Legal category: POM **List price:** 50 Units powder for solution for injection per vial: £75.50

Before prescribing, please read the latest Summary of Product Characteristics (SmPC) on www.medicines.org.uk/emc

Adverse events should be reported.

Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search MHRA Yellow Card in the Google Play or Apple App store. Adverse events should also be reported to Evolus International Ltd at medicalinformation@evolus.com or 08000541302.

Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

NUCEIVA 50 Units powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 Units botulinum toxin type A produced by *Clostridium botulinum.*

After reconstitution each 0.1 mL of the solution contains 4 Units.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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

Posology

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.

Elderly

There are limited clinical data with this medicine in patients older than 65 years (see section 5.1). This medicine is not recommended for use in patients over 65 years of age.

No specific dose adjustment is required for use in the elderly.

Paediatric population

There is no relevant use of this medicine in the paediatric population.

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 medicinal product

For instructions for use, precaution before manipulating or administering the medicinalproduct, handling and disposal of the vials, see section 6.6.

Care should be taken to ensure that this medicine 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 section 4.4).

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.

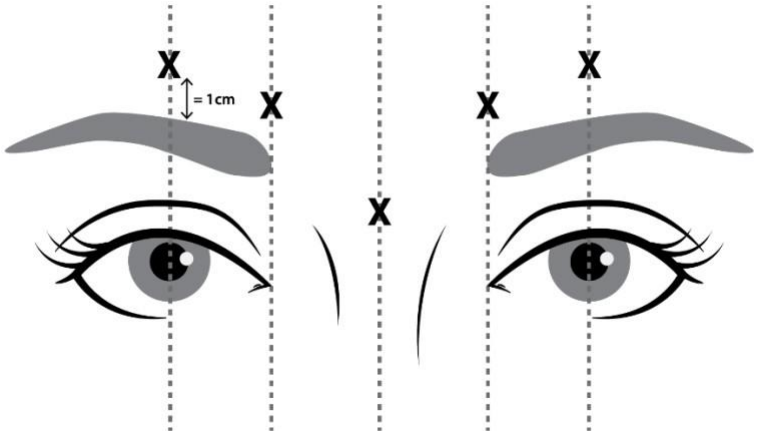
In order to reduce the complication of eyelid ptosis the following steps should be taken:

- 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



4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Generalised disorders of muscle activity (e.g. myasthenia gravis or Eaton Lambert Syndrome)

Infection or inflammation at the proposed injection sites.

4.4 Special warnings and precautions for use

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 this medicine. 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 pronounced weakness or atrophy.

Care should be taken to ensure that this medicine is not injected into a blood vessel when it is injected in the glabellar lines seen at maximum frown (see section 4.2).

There is a risk of eyelid ptosis following treatment (see section 4.2).

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

Bleeding disorders

Caution should be exercised when this medicine 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 section 4.8). Swallowing and breathing difficulties are serious and can result in death. Injection of this medicine 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 section 4.3).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and 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 section 5.3). This medicine is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There is no information on whether botulinum toxin type A is excreted in human breast milk. This medicine should not be used during breast-feeding.

Fertility

The effect of this medicine on human fertility is unknown. However, another botulinum toxin type A has been shown to impair the fertility of male and female animals.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

Serious adverse reactions that may occur following treatment with this medicine include eyelid ptosis, an immune response, distant spread of toxin, development or exacerbation of a neuromuscular disorder, and hypersensitivity reactions. The most commonly reported adverse reactions during treatment are headache, occurring in 9% of patients, followed by eyelid ptosis, occurring in 1% of patients.

Tabulated list of adverse reactions

Table 1 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).

System organ class	**Preferred term**	**Frequency**
Infections and infestations	Upper respiratory tract infection	Rare
Psychiatric disorders	Depression	Rare
Nervous system disorders	Headache	Common
	Dizziness, migraine, muscle tone disorder, speech disorder	Uncommon
	Dysaesthesia, head discomfort, hypoaesthesia, paraesthesia, sensory disturbance	Rare
Eye disorders	Eyelid ptosis	Common
	Asthopenia, blepharospasm, brow ptosis, eyelid oedema, eye swelling, vision blurred	Uncommon
	Diplopia, dry eye, eyelid sensory disorder	Rare
Ear and labyrinth disorders	Vertigo	Rare
Vascular disorders	Flushing	Rare
Respiratory, thoracic and mediastinal disorders	Epistaxis	Rare
Gastrointestinal disorders	Diarrhea	Rare

Skin and subcutaneous tissue disorders	Pruritis	Uncommon
	Dermal cyst, erythema, photosensitivity reaction, skin mass, skin tightness	Rare
Musculoskeletal and connective tissue disorders	Muscle twitching, musculoskeletal pain, myalgia, neck pain	Rare
General disorders and administration site conditions	Application site bruising, influenza like illness, injection site bruising, injection site pain, injection site swelling	Common
	Injection site: erythema, injection site paresthesia, injection site pruritis, pain, tenderness	Rare
Investigations	Intraocular pressure test	Rare
Injury, poisoning and procedural complications	Contusion	Uncommon
	Post-procedural swelling, procedural headache	Rare

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 selected adverse reactions

Application related adverse reactions
Application related adverse reactions that have been reported following administration of this medicine 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 section 4.4).

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 of suspected adverse reactions

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 via
United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose

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 this medicine 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.

Management of overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, other muscle relaxants, peripherally acting agents, ATC code: M03AX01.

Mechanism of action

Botulinum toxin type A 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.

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 and safety

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 2 – 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	BOTOX	NUCEIVA	Absolute Difference		
				BOTOX Vs. Placebo	NUCEIVA Vs. Placebo	NUCEIVA Vs. BOTOX
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) Botox treated patients and 54.2% (130/240) of NUCEIVA were considered by investigators as treatment responders (none or mild severity at maximum frown).

Table 3 – Exploratory Efficacy Endpoint - Glabellar Line Scale Score of 0 (none) or 1 (mild) at Day 30 by Investigator Assessment at Maximum Contraction for NUCEIVA Treated Subjects, by Baseline GLS Score at Maximum Contraction, ITT Population

Baseline GLS Score at Maximum Contraction	NUCEIVA (N=245)	
	GLS=0 at Day 30 at Maximum Contraction	GLS=1 at Day 30 at Maximum Contraction
2 (Moderate)		
Number	35/62	25/62
Percentage	56.5%	40.3%
3 (Severe)		
Number	41/179	108/179
Percentage	22.9%	60.3%

Glabellar Line Scale (GLS); 0=no lines, 1=mild, 2=moderate, 3=severe. Denominators are based on the number of subjects with the specified baseline severity at maximum contraction who had both baseline and Day 30 GLS scores at maximum contraction by investigator assessment

Table 4 – Exploratory Efficacy Endpoint - Glabellar Line Scale Score of 0 (none) or 1 (mild) at Day 30 by Investigator Assessment at Maximum Contraction for NUCEIVA Treated Subjects, by Baseline GLS Categories at Rest, ITT Population

Baseline GLS Category at Rest	NUCEIVA (N=245)	
	GLS=0 at Day 30 at Maximum Contraction	GLS=1 at Day 30 at Maximum Contraction
≤1 (i.e., none or mild)		
Number	61/103	40/103
Percentage	59.2%	38.8%
>1 (i.e., moderate or severe)		
Number	15/138	93/138
Percentage	10.9%	67.4%

Glabellar Line Scale (GLS); 0=no lines, 1=mild, 2=moderate, 3=severe. Denominators are based on the number of subjects with the specified baseline severity at rest who also had both baseline and Day 30 GLS scores at maximum contraction by investigator assessment

NUCEIVA injections also reduced the severity of glabellar lines at rest, an exploratory endpoint.

Table 5 – Exploratory Efficacy Endpoint – Glabellar Line Scale Score >/=2 points better at day 30 by Investigator Assessment At Rest, PP Population

Responders for the Exploratory Efficacy Endpoint	Placebo	BOTOX	NUCEIVA	Absolute Difference		
				BOTOX Vs. Placebo	NUCEIVA Vs. Placebo	NUCEIVA Vs. BOTOX
Number	0/27	36/149	32/133			
Percentage	0%	24.2%	24.1%	24.2%	24.1%	-0.1%
(% CI)	(0.0, 12.8)	(17.5, 31.8)	(17.1, 32.2)	(11.4, 32.3)	(11.3, 32.4)	(-10.1, 9.9)
PValue				0.003	0.003	0.984

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. Further, the effects of NUCEIVA on psychological wellbeing and patient reported outcomes were comparable to BOTOX, the active control used in the pivotal study.

5.2 Pharmacokinetic properties

This medicine 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.

5.3 Preclinical safety data

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

Reproduction toxicity

The potential impact of this medicine on fertility has not been investigated in animals. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin
Sodium chloride

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

30 months

Reconstituted solution

Chemical and physical in-use stability has been demonstrated for 72 hours at 2°C to 8°C.

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°C to 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vial (Type I glass) fitted with a stopper (chlorobutyl rubber) and a seal (aluminium).

Pack size of one.

6.6 Special precautions for disposal and other handling

Reconstitution should be performed in accordance with aseptic technique principles. This medicine 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.

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.

7. MARKETING AUTHORISATION HOLDER

Evolus Pharma B.V.
Apollolaan 151
1077 AR Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

PLGB 55681/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

27/09/2024

10. DATE OF REVISION OF THE TEXT

07/2024

April 2025 | GB-P-2500021