Swiss Summary of the Risk Management Plan (RMP)

NUCEIVA®

(Botulinum toxin type A)

Active substances

Botulinum toxin type A produced by Clostridium botulinum.

Pharmaceutical form and active substance per unit

Powder for solution for injection

50 and 100 Units botulinum toxin type A per vial

After reconstitution each 0.1 mL contains 4 Units

Excipients

Human albumin, 0.45 mg sodium chloride (50 Units) resp. 0.9 mg sodium chloride (100 Units).

A vial contains 0.45 mg sodium (50 units) and 0.9 mg sodium (100 units).

Version 1 (01 December 2023)

Based on RMP, version 4.0, dated 27 October 2023

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 minimize them. The RMP summary of NUCEIVA® 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 NUCEIVA in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Evolus is fully responsible for the accuracy and correctness of the content of the published summary RMP of NUCEIVA.

While the RMP details both the 100 unit and 50 unit vial, only the 50 unit vial is approved for marketing in Switzerland.

Part VI: Summary of the Risk Management Plan

This is a summary of the risk management plan (RMP) for NUCEIVA®. The RMP details important risks of NUCEIVA®, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information).

The summary of product characteristics (SmPC) for NUCEIVA® and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how NUCEIVA® should be used. Important new concerns or changes to the current ones will be included in updates of the NUCEIVA® RMP.

I. The Medicine and What it Is Used For

NUCEIVA® is authorised for the temporary improvement in the appearance of moderate to severe vertical lines between the eyebrows seen at maximum frown (glabellar lines), when the severity of the above facial lines has an important psychological impact in adults below 65 years of age.

NUCEIVA® contains *Clostridium botulinum* type A neurotoxin as the active substance and it is given by injection.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of NUCEIVA®, together with measures to minimise such risks and the proposed studies for learning more about the risks of NUCEIVA®, are outlined below:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL 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 (eg, 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, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of NUCEIVA® are risks that need 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. Identified risks are concerns for which there is sufficient proof of a link with the use of NUCEIVA®. 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 (eg, on the long-term use of the medicine).

Summary of safety concerns	
Important identified risks	Eyelid ptosis Immunogenicity Distant spread of toxin Development of or exacerbation of neuromuscular disorders Hypersensitivity
Important potential risks	Incorrect drug administration due to 100U vial Long-term use
Missing information	Use during pregnancy and lactation

II.B Summary of Important Risks

Important identified risk: Eyelid ptosis	
Evidence for linking the risk to the medicine	Events indicative of eyelid ptosis were observed in the EVOLUS pre-registration clinical development programme related to administration of NUCEIVA.
Risk factors and risk groups	Incorrect administration near/into the upper eyelid levator muscle and patients with reduced or absent orbital septum[1] [1]Finsterer J. Ptosis: causes, presentation, and management. Aesthetic Plast Surg. 2003;27(3):193-204.
Risk minimisation measures	Routine risk minimisation measures: NUCEIVA is a prescription medicine administered by clinicians. Text in NUCEIVA EU SmPC and EU PIL: EU SmPC: • Information and diagrams in section 4.2 of the EU SmPC regarding the administration steps to be taken in order to reduce the complication of eyelid ptosis. • Information in section 4.4 of the EU SmPC that the relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering NUCEIVA and injection into vulnerable anatomic structures must be avoided. • Information in section 4.4 of the Eu SmPC communicates a specific warning regarding the risk of eyelid ptosis • Information in section 4.8 of the EU SmPC that eyelid ptosis is a common adverse drug reaction EU PL: • Information in section 2 of the EU PL that drooping of the eyelid may occur after treatment • Information in section 4 of the EU PL that drooping eyelid is a common adverse drug reaction Additional risk minimisation measures: *None*

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional PASS

Important identified risk: Immunogenicity	
Evidence for linking the risk to the medicine	The immunogenicity properties of NUCEIVA were assessed in the EVOLUS pre-registration clinical development programme. Immunogenicity was observed in the EVOLUS pre-registration clinical development programme.
Risk factors and risk groups	Excessive (including too frequent) dosing may enhance the risk of seroconversion.
Risk minimisation measures	Routine risk minimisation measures: NUCEIVA is a prescription medicine administered by clinicians Text in NUCEIVA EU SmPC and EU PIL: EU SmPC: • Information in section 4.2 of the EU SmPC that NUCEIVA treatment intervals should not be more frequent than every three months. • Information in section 4.4 of the EU SmPC communicates a specific warning regarding the risk of immunogenicity • Information in section 4.8 of the EU SmPC communicates immune response as undesirable effect EU PL: • Guidance in section 2 of the EU PL that to limit the risk of antibody formation, the interval between two treatments must not be less than three months. Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional immunogenicity analysis and neutralising antibody analysis for non-responders who volunteer blood samples.

Important identified risk: Distant spread of toxin	
Evidence for linking the risk to the medicine	Events indicative of distant spread of toxin were observed in the EVOLUS pre-registration clinical development programme related to administration of NUCEIVA.
Risk factors and risk groups	Patients with an underlying condition that would make them more susceptible to the clinical consequences of the distant spread of toxin, such as those with dysphagia. Physical manipulation (such as rubbing) of the injection site in the immediate post-administration period.
Risk minimisation measures	Routine risk minimisation measures: NUCEIVA is a prescription medicine administered by clinicians. Text in NUCEIVA EU SmPC and EU PIL: EU SmPC: • Information in section 4.2 of the EU SmPC that physical manipulation (such as rubbing) of the injection site in the immediate post-administration period should be avoided. • Information in section 4.4 of the EU SmPC that injection of NUCEIVA is not recommended in patients with a history of dysphagia and aspiration and that patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. • Adverse reactions possibly related to the spread of toxin distant from the site of administration listed as class effect in section 4.8 of the EU SmPC EU PL: • Information in section 2 of the EU PL communicates a specific warning regarding the risk of local and distant spread of toxin effect. • Guidance in section 2 of the EU PL that patient should visit their doctor immediately if they find it difficult to swallow, to speak or to breathe after treatment. • Information in section 4 of the EU PL that patient should visit their doctor immediately if they have any difficulty in breathing, swallowing or speaking after receiving NUCEIVA (in upper case text). Additional risk minimisation measures: *None*

Important identified risk: Development of or exacerbation of neuromuscular disorders	
Evidence for linking the risk to the medicine	Events indicative of development exacerbation of neuromuscular disorders were observed in the EVOLUS clinical development programme related to administration of NUCEIVA.

Risk factors and risk groups	Patients with pre-existing neuromuscular transmission disorders.
Risk minimisation measures	Routine risk minimisation measures: NUCEIVA is a prescription only medicine administered by clinicians. Text in NUCEIVA EU SmPC and EU PIL: EU SmPC: • Information in section 4.3 of the EU SmPC that NUCEIVA is contraindicated in the presence of myasthenia gravis or Eaton Lambert Syndrome. • Information in section 4.4 of the EU SmPC communicates a specific warning regarding use in patients with pre-existing neuromuscular disorders. • Information in section 4.4 of the EU SmPC that patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. EU PL: • Information in section 2 of the EU PL that NUCEIVA must not be used if patient has a pre-existing myasthenia gravis or Eaton-Lambert syndrome and is not recommended in patients with dysphagia or breathing problems • Information in section 2 of the EU PL that patient should visit their doctor immediately if they find it difficult to swallow, to speak or to breathe after treatment. • Information in section 4 of the EU PL that patient should visit their doctor immediately if they have any difficulty in breathing, swallowing or speaking after receiving NUCEIVA (in upper case text). Additional risk minimisation measures: *None*

Important identified risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Events indicative of hypersensitivity were observed in the EVOLUS pre-registration clinical development programme related to administration of NUCEIVA. All events were considered non-serious and resolved.
Risk factors and risk groups	Patients with hypersensitivity to any components of NUCEIVA, it's excipients or other Botulinum toxin (Type A or B) products.
Risk minimisation measures	Routine risk minimisation measures: NUCEIVA is a prescription medicine administered by clinicians

	Text in NUCEIVA EU SmPC and EU PIL: EU SmPC: • Information in section 4.3 of the EU SmPC that NUCEIVA is contraindicated in patients with known hypersensitivity to active substance or to any of the excipients of the formulation • Information in section 4.4 of the EU SmPC communicates a specific warning regarding the risk of hypersensitivity. • Information in section 4.4 of the EU SmPC that patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise. EU PL: • Information in section 2 of the EU PL that patient should visit their doctor immediately if they find it difficult to swallow, to speak or to breathe after treatment. • Information in section 2 of the EU PL that NUCEIVA must not be used if patient has a known allergy to botulinum toxin type A or any other ingredient • Information in section 2 of the EU PL communicates allergic reaction as a potential adverse drug reaction • Information in section 4 of the EU PL that patient should visit their doctor immediately if they have any difficulty in breathing, swallowing or speaking after receiving NUCEIVA (in upper case text). Additional risk minimisation measures: *None*

Important potential risk: Incorrect drug administration due to 100U vial	
Evidence for linking the risk to the medicine	No occurrences of incorrect drug administration due to 100U vial have been observed. However, it cannot be excluded due to the approved indications for other Botulinum toxin Type A products and publicly reported use of single-use vials of other Botulinum toxin Type A products into multiple patients[1]. [1] Yang GC, Chiu RJ and Gillman G., Questioning the Need to Use Botox Within 4 Hours of Reconstitution; A Study of Fresh vs 2-Week-Old Botox. JAMA Facial Plastic surgery, 2008:10(4):273-9
Risk factors and risk groups	Prescribers wishing to treat multiple patients with a single vial to reduce wastage. Patients who have developed immunogenicity to other Botulinum toxin Type A products and lack alternative treatment options.
Risk minimisation measures	Routine risk communication: EU SmPC:

	• Information in section 4.2 of the EU SmPC that NUCEIVA is for single use and after reconstitution, must be used only for one session of injection(s) per patient. • Information in section 6.3 of the EU SmPC that from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2° to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions. • Information in section 6.6 of the EU SmPC that it is mandatory that NUCEIVA is used for one single patient treatment only during a single session. EU PL: • *None*. Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Development and replacement of 100U vial by 50U vial size

Important potential risk: Long-term use	
Evidence for linking the risk to the medicine	No direct comparison between multiple vs single administration of NUCEIVA is available in the absence of an active controlled extension of the pivotal study EVB003. Indirect comparison of multiple vs single administration of NUCEIVA is limited by several confounders.
Risk factors and risk groups	Repeated NUCEIVA dosing
Risk minimisation measures	Routine risk communication: EU SmPC: • Information in section 4.2 of the EU SmPC that the efficacy and safety of repeat injections beyond 12 months has not been evaluated. EU PL: • *None* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional PASS.

Missing information: Use in pregnancy and lactation	
Evidence for linking the risk to the medicine	No embryofoetal toxicity was observed in the EVOLUS pre-registration clinical development programme. However, other Botulinum toxin Type A products approved for marketing in the USA have a Pregnancy Category C FDA label.[1,2] There is limited data on the safety of use of NUCEIVA in breastfeeding women, including no information on whether NUCEIVA is excreted in human milk. [1] Xeomin® (incobotulinum A) for injection, USA Prescribing Information, Dec 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125360lbl.pdf [2] BOTOX® Cosmetic (onabotulinum A) for injection, USA Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5236lbl.pdf
Risk factors and risk groups	Pregnant and breastfeeding women
Risk minimisation measures	Routine risk minimisation measures: NUCEIVA will be a prescription only medicine administered by clinicians. Text in NUCEIVA EU SmPC and EU PIL: EU SmPC: • Information in section 4.6 of the EU SmPC that NUCEIVA is not recommended during pregnancy and in women of childbearing potential not using contraception. • Information in section 4.6 of the EU SmPC that NUCEIVA should not be used during breast-feeding. EU PL: • Guidance in section 2 of the EU PL that patients should contact their doctor if they are pregnant, planning pregnancy or become pregnant while being treated. Additional risk minimisation measures: *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 NUCEIVA®.

II.C.2 Other Studies in Post-Authorisation Development Plan

A non-interventional PASS is being conducted. Its objective is to provide additional characterisation of the long-term safety of NUCEIVA®. The study protocol includes the systematic recording of previous exposure to botulinum toxin A. (ONGOING)

Retesting of previously negative sera from studies EV-001, EV-002, EV-004, EV006 was undertaken using alternative binding Anti-Drug Antibody (ADA) assays for screening, confirmation and determination of ADA titres, supported by a sensitive assay for neutralising ADA. (COMPLETE)

Upon receipt of any product complaint regarding lack of response, EVOLUS will contact the treating physician and offer blood sample testing for neutralising antibodies (NAb), to be organised and funded by Evolus. The testing will be performed using validated NAb detection method (recognizing that they may have already had pre-existing NAb to botulinum toxin before exposure to NUCEIVA). Results of the testing will be provided back to the treating physician, factored into routine signal detection and reported in PSURs. (ONGOING)

Lastly, a 50U vial size has been developed and approved to replace the 100U vial to reduce the potential risk of incorrect drug administration (misuse) due to 100U vial administration. (COMPLETE)