Swiss Summary of the Risk Management Plan (RMP) for RELFYDESS (QM1114-DP)

Based on the EU-RMP RELFYDESS® (QM1114-DP) version 4.0 dated 30-Jul-2024, with Data Lock Point 20-Jul-2022 and on the Switzerland-Specific Annex (SSA) to the EU-RMP for RELFYDESS® version 1.0 dated 11-Dec-2024, with Data Lock Point 20-Jul-2022

Generic name	QM1114-DS (Drug Substance) (Botulinum toxin type A; relabotulinumtoxinA)
Active substance(s) (INN or common name):	*Clostridium botulinum* Toxin Type A1
Invented name(s) in Switzerland	RELFYDESS® (QM1114-DP [Drug Product])
Name of Marketing Authorisation Holder:	Ipsen Pharma Schweiz GmbH, Industriestrasse 47, 6300 Zug, Switzerland
Swiss Summary RMP Version	1.0
Date of document:	20-Mar-2025

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The Swiss RMP summary of RELFYDESS® (QM1114-DP) is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of RELFYDESS® (QM1114-DP) in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Galderma SA is fully responsible for the accuracy and correctness of the content of the published summary RMP of RELFYDESS®.

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Part VI: Summary of the Risk Management Plan

This is a summary of the risk management plan (RMP) for Relfydess (QM1114-DP). The RMP details important risks of Relfydess, how these risks can be minimised, and how more information will be obtained about Relfydess's risks.

Relfydess's Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Relfydess should be used.

Important new concerns or changes to the current ones will be included in updates of Relfydess's RMP.

I. The Medicine and What it is used for

RELFYDESS is authorised for the temporary improvement in the appearance of:

- moderate to severe glabellar (frown) lines
- moderate to severe lateral canthal (crow's feet) lines

alone, or in combination.

See the SmPC (Section 4.1) for the full indications. It contains botulinum toxin type A as the active substance, and it is given by intramuscular injection with the dose and location of injection dependent on which indication RELFYDESS is being used to treat.

II. Risks associated with the medicine and activities to minimize or further characterise the risks

Important risks of RELFYDESS, together with measures to minimise such risks, are outlined below. Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, via Periodic Safety Update Reports (PSUR) and signal detection activities, so that action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

There are no additional risk minimisation measures for RELFYDESS.

If important information that may affect the safe use of RELFYDESS is not yet available, it will be listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Relfydess are risks that need further characterisation and/or special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Important identified risks are concerns for which there is sufficient proof of a link with the use of the product. Important potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

The important identified risks, important potential risks and missing information for Relfydess are listed below.

List of important risks and missing information	
Important identified risks	• Eyelid ptosis
Important potential risks	• Distant spread of toxin • Hypersensitivity • Development of neutralising antibodies • Development or exacerbation of neuromuscular disorders • Incorrect drug administration or inappropriate use due to 150 U vial size
Missing information	• Use in pregnancy and lactation

II.B Summary of important risks

The important identified risks, important potential risks and missing information for Relfydess are summarised below.

Important identified risk: Eyelid ptosis	
Evidence for linking the risk to the medicine	Evidence for this risk classification comes from the clinical development programme for Relfydess, where eyelid ptosis was reported in ≤ 3% of subjects treated in the double-blind placebo-controlled studies. Eyelid ptosis has been included as an adverse drug reaction for use of Relfydess for the treatment of glabellar lines. Eyelid ptosis is also reported in clinical trials with other approved botulinum toxin products following treatment of upper facial lines and is considered a class effect of botulinum toxin injections due to local spread of the toxin.
Risk factors and risk groups	Risk factors include administration of excessive doses of the product, very frequent re-injections, injection of the product into inappropriate muscles around the eye area and incorrect administration technique by an inexperienced injector near or into the upper eyelid muscle. Patients with bell’s palsy, pre-existing ptosis, altered facial anatomy with reduced or absent orbital septum, or who have excessive weakness or atrophy of the target muscle as a result of previous injection(s)/intervention(s) are also at increased risk of developing eyelid ptosis.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: Dosage/Use; Warnings and precautions; Undesirable effects • Ready to use solution in a vial • Prescription only medicine **Additional risk minimisation measures:** Routine pharmacovigilance activities are considered adequate as the risk is already well characterised. There are no additional risk minimisation measures.
Additional pharmacovigilance activities	None

Important potential risk: Distant spread of toxin	
Evidence for linking the risk to the medicine	No adverse events suggestive of distant spread of toxin were reported during the Relfydess clinical development programme for treatment of glabellar lines and lateral canthal lines, alone or in

	combination, with up to 7 treatments with Relfydess and with a maximum follow-up for 12 months. Distant spread of toxin is a rare but well-recognised safety concern with botulinum toxin, first identified from post-marketing surveillance (i.e., real world use) of other approved botulinum toxin products following use in therapeutic indication(s) and is included as a warning for the majority of botulinum toxin products. Adverse events due to distant spread of toxin are unlikely at the relatively low doses of Relfydess recommended for the treatment of GL and/or LCL (maximum of 110 units). It has been classified as an important potential risk for Relfydess based on class effect, as the distant spread of the toxin can produce unwanted weakness of other muscles or more generalised systemic effects (effects throughout the body) such as dysphagia (difficulty swallowing), dyspnoea (difficulty breathing) and respiratory failure (not breathing in sufficient oxygen) which can sometimes be life-threatening.
Risk factors and risk groups	Patients with neuromuscular disorders and those with a risk of marked defective neuromuscular transmission (disorders that impair muscle function) have an increased sensitivity to botulinum toxin which may make them more susceptible to the clinical consequences of distant spread of toxin. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to complications of distant spread of toxin. Caution should be exercised when treating such patients with Relfydess.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: Dosage/Use; Warnings and precautions; Overdose • Ready to use solution in a vial • Prescription only medicine **Additional risk minimisation measures:** Routine pharmacovigilance activities are considered adequate as the risk is already well characterised. There are no additional risk minimisation measures.
Additional pharmacovigilance activities	None

Important potential risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Evidence for this risk classification comes from the clinical development programme for Relfydess where hypersensitivity events potentially related to treatment were reported occasionally (≤ 0.5%) in the double-blind and open-label clinical studies with

	Relfydess (≥ 50 units) for treatment of glabellar lines and lateral canthal lines, alone or in combination.
Risk factors and risk groups	Botulinum toxin, a protein secreted by Clostridium botulinum, undergoes a series of purification processes before clinical application. The more complex proteins contained in the drug, the higher the probability of causing allergies. Relfydess formulation is, however, free from any accessory or complexing proteins and is also devoid of animal or human derived proteins. Patients who are atopic and/or who have underlying allergic conditions such as eczema, asthma and allergic rhinitis are considered to be at increased risk of severe hypersensitivity reactions and/or anaphylaxis. Confounding factors like drug-induced hypersensitivity from the use of concomitant medications and a patient's pre-existing history of hypersensitivity of any aetiological form or subtypes, whether drug or non-drug induced, may predispose a patient to develop hypersensitivity events.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: Contraindications; Warnings and precautions • Ready to use solution in a vial • Prescription only medicine **Additional risk minimisation measures:** Routine pharmacovigilance activities are considered adequate as the risk is already well characterised. There are no additional risk minimisation measures.
Additional pharmacovigilance activities	None

Important potential risk: Development of neutralising antibodies	
Evidence for linking the risk to the medicine	No subject showed seroconversion for neutralising antibodies following treatment with Relfydess in the clinical development programme with a maximum follow-up for 12 months. It should be noted that the active substance in Relfydess is specifically formulated without any accessory or complexing proteins and is also devoid of animal or human derived proteins. Development of neutralising antibodies is a well-recognised safety concern with use of other approved botulinum toxin products observed mostly following long-term treatment of therapeutic indication(s). It has been included as an important risk for Relfydess based on class effect, as the development of neutralising antibodies could neutralise the activity of Relfydess and cause secondary lack of response to subsequent treatments. The majority of patients in the postmarketing setting are normally tested for

	neutralising antibodies only if they develop lack of treatment effect. However, it should be noted that a reduced treatment effect is not a definitive measure of the presence of neutralising antibodies as there could be other potential causes for lack of efficacy.
Risk factors and risk groups	Theoretically, the higher the dose, the more is the protein load and therefore bigger the risk of developing the antibodies. Clinical immunogenicity, most often, has been reported to be dose dependent. Excessive doses per visit, higher total cumulative doses, prior botulinum toxin treatments for any indication, and shorter interval between consecutive treatments may provoke immune response leading to antibody production. Genetic predisposition or major histocompatibility susceptibility of patients may play a role in developing immunoresistance; association between production of antibody against botulinum toxin type A and certain major histocompatibility complex class II molecules has been demonstrated in patients treated with botulinum toxin type A.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: Dosage/Use; Warnings and precautions; Properties/effects (*Clinical efficacy*) • Ready to use solution in a vial • Prescription only medicine **Additional risk minimisation measures:** Routine pharmacovigilance activities are considered adequate as the risk is already well characterised. There are no additional risk minimisation measures.
Additional pharmacovigilance activities	None

Important potential risk: Development or exacerbation of neuromuscular disorders	
Evidence for linking the risk to the medicine	Patients with history or presence of any disorders of neuromuscular function were excluded from the Relfydess clinical development programme. Events indicative of exacerbation of or unmasking of subclinical neuromuscular disorders have been reported with other approved botulinum toxin type A products from clinical trials following treatment of aesthetic indications and from isolated postmarketing case reports in literature following treatment of other indications.

	'Development of or exacerbation of neuromuscular disorders' is also an important identified risk with a more recently approved botulinum toxin type A product. 'Development or exacerbation of neuromuscular disorders' has been classified as an important potential risk for Relfydess based on class effect, as Relfydess injection in such patients can worsen the symptoms of pre-existing or subclinical disease and may result in excessive muscle weakness.
Risk factors and risk groups	Use of Relfydess in patients with myasthenia gravis, Eaton Lambert Syndrome or amyotrophic lateral sclerosis is contraindicated. Relfydess should be used with caution in patients with a risk of marked defective neuromuscular transmission, as they may have an increased sensitivity to botulinum toxin. Relfydess injections in such patients may make them more susceptible to clinical effects of Relfydess, may worsen symptoms of the pre-existing disease condition or unmask the subclinical disease potentially leading to excessive muscle weakness and other local or systemic adverse reactions.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Section: Contraindications • SmPC Section: Warnings and precautions • Ready to use solution in a vial • Prescription only medicine **Additional risk minimisation measures:** Routine pharmacovigilance activities are considered adequate as the risk is already well characterised. There are no additional risk minimisation measures.
Additional pharmacovigilance activities	None

Important potential risk: Incorrect Drug Administration or Inappropriate Use Due to 150 U Vial Size	
Evidence for linking the risk to the medicine	The recommended total Relfydess dose in adults for the treatment of glabellar lines is 50 units, for the treatment of lateral canthal lines is 60 units and for the combination treatment of glabellar lines and lateral canthal lines is 110 units. The vial supplied contains 150 units of Relfydess for injection. If a patient is treated only for the glabellar lines indication (total recommended dose 50 units) or only for the lateral canthal lines indication (total recommended dose 60 units), the residual Relfydess dose in the vial has the potential to be inappropriately

	used or intentionally misused to treat off-label indications or it could potentially lead the physician to incorrectly administer the product.
Risk factors and risk groups	Patients seeking treatment with Relfydess for improving their aesthetic appearance.
Risk minimisation measures	**Routine risk minimisation measures:** • SmPC Sections: Dosage/Use; Other information (Instructions for handling) • Ready to use solution in a vial • Prescription only medicine **Additional risk minimisation measures:** Routine pharmacovigilance activities are considered adequate. There are no additional risk minimisation measures.
Additional pharmacovigilance activities	None

Missing Information: Use in Pregnancy and lactation	
Risk Minimization Measures	**Routine risk minimisation measures:** • SmPC Sections: Pregnancy, breastfeeding; Preclinical data • Ready to use solution in a vial • Prescription only medicine **Additional risk minimisation measures:** Routine pharmacovigilance activities are considered adequate. There are no additional risk minimisation measures.
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Relfydess.

II.C.2 Other studies in post-authorisation development plan

There are no other studies required for Relfydess.