: Moderate to severe glabellar lines

The following adverse reactions have been observed in patients receiving Relfydess for temporary improvement in the appearance of moderate to severe glabellar lines.

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	common	Headache
Eye disorders	common	Eyelid ptosis
Skin and subcutaneous tissue disorders	uncommon	Eyebrow ptosis
Musculoskeletal and connective tissue disorders	uncommon	Muscular weakness
General disorders and administration site conditions	common	Injection site bruising

Table 3: Moderate to severe lateral canthal lines

The following adverse reactions have been observed in patients receiving Relfydess for temporary improvement in the appearance of moderate to severe lateral canthal lines.

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	common	Headache
Musculoskeletal and connective tissue disorders	uncommon	Muscular weakness
General disorders and administration site conditions	common	Injection site bruising
	uncommon	Injection site pain

Related TEAEs (injection site reactions)*

In addition, the following treatment-emergent adverse effects (TEAEs) associated with injection site reactions in Relfydess-treated subjects (receiving ≥ 50 U) were specified in the “pool of all placebo-controlled studies”: Injection site pruritus, swelling, erythema, discomfort, haematoma, hypersensitivity and warmth.

Related TEAEs (Spock brow)*

Spock brow (Mephisto sign) has been reported in one subject as a related TEAE of mild intensity in the open-label long-term study. This event subsided after three weeks. This results in an overall incidence of 0.06% (1/1708 subjects) for Spock brow in the safety pool of phase III studies, in which subjects received ≥ 50 U.

*Considered related by the investigator at the individual adverse event level
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 new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

Excessive doses can lead to extensive and profound neuromuscular paralysis. An overdose may lead to an increased risk of the botulinum toxin entering the bloodstream, and may cause complications associated with the effects of oral botulinum poisoning (e.g. dysphagia and dysphonia).
Symptoms of an overdose may not appear immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically monitored for several weeks for signs and/or symptoms of excessive muscle weakness or muscle paralysis.

Treatment

Hospitalisation should be considered in patients with obvious symptoms of botulinum toxin overdose. In the event of an overdose, the patient should be medically monitored for signs and/or symptoms of excessive muscle weakness or muscle paralysis. General supportive care is recommended and, if necessary, symptomatic treatment should be instituted. Ventilation may be required in the event of an overdose leading to paralysis of the respiratory muscles.

Properties/Effects

ATC code

M03AX01

Mechanism of action

The known mechanism of action for botulinum type A products consists in blocking the release of acetylcholine from the presynaptic neuronal synapse. The heavy chain of botulinum toxin type A mediates attachment and internalisation of the toxin protein, while the light chain is an enzyme that cleaves the synaptosome-associated protein of 25 kDa (SNAP-25).
When injected intramuscularly, the toxin leads to partial paralysis of the affected muscle, which temporarily reduces muscle activity, leading to a transient reduction of glabellar lines or lateral canthal lines. Botulinum toxin type A products have a long duration of action in animals and humans measured in weeks to months. Muscle function returns gradually when nerve fibres grow back with

new nerve terminals, thus innervating the muscles and reversing the denervation caused by administration of the toxin.

Pharmacodynamics

Known effects of botulinum toxin type A products include blocking the release of acetylcholine from the presynaptic neuronal synapse.

Clinical efficacy

The data described below reflect results in the phase III placebo-controlled studies READY-1, READY-2 and READY-3. A total of 1,012 patients were treated in three pivotal studies, including 806 patients treated with Relfydess and 206 patients treated with placebo. A further 902 patients treated with Relfydess took part in an open-label, long-term safety study (READY-4). A total of 1708 patients were treated with Relfydess in all phase III studies.
The subjects' psychological functions were observed using the FACE-Q™ mental well-being scale (which incorporates subject ratings on the themes of self-liking, feeling positive, feeling good, feeling happy, satisfaction with self, self-acceptance, feeling confident, feeling attractive and feeling great). The FLTSQ scale (Facial Line Treatment Satisfaction Questionnaire) was used to determine subject satisfaction with GL and/or LCL appearance (the subjects rated whether they were comfortable with certain facial expressions or positions, whether the facial lines were visible, whether the skin was smooth, whether it looked youthful, whether it looked good for its age, whether it looked relaxed, whether it looked attractive, whether it looked rested and whether it looked rejuvenated), but also to determine subject satisfaction with the treatment (the subjects rated whether they were satisfied with repeat treatment, treatment recommendations, expected results, naturalness, right treatment choice, satisfaction with treatment results, but also the treatment outcome itself and satisfaction with the improvement as a result of treatment).
Responses to the FACE-Q™ psychological function scale and FLSTQ scale showed that Relfydess-treated subjects showed an improvement in psychological functions at all post-treatment time points and were more satisfied with their treatment and appearance than subjects on placebo. As demonstrated by the FACE-Q™ and FLTSQ scales, positive psychological function and subject satisfaction were furthermore still maintained 6 months after treatment.
Patients receiving Relfydess (1699 in total) were tested for antibody formation against the drug at baseline and after each treatment. No patients tested positive for toxin-neutralising antibodies.

Glabellar lines (READY-1 and READY-3)

In two pivotal, multicentre, double-blind, placebo-controlled phase III studies, 451 patients were treated in glabellar lines (GL) at the recommended dose of 50 units. READY-1 investigated Relfydess only for the treatment of treatment of glabellar lines; READY-3 investigated combination treatment of glabellar lines and lateral canthal lines (LCL). The results from READY-3 are described for patients receiving Relfydess for both GL and LCL in combination.

The primary efficacy endpoint was the proportion of subjects responding to treatment, defined as achievement of a score of 0 or 1 in glabellar line severity on the GL-ILA 4-point scale (Investigator Live Assessment) for glabellar line severity at maximum frown at the Month 1 visit. The majority of subjects in both the Relfydess and placebo groups had severe glabellar lines at study baseline, as determined by the investigator (74.5% and 75.8% respectively).

Treatment success for GL as measured by the investigator (GL-ILA, using a 4-point scale [0 = none, 1 = mild, 2 = moderate, 3 = severe], at maximum frown) was statistically significantly greater ($p < 0.001$) in the Relfydess group compared to the placebo group after one month (Table 4).

Table 4: Investigator assessment of glabellar line treatment success[a] (% and number of subjects) at Month 1[b] in double-blind, placebo-controlled clinical studies

Study	Relfydess 50 units GL	Relfydess 50 units GL and 60 units LCL	Placebo
READY- 1, GL only	96.3% N = 199	-	4.5% N = 67
READY- 3 LCL & GL treatment	94.3% N = 106	96.3% N = 108	1.8% N = 55

[a] achieved a score of 0 or 1 in GL severity on GL-ILA

[b] priimary efficacy endpoint on day 30; $p < 0.001$

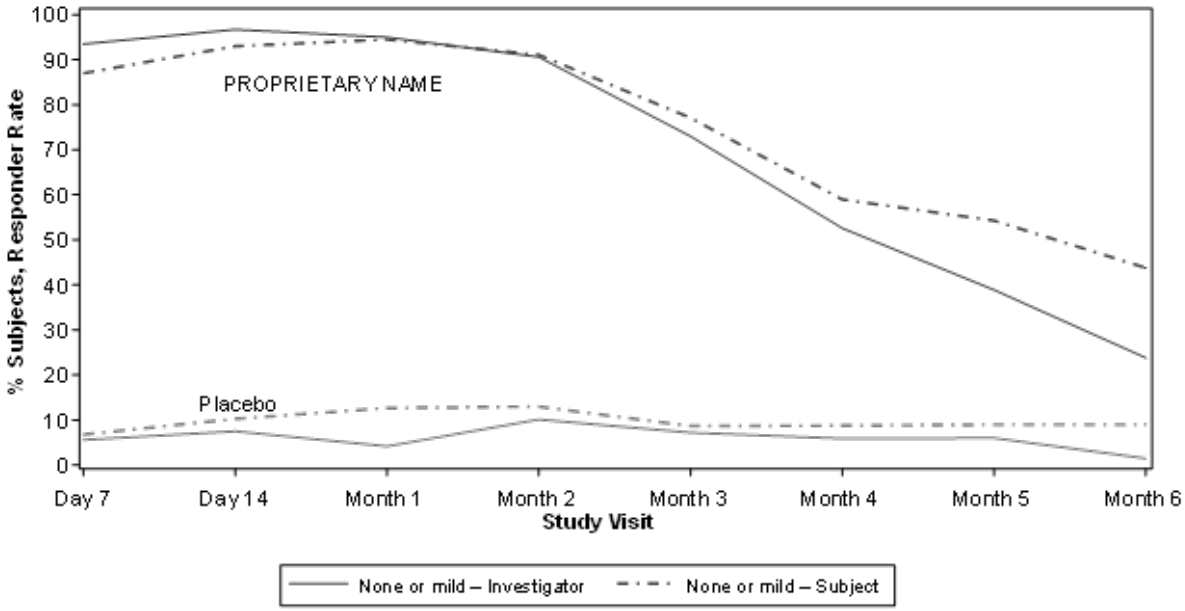
Subgroup analyses of the primary efficacy endpoint of response rates based on the GL-ILA 4-point scale at maximum frown at Month 1 showed the efficacy of Relfydess regardless of age, race, prior botulinum toxin use or baseline severity on the GL-ILA at maximum frown.

For subjects achieving a score of 0 or 1 on both the photographic GL-ILA 4-point scale and the static GL-SLA 4-point scale at maximum frown, the median number of days to a loss of a score of 0 or 1 was 168 days (24 weeks) in READY-1 and 140 days (20 weeks) in READY-3.

One month post-injection, 98% of patients treated with Relfydess in READY-1 and READY-3 showed an improvement in glabellar lines of at least one grade at maximum frown, based on investigator assessment of glabellar line severity. Six months post-injection, 58% of patients treated with Relfydess in the READY-1 study and 46% of patients in the READY-3 study still showed an improvement, compared with patients treated with placebo (10% in the READY-1 study and 4% in the READY-3 study, $p < 0.001$).

For these READY-1 subjects, the median number of days to return to baseline GL severity could not be calculated, as more than half of the subjects had not returned to baseline by the end of the study (≥ 24 weeks). 75% of the subjects in the Relfydess group returned to baseline after 169 days (> 24 weeks). In the READY-3 subjects, the median number of days to return to baseline in the Relfydess group was 179 days (26 weeks) in the glabellar lines treatment pool and 172 days (25 weeks) in the GL-Relfydess/LCL placebo group and 189 days (27 weeks) in the GL-Relfydess/LCL Relfydess group.
An investigator-assessed improvement in GL severity was determined in the Relfydess group, compared to the placebo group over a 6-month period (Figure 3).

Figure 3: Relfydess investigator- and subject assessment of the glabellar line response rate (achieving a score of none[a] or mild[b] in GL severity) compared to placebo over time (READY-1)[c, d]



[a] score of none = 0
[b] score of mild = 1
[c] Statistically significantly higher responder rate (based on GL-ILA 4-point scale at maximum frown in the Relfydess group) compared to placebo (p-value < 0.001) at all time points up to Month 6.
[d] Statistically significantly higher responder rate (based on GL-SLA 4-point scale at maximum frown in the Relfydess group) compared to placebo (p-value < 0.001) at all time points up to Month 6.

In combined treatment with LCL, response (achieving 0 or 1 on the GL-ILA at maximum frown) was statistically significantly higher in the Relfydess-GL/Relfydess LCL group compared to the placebo-GL/placebo-LCL group throughout the entire 6 months post-treatment.

Lateral canthal lines (READY-2 and READY-3)

In two pivotal, multicentre, double-blind, placebo-controlled phase III studies, 471 patients were treated in lateral canthal lines (LCL) at the recommended dose of 60 units. READY-2 investigated Relfydess for the treatment of LCL only; READY-3 investigated the combination treatment of GL and

LCL. The results for READY-3 are described for patients receiving Relfydess for both GL and LCL in combination.

The primary efficacy measure was the proportion of subjects achieving a score of 0 or 1 on the LCL-ILA 4-point scale (LCL-Investigator Live Assessment) for the severity of lateral canthal lines at maximum smile at the Month 1 visit. Approximately 40% of subjects both in the Relfydess and placebo group had severe bilateral symmetrical lateral canthal lines at study baseline, as determined by the investigator (42.3% and 42.7%, respectively).

Treatment success for LCL as measured by the investigator (LCL Investigator Live Assessment, using a 4-point scale [0 = none, 1 = mild, 2 = moderate, 3 = severe], at maximum smile) was statistically significantly greater in the Relfydess group compared to the placebo group after one month ($p < 0.001$) (Table 5).

Table 5: Investigator assessment of lateral canthal line treatment success[a] (% and number of subjects) at Month 1[b] in double-blind, placebo-controlled clinical studies

Study	Relfydess 60 units LCL	Relfydess 60 units LCL & 50 units GL	Placebo
READY-2, LCL only	87.2% N = 204	-	11.9% N = 69
READY-3 , LCL & GL treatment	78.1% N = 117	83.3% N = 108	19.3% N = 55

[a] achieved a score of 0 or 1 in LCL severity on LCL-ILA

[b] priimary efficacy endpoint on day 30; $p < 0.001$

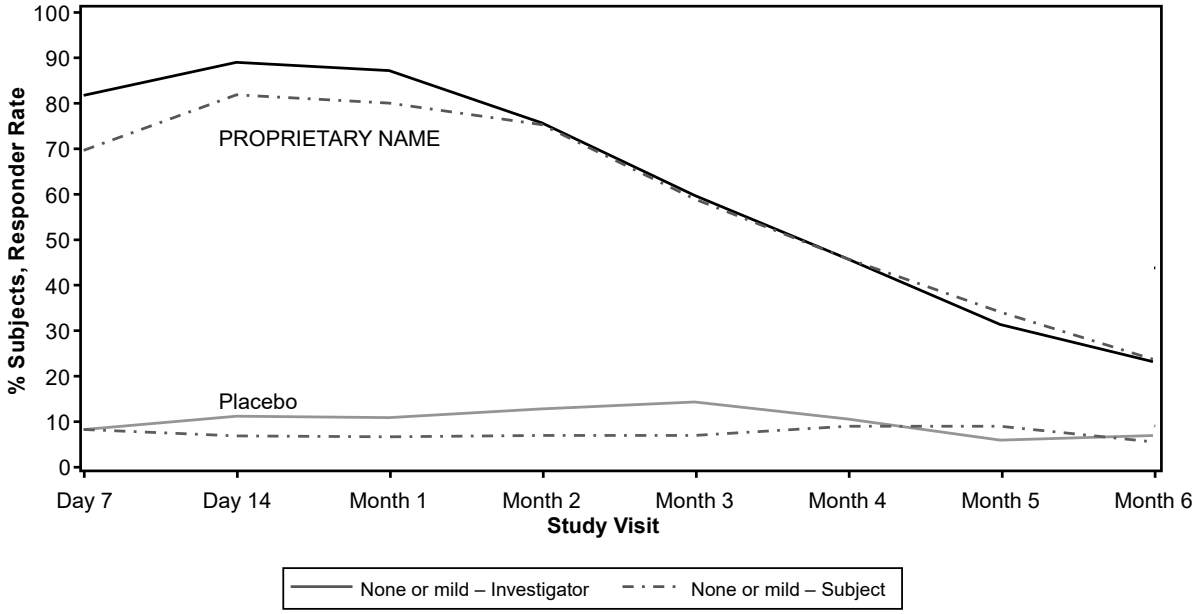
Subgroup analyses of the primary efficacy endpoint of responder rates based on the LCL-ILA 4-point photoscale at maximum smile at Month 1 showed the efficacy of Relfydess regardless of age, race, prior botulinum toxin use or baseline severity on the LCL-ILA at maximum smile.

In subjects scoring 0 or 1 on both the LCL-ILA 4-point scale and LCL-SLA static 4-point scale at maximum smile, the median number of days to loss of a score of 0 or 1 in the Relfydess group was 144 days (21 weeks) in the lateral canthal lines treatment pool and 162 days (23 weeks) in READY-2, 140 days (20 weeks) in the GL Placebo/LCL Relfydess group and 142 days (20 weeks) in the GL Relfydess/LCL Relfydess group in READY-3.

One month post-injection, 93% of patients treated with Relfydess in READY-2 and 3 showed an improvement in LCL of at least one grade at maximum smile, based on investigator assessment of lateral canthal line severity. Six months post-injection, 36% of patients treated with Relfydess in the READY-2 study and 33% of patients in the READY-3 study still showed an improvement, compared with patients treated with placebo (15% in the READY-2 study and 13% in the READY-3 study, $p < 0.003$).

In these subjects, the median number of days to return to baseline LCL severity in the Relfydess group was 173 days (25 weeks) in the treatment pool for lateral canthal lines and in the READY-2 study, 168 days (24 weeks) in the GL-placebo/LCL Relfydess group and 174 days (25 weeks) in the GL-Relfydess/LCL Relfydess group in READY-3. In the READY-2 study, 75% of subjects in the Relfydess group returned to baseline after 147 days (21 weeks), and in the LCL group after 141 days (20 weeks). In the READY-3 study, 75% of subjects in the GL placebo/LCL Relfydess group returned to baseline after 139 days (20 weeks), and after 147 days (21 weeks) for subjects in the GL Relfydess/LCL Relfydess group.
Improvement in LCL severity, as assessed by investigators and subjects, was demonstrated in the Relfydess group beyond 6 months, compared to the placebo group (Figure 4).

Figure 4: Relfydess investigator- and subject-assessed lateral canthal line response rate (achieving a score of none[a] or mild[b] in LCL severity) compared to placebo over time (READY-2)[c, d]



[a] score of none = 0

[b] score of mild = 1

[c] Statistically significantly higher responder rate (based on LCL-ILA 4-point scale at maximum smile in the Relfydess group) compared to placebo ($p < 0.001$) at all time points up to Month 5; Month 6, p-value = 0.002

[d] Statistically significantly higher responder rate (based on LCL-SLA 4-point scale at maximum smile in the Relfydess group) compared to placebo ($p < 0.001$) at all time points up to Month 6.

In combined treatment with GL, response (achieving 0 or 1 on the LCL-ILA at maximum smile) was statistically significantly higher ($p = 0.052$) in the Relfydess-GL/Relfydess LCL group compared to the placebo-GL/placebo-LCL group at all post-treatment time points except Month 6 ($p = 0.052$).

Open-label study (READY- 4)

READY-4 was a multicentre, open-label, phase III study to investigate the safety of repeated injections of Relfydess for the long-term treatment of moderate to severe glabellar lines and lateral canthal lines (with an interval of at least 12 weeks between treatment cycles).
In READY-4, Relfydess administration of up to 110 IU and up to 7 GL and/or LCL treatments over a 52-week study period showed favourable efficacy results for both glabellar lines and lateral canthal lines, whether treated concomitantly or independently.

Pharmacokinetics

Absorption

Relfydess is not expected to be present in peripheral blood at measurable amounts after intramuscular injection. Pharmacokinetic studies have therefore not been performed.

Distribution

Not applicable

Metabolism

Not applicable

Elimination

Not applicable

Kinetics in specific patient groups

No data.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of acute toxicity and repeated dose toxicity.

Mutagenicity and carcinogenicity
No studies have been conducted on the genotoxic or carcinogenic potential of Relfydess.

Reproductive toxicity
No fertility and embryotoxicity studies have been conducted with Relfydess. However, impairment of male and female fertility has been observed in rats after high dosages of other products containing botulinum toxin type A. Embryofetal effects have been observed in reproductive studies with other botulinum toxin type A. The effects on peri-/postnatal development have not been investigated.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date marked as "EXP" on the pack.

Special precautions for storage

Store in the refrigerator (2-8°C). Do not freeze.
Store in the original package in order to protect the contents from light.
Keep out of the reach of children.

The unopened vial can be stored protected from light at a maximum of 25°C for 24 hours.

Instructions for handling

Immediately after treating the patient, any Relfydess remaining in the ampoule or syringe should be inactivated with dilute hypochlorite or sodium hydroxide solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Recommendations in the event of an incident occurring while handling botulinum toxin:

- Spilled product must be wiped up with dry, absorbent material.
- Contaminated surfaces should be cleaned with dilute hypochlorite or sodium hydroxide solution and then dried.
- If a vial is broken, proceed as mentioned above by carefully collecting the pieces of broken glass and wiping up the product, without injuring the skin.
- If the product comes into contact with the skin, wash the affected site with soap and water.
- In the event of contact with the eyes, rinse thoroughly with plenty of water or an eyewash solution.
- If the product comes into contact with a wound, cut or skin injury, rinse thoroughly with plenty of water and consult a physician.

These instructions for use, handling and disposal must be strictly observed.

Authorisation number

69620 (Swissmedic)

Packs

Pack of 1 vial with 100 units/mL solution for injection. [A]

Pack of 10 vials with 100 units/mL solution for injection. [A]

Marketing authorisation holder

Ipsen Pharma Schweiz GmbH, 6300 Zug, Switzerland

Manufacturer

Q-Med AB, Uppsala, Sweden

Supplier company

Galderma Ltd, 6300 Zug

Date of revision of the text

October 2024