swissmedic

Date: 2 February 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Nuceiva

International non-proprietary name: botulinum toxin type A (strain KCDC)
Pharmaceutical form: powder for solution for injection
Dosage strength(s): 50 units
Route(s) of administration: intramuscular use
Marketing authorisation holder: PharmaCons GmbH
Marketing authorisation no.: 69120
Decision and decision date: approved on 16.11.2023

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.

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
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
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)

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 KCDC) in the above-mentioned medicinal product.

2.2 Indication and dosage

2.2.1 Requested indication

Nuceiva is indicated 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.

2.2.2 Approved indication

Nuceiva is indicated 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.

2.2.3 Requested dosage

Summary of the requested standard dosage:

The recommended injection per muscle site is 4 U/0.1 mL. Five injection sites: 2 injections in each corrugator muscle (inferior medial and superior medial aspect) and 1 injection in the procerus muscle for a total dose of 20 units.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	8 September 2022
Formal objection	6 October 2022
Response to formal objection	13 October 2022
Formal control completed	24 October 2022
List of Questions (LoQ)	6 February 2023
Response to LoQ	25 April 2023
Preliminary decision	18 July 2023
Response to preliminary decision	20 August 2023
Final decision	16 November 2023
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 (DWP-450 DS) is a covalently bonded dimer of 2 complexes consisting of a neurotoxin, NTNH (non-toxic, non-haemagglutinin) protein, and HA (haemagglutinin) proteins (HA50, HA33, HA20, and HA17).
The manufacturing process for DWP-450 DS consists of fermentation of botulinum toxin type A in *Clostridium botulinum* bacterium. The original *Clostridium botulinum* bacterial cell line was isolated from a soil sample. After fermentation under anaerobic conditions, the neurotoxin product is harvested by precipitation steps, extraction, and clarification by centrifugation. The toxin complex is further purified by chromatographic steps, precipitation, and filtration.
The drug substance manufacturing process is performed by Daewoong Pharmaceutical Co., Ltd, Hwaseong-si, Korea. The manufacturing process was validated and the validation demonstrated a consistent manufacturing process that effectively reduces process-related impurities. Characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed 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 impurities 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 under appropriate storage conditions. No significant changes have been observed within the proposed shelf life. A shelf life of 36 months at long-term (<-70°C) storage conditions has been accepted.

4.2 Drug product

Nuceiva is available as 50 units of drug product solution for injection. Nuceiva (50 units) is supplied as a sterile, white to yellowish, preservative free, vacuum dried powder for solution for intramuscular injection to be reconstituted with 0.9% (w/v) sodium chloride solution. Each vial contains botulinum toxin type A (from *Clostridium botulinum* 50 U), human serum albumin, and sodium chloride as excipients. The excipients – human serum albumin, sodium chloride, and water for injection (removed upon vacuum drying) – comply with the requirements of the respective Ph. Eur. monograph. Each vial of vacuum-dried Nuceiva is reconstituted with 1.25 mL of 0.9% sterile, non-preserved saline solution to give a final concentration of 4 U/0.1 mL.
The manufacturing process for the finished drug product consists of formulation, sterile filtration, filling and half-stoppering, vacuum drying and stoppering, cap sealing, visual inspection, labelling, and secondary packaging. The whole process is conducted at Daewoong Pharmaceutical Co., Ltd, Hwaseong-si, Korea. Process validation studies were executed at commercial scale using several validation batches for each Nuceiva strength.
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, content, potency, purity and impurities, pH, visible and subvisible particles, bacterial endotoxins, and sterility. All non-compendial methods are validated in accordance with ICH guidelines.
Batch analysis data for non-clinical, clinical, and process validation batches were provided. All batch release data comply with the commercial drug product specifications. Comparability between batches used in the development phase and batches of the commercial manufacturing process was demonstrated.
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.

The vials are stored at 2°C to 8°C, protected from light. The stability data support a shelf life of 30 months.

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 and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

5 Nonclinical aspects

5.1 Nonclinical conclusions

Regarding the marketing authorisation application for Nuceiva, the Division Nonclinical Assessment conducted an abridged evaluation, which was based on the EU EPAR assessment reports EMA/CHMP/421730/2019 and EMA/CHMP/551456/2020 dated 25 July 2019 and 12 November 2020 provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Nuceiva in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

There are no safety concerns regarding impurities and excipients.

Nuceiva does not represent a risk for the environment at the prescribed dose.

EMA/PDCO granted a product-specific waiver for all subsets of the paediatric population.

In conclusion, from a nonclinical point of view, approval is supported.

6 Clinical aspects

6.1 Final clinical benefit-risk assessment

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions (EMEA/H/C/004587/0000). The available assessment report issued by the European Medicines Agency (EMA) on 25 July 2019 (*CHMP assessment report Nuceiva, botulinum toxin type A, Procedure No. EMEA/H/C/004587/0000)* and the corresponding product information were used as a basis for the clinical evaluation.

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 Nuceiva 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 section ”Undesirable effects” for how to report adverse reactions.

NUCEIVA®

Composition

Active substances

Botulinum toxin type A produced by *Clostridium botulinum (KCDC strain).*

Excipients

Human albumin, 0.45 mg sodium chloride.

A vial contains 0.18 mg sodium.

Pharmaceutical form and active substance quantity per unit

Powder for solution for injection.

50 Units botulinum toxin type A per vial.

After reconstitution each 0.1 mL contains 4 Units.

The botulinum toxin units of different drugs are not interchangeable. The recommended dosages differ from those of other botulinum toxin drugs.

One unit corresponds to the LD_{50} after intraperitoneal injection in mice under defined conditions.

For intramuscular use.

Indications/Uses

NUCEIVA is indicated 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.

Dosage/Administration

NUCEIVA should only be administered by physicians with appropriate qualifications and expertise in the treatment of glabellar lines and the use of required equipment.

Usual dosage

The recommended injection per muscle site is 4 U/0.1 mL. Five injection sites (see Figure 1): 2 injections in each corrugator muscle (inferior medial and superior medial aspect) and 1 injection in the procerus muscle for a total dose of 20 Units.

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

In the absence of adverse reactions during the initial treatment, an additional course of treatment can be performed subject to a minimum interval of 3 months between the initial and repeat treatment.
In the event of treatment failure (no visible improvement of glabellar lines at maximum frown) one month after the first course of treatment, the following approaches may be considered:

- Examination of the causes of failure, e.g. inappropriate injection technique, incorrect muscles injected, and formation of botulinum toxin-neutralising antibodies.
- Re-evaluation of the appropriateness of treatment with botulinum toxin type A.

The efficacy and safety of repeat injections beyond 12 months has not been evaluated.
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 limited clinical data with NUCEIVA in patients older than 65 years (see ”Properties/Effects”). NUCEIVA is not recommended for use in patients over 65 years of age.

Children and adolescents
There is no relevant use of NUCEIVA in children and adolescents. The safety and efficacy of NUCEIVA in persons under 18 years of age have therefore not been investigated. The use of NUVCEIVA in persons under 18 years of age is not recommended.

Method of administration
Intramuscular use.
Once reconstituted, NUCEIVA should only be used to treat a single patient, during a single session.
Precaution to be taken before manipulating or administering the product
For instructions for use, precaution before manipulating or administering the product, handling and disposal of the vials, see ”Other information - Special precautions for disposal and other handling”.
Care should be taken to ensure that NUCEIVA is not injected into a blood vessel when it is injected in the vertical lines between the eyebrows seen at maximum frown (also known as glabellar lines) (see ”Warnings and precautions”).
Physical manipulation (such as rubbing) of the injection site in the immediate post-administration period should be avoided.

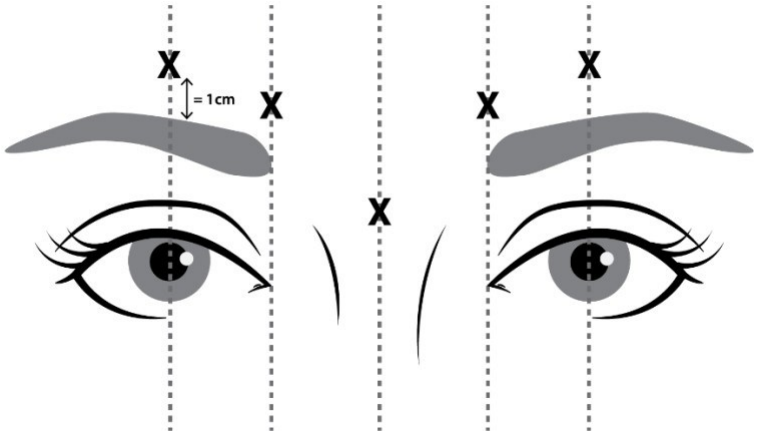
Administration instructions for Glabellar Lines seen at maximum frown
Reconstituted NUCEIVA (50 Units/1.25 mL) is injected using a sterile 30 gauge needle.
In order to reduce the complication of eyelid ptosis the following steps should be taken:

- Two injections should be administered in each corrugator muscle (inferior medial and superior

medial aspect) and 1 injection in the procerus muscle for a total dose of 20 Units.

- Injection near the levator palpebrae superioris should be avoided, particularly in patients with larger brow depressor complexes.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

Figure 1: Injection Points



Contraindications

NUCEIVA must not be used in:

- Hypersensitivity to the active substance or one of the excipients according to composition.
- Generalised disorders of muscle activity (e.g. myasthenia gravis or Eaton Lambert Syndrome).
- Infection or inflammation at the proposed injection sites.

Warnings and precautions

General

The anatomy and anatomical land marks of procerus corrugator supercilli muscles and the surrounding vasucular and nervous structures in the glabellar region must be understood prior to administration of NUCEIVA. Injection into vulnerable anatomical structures, such as nerves and blood vessels, must be avoided.

Localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

Caution should be taken when the targeted muscle shows pronouced weakness or atrophy.

Care should be taken to ensure that NUCEIVA is not injected into a blood vessel when it is injected in the glabellar lines seen at maximum frown (see ”Dosage/Administration”).

There is a risk of eyelid ptosis following treatment (see ”Dosage/Administration”).

Caution should be taken if complications have resulted with previous botulinum toxin injections.

The use of NUCEIVA is not recommended in persons under 18 years of age or over 65 years of age.

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

Local and distant spread of toxin effect
Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin (see ”Undesirable effects”). Swallowing and breathing difficulties are serious and can result in death. Injection of NUCEIVA is not recommended in patients with a history of dysphagia and aspiration.
Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

Pre-existing neuromuscular disorders
Patients with unrecognised neuromuscular disorders may be at increased risk of clinically significant systemic effects, including severe dysphagia and respiratory compromise from typical doses of botulinum toxin type A. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube (see ”Contraindications”).
Caution should also be exercised when botulinum toxin type A is used for treatment of patients with amyotrophic lateral sclerosis or with peripheral neuromuscular disorders.

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.

Antibody formation
Antibodies to botulinum toxin type A may develop during treatment with botulinum toxin. Some of the antibodies formed are neutralising which may lead to treatment failure of botulinum toxin type A.
It is mandatory that NUCEIVA is used for one single patient treatment only during a single session.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is almost “sodium-free”.

Interactions
No interaction studies have been performed.
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

There are no adequate data from the use of botulinum toxin type A in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see ”Preclinical data”). NUCEIVA is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There is no information on whether NUCEIVA is excreted in human breast milk. NUCEIVA should not be used during breast-feeding.

Fertility

The effect of NUCEIVA on human fertility is unknown. Animal studies with botulinum toxin type A have shown a reduction in fertility.

Effects on ability to drive and use machines

NUCEIVA has a minor or moderate influence on the ability to drive and use machines. There is a potential risk for asthenia, muscle weakness, dizziness and visual disturbance, which could affect driving and the operation of machinery.

Undesirable effects

Summary of the safety profile

Serious undesirable effects that may occur following treatment with NUCEIVA include eyelid ptosis, an immune response, distant spread of toxin, development or exacerbation of a neuromuscular disorder, and hypersensitivity reactions. The safety profile is based on 5 clinical studies comprising 1,659 patients who had exposure to NUCEIVA. In these studies, the most commonly reported adverse effects during treatment were headache, occurring in 9.0% of patients, followed by eyelid ptosis, occurring in 1.0% of patients. Of the total 1,659 patients treated with NUCEIVA, 816 received a single treatment of 20 Units, 150 who received 2 treatments, 325 who received 3 treatments, and 368 who received 4 treatments. A pattern of progressively lower frequencies with each repeat treatment was observed for all study drug related adverse effects.

List of undesirable effects

The NUCEIVA related adverse reactions are classified by System Organ Class and frequency defined as follows: Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000).

Infections and infestations

Rare: Upper respiratory tract infection.

Psychiatric disorders

Rare: Depression.

Nervous system disorders

Common: Headache.

Uncommon: Dizziness, migraine, muscle tone disorder, speech disorder.

Rare: Dysaesthesia, head discomfort, hypoaesthesia, paraesthesia, sensory disturbance.

Eye disorders

Common: Eyelid ptosis.

Uncommon: Asthopenia, blepharospasm, brow ptosis, eyelid oedema, eye swelling, vision blurred.

Rare: Diplopia, dry eye, eyelid sensory.

Ear and labyrinth disorders

Rare: Vertigo.

Vascular disorders

Rare: Flushing.

Respiratory, thoracic and mediastinal disorders

Rare: Epistaxis.

Gastrointestinal disorders

Rare: Diarrhea.

Skin and subcutaneous tissue disorders

Uncommon: Pruritis.

Rare: Dermal cyst, erythema, photosensitivity reaction, skin mass, skin tightness.

Musculoskeletal and connective tissue disorders

Rare: Muscle twitching, musculoskeletal pain, myalgia, neck pain, Mephisto sign.

General disorders and administration site conditions

Common: Application site bruising, influenza like illness, injection site bruising, injection site pain, injection site swelling.

Rare: Injection site: erythema, injection site paresthesia, injection site pruritis, pain, tenderness.

Investigations

Rare: Intraocular pressure test.

Injury, poisoning and procedural complications

Uncommon: Contusion.
Rare: Post-procedural swelling, procedural headache.
Note: Of the 1659 subjects treated with NUCEIVA, rare events occurred in 1 subject only. Uncommon events occurred in between 2 and 7 subjects.

Description of specific adverse reactions and additional information
Application related adverse reactions
Application related undesirable effects that have been reported following administration of NUCEIVA are uncommon events individually, common when added together. These include application and injection site bruising, injection site pain and injection site swelling. Rarely occurring injection site events that have been reported include erythema, paraesthesia, pruritis, pain and tenderness.

Undesirable effects of the substance class botulinum toxin type A
Muscle atrophy
Muscle atrophy is expected after repeated botulinum treatment secondary to the flaccid paralysis of the treated muscles.

Toxin spread
Adverse reactions possibly related to the spread of toxin distant from the site of administration have been reported very rarely with botulinum toxin (e.g. muscle weakness, breathing difficulties, dysphagia or constipation) (see “Warnings and precautions”).

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.

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

Overdose
Signs and symptoms
Signs of overdose may not be apparent immediately post-injection. Should accidental injection or ingestion occur, the patient should be medically monitored for several days 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).
Too frequent or excessive dosing may enhance the risk of antibody formation. Antibody formation may lead to treatment failure.
Overdose of NUCEIVA depends upon dose, site of injection, and underlying tissue properties. No cases of systemic toxicity resulting from accidental injection of botulinum toxin type A have been observed. Excessive doses may produce local or distant generalised and profound neuromuscular paralysis. No cases of ingestion of botulinum toxin type A have been reported.

Treatment
In the event of overdose the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment should be instigated if necessary.

Properties/Effects

ATC code
M03AX01

Mechanism of action
Botulinum toxin type A (*Clostridium botulinum* neurotoxin) blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals 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.

Pharmacodynamics
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 are manifest within 2-3 days, with peak effect seen within 4 weeks of injection. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

Clinical efficacy
Glabellar lines
540 patients with moderate to severe glabellar lines seen at maximum frown who felt their glabellar lines had an important psychological impact (on mood, anxiety/or depressive symptoms) have been included in the European/Canadian clinical study.
NUCEIVA injections significantly reduced the severity of glabellar lines by 1 point or greater at

maximum frown for up to 139 days, as measured by the investigator assessment of glabellar line severity at maximum frown.

Table 1 – Primary Efficacy Endpoint – Glabellar Line Scale Score of 0 (none) or 1 (mild) at Day 30 by Investigator Assessment at Maximum Contraction, PP Population

Responders for the Primary Efficacy Endpoint	Placebo	Botulinum toxin comparator	NUCEIVA	Absolute Difference		
				Botulinum toxin comparator Vs. Placebo	NUCEIVA Vs. Placebo	NUCEIVA Vs. Botulinum toxin comparator
Number	2/48	202/244	205/235			
Percentage	4.2%	82.8%	87.2%	78.6%	83.1%	4.4%
(% CI)	(0.0, 9.8)	(78.1, 87.5)	(83.0, 91.5)	(66.5, 85.5)	(70.3, 89.4)	(-1.9, 10.8)
PValue				<0.001	<0.001	

Glabellar Line Scale (GLS); 0=no lines, 1=mild, 2=moderate, 3=severe

Two days after injection, 12.2% (6/49) of placebo, 57.0% (139/244) botulinum toxin comparator treated patients and 54.2% (130/240) of NUCEIVA were considered by investigators as treatment responders (none or mild severity at maximum frown).
There are limited phase 3 clinical data with NUCEIVA in patients older than 65 years.
Duration of response in the phase 3 study was 139 days, based on a 1 point GLS improvement.
A total of 922 patients participated in two 1-year open label uncontrolled studies, and over the course of these studies, the average patient received 3 treatments.
The psychological impact of glabellar lines was confirmed at study entry and although a beneficial effect could not be demonstrated on psychological wellbeing, significant effects on patient reported outcomes were demonstrated as compared to placebo. Study results indicate that NUCEIVA and the comparator have a comparable efficacy and safety profile in patients with moderate to severe glabellar wrinkles when used in a 1:1 conversion ratio.

Pharmacokinetics
NUCEIVA has not been detected in the peripheral blood following intramuscular injection at the recommended dose.
Absorption, distribution, biotransformation and elimination (ADME) studies on the active substance have not been performed due to the nature of this product.
Absorption
No data
Distribution
No data
Metabolism
No data

Elimination
No data

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

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

Reproduction toxicity
The potential impact of NUCEIVA on fertility has not been investigated in animals. However, impairments in male and female fertility were observed in rats following high doses of other botulinum toxin type A-containing products.
In pregnant rats, daily intramuscular injections of 0.5, 1, or 4 Units/kg during the period of organogenesis (from gestation days 6 to 16), did not induce significant test article-related toxicological effects on the dams and on embryo-fetal development. Effects on peri-/postnatal development have not been evaluated.

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 ("EXP") stated on the pack.

Shelf life after opening
The reconstituted injection solution does not contain preservatives. Chemical and physical in-use stability has been demonstrated at 2-8 °C for a period of 24 hours. From a microbiological point of view, the ready-to-use reconstituted solution should be used immediately. If the solution is not used immediately, storage conditions and duration are the responsibility of the user and should not normally exceed 24 hours at 2- 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Special precautions for storage
Keep out of the reach of children.
Store in the refrigerator (2-8°C). Keep the container in the outer carton in order to protect the contents

from light.

Instructions for handling

Reconstitution should be performed in accordance with aseptic technique principles. NUCEIVA is reconstituted with sodium chloride 9 mg/ml (0.9%) solution for injection. As per the dilution table below, the amount of sodium chloride 9 mg/ml (0.9%) solution for injection is drawn up into a syringe in order to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL.

	50 Unit vial
Amount of solvent added (sodium chloride 9 mg/ml (0.9%) solution for injection)	1.25 mL
Resulting dose (Units per 0.1 mL)	4 Units

The central part of the rubber cap should be cleaned with alcohol.

The solution is prepared by injecting the solvent slowly into the vial with a needle through the rubber stopper and by gently rotating the vial avoiding bubble formation. The vial has to be discarded if the vacuum does not pull the solvent into the vial. Once reconstituted, the solution should be visually inspected prior to use. Only clear, colorless solution without particles should be used.

Reconstituted NUCEIVA (50 Units/1.25 mL) is injected using a sterile 30 gauge needle. Four Units (4 U/ 0.1 mL) are administered in each of the 5 injection sites (see Figure 1): 2 injections in each corrugator muscle (inferior medial and superior medial aspect) and 1 injection in the procerus muscle for a total dose of 20 Units.

It is mandatory that NUCEIVA is used for one single patient treatment only during a single session.

Procedure to follow for a safe disposal of vials, syringes and materials used

Immediately after use, and prior to disposal, unused reconstituted NUCEIVA solution in the vial and/or the syringe must be inactivated, with 2 mL of dilute sodium hypochlorite solution at 0.5% or 1% (Javel solution) and should be disposed of in accordance with local requirements.

Used vials, syringes, and materials should not be emptied and must be discarded into appropriate containers and disposed as a Medical Biohazardous Waste in accordance with local requirements.

Recommendations in the event of an accident when handling botulinum toxin

In the event of an accident when handling the product, whether in the vacuum-dried state or reconstituted, the appropriate measures described below must be initiated immediately.

- The toxin is very sensitive to heat and certain chemical agents.
- Any spillage must be wiped up: either with an absorbent material soaked in a solution of sodium hypochlorite (Javel solution) in the case of the vacuum-dried product, or with a dry absorbent material in the case of the reconstituted product.

- Contaminated surfaces must be cleaned with an absorbent material soaked in a solution of sodium hypochlorite (Javel solution) and then dried.
- If a vial is broken, carefully collect the pieces of glass and wipe up the product as stated above, avoiding cuts to the skin.
- If splashed on skin, wash with a solution of sodium hypochlorite and then rinse thoroughly with plenty of water.
- If splashed into the eyes, rinse eyes thoroughly with plenty of water or with an eye wash solution.

If the injector injures himself (cuts, pricks himself), proceed as above and take the appropriate medical steps.
These instructions for use, handling, and disposal should be strictly followed.

Authorisation number
69120 (Swissmedic)

Packs
NUCEIVA
Vial with 50 Units: 1 [A]

Marketing Authorisation Holder
PharmaCons GmbH, Liestal

Date of revision of the text
July 2023