

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS



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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

NUCEIVA 100 Units powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 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 physicians 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 patients

There are limited clinical data with NUCEIVA in patients older than 65 years (see section 5.1). NUCEIVA 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 NUCEIVA 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 product

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

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 section 4.4).

Physical manipulation (such as rubbing) of the injection site in the immediate post-administration period should be avoided.

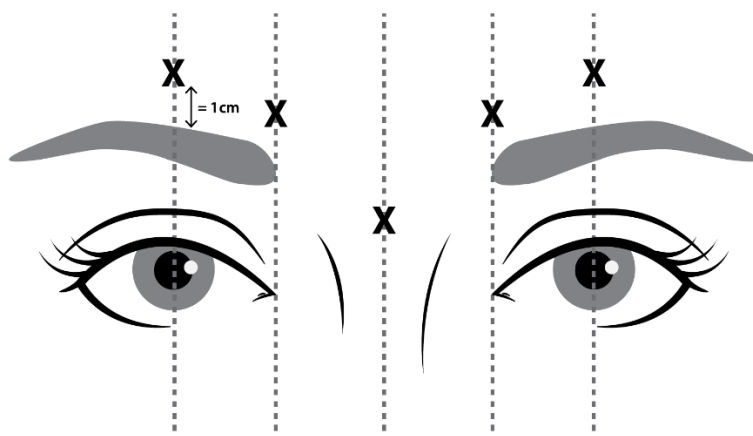
Administration instructions for Glabellar Lines seen at maximum frown

Reconstituted NUCEIVA (100 Units/2.5 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 vascular 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 pronounced 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 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 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 section 4.8). 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 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.

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

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). 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. 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 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 most commonly reported adverse effects during treatment are headache, occurring in 9.0% of patients, followed by eyelid ptosis, occurring in 1.0% 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 ($\geq 1/10$); common ($\geq 1/100$ to $<1/10$); uncommon ($\geq 1/1,000$ to $<1/100$); rare ($\geq 1/10,000$ 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 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 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 the national reporting system listed in Appendix V.

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 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.

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 (*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.

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 \geq /=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

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.

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 NUCEIVA 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 - 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° 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 - 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. 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.

Amount of solvent added (sodium chloride 9 mg/ml (0.9%) solution for injection) to a 100 Unit vial	Resulting dose (Units per 0.1 mL)
2.5 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 (100 Units/2.5 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.

7. MARKETING AUTHORISATION HOLDER

Evolus Pharma Ltd
70 Sir John Rogerson's Quay
Dublin 2
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1364/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Daewoong Pharmaceutical Co. Limited
35-14 Jeyakgongdan 4-gil
Hyangnam-eup
Hwaseong-si
Gyeonggi-do
18623
KOREA, REPUBLIC OF

Name and address of the manufacturer(s) responsible for batch release

Millmount Healthcare Limited
Block 7 City North Business Campus
Stamullen
Co. Meath, K32YD60
IRELAND

PCI Pharma Services
Biotec House
Central Park
Western Avenue
Bridgend Industrial Estate
Bridgend
CF31 3RT
UNITED KINGDOM

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Introduction of an <i>in vitro</i> method as a replacement for the potency assay of the Nuceiva finished product.	September 2020

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

NUCEIVA 100 Units powder for solution for injection
botulinum toxin type A

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 Units botulinum toxin type A
After reconstitution each 0.1 mL of the solution contains 4 Units

3. LIST OF EXCIPIENTS

Human albumin, sodium chloride

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Intramuscular use
Single use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Read the leaflet for the shelf life of the reconstituted medicine

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Evolus Pharma Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1364/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

NUCEIVA 100 Units powder for solution for injection
botulinum toxin type A
IM

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 Units

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

NUCEIVA 100 Units powder for solution for injection botulinum toxin type A

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you have any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What NUCEIVA is and what it is used for
2. What you need to know before NUCEIVA is used
3. How to use NUCEIVA
4. Possible side effects
5. How to store NUCEIVA
6. Contents of the pack and other information

1. What NUCEIVA is and what it is used for

NUCEIVA contains the active substance botulinum toxin type A. It prevents muscles from contracting, leading to a temporary paralysis. It works by blocking the nerve impulses to the muscles in which it has been injected.

NUCEIVA is used for the temporary improvement in the appearance of vertical lines between the eyebrows. It is used in adults less than 65 years of age in whom those facial lines have an important psychological impact.

2. What you need to know before NUCEIVA is used

NUCEIVA must not be used:

- if you are allergic to botulinum toxin type A or any of the other ingredients of this medicine (listed in section 6);
- if you have myasthenia gravis or Eaton Lambert syndrome (chronic diseases affecting the muscles);
- if you have an infection or inflammation at the proposed injection sites.

Warnings and precautions

Side effects possibly related to the spread of botulinum toxin from the site of injection can occur very rarely (e.g. muscle weakness, difficulty in swallowing or food or liquid entering the airways). Patients receiving recommended doses may have exaggerated muscle weakness.

Visit your doctor immediately if you find it difficult to swallow, to speak or to breathe after treatment.

- NUCEIVA is not recommended in patients who have had problems swallowing (dysphagia) and breathing.
- Too frequent or excessive dosing may lead to antibody formation. Antibody formation can stop botulinum toxin type A from working even for other uses. To prevent this, there must be a gap of at least three months between doses.
- Very rarely, an allergic reaction can occur after the injection of botulinum toxin.
- Drooping of the eyelid may occur after treatment.

Please tell your doctor if:

- you had problems with previous botulinum toxin injections;
- you see no significant improvement of your lines one month after your first course of treatment;
- you suffer from certain diseases affecting your nervous system (such as amyotrophic lateral sclerosis or motor neuropathy);
- you have inflammation at the proposed injection site(s);
- the muscles to be injected are weak or wasted;
- you have a bleeding disorder as injection may lead to bruising.

Children and adolescents

The use of NUCEIVA is not recommended in individuals under 18 years.

Other medicines and NUCEIVA

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The use of botulinum toxin is not recommended in association with aminoglycoside antibiotics, spectinomycin or other medicines that interfere with nerve impulses to the muscle.

Tell your doctor if you have recently been injected with a medicine containing botulinum toxin (the active substance of NUCEIVA), as this may increase the effect of NUCEIVA excessively.

Pregnancy and breast-feeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby ask your doctor for advice before you receive this medicine.

The use of NUCEIVA is not recommended during pregnancy and in women able to have children who are not using contraception.

NUCEIVA is not recommended in breast-feeding women.

Driving and using machines

Muscle weakness, dizziness, and visual disturbance with this medicine could make driving or the use of machines dangerous. Do not drive or use machinery until such effects have cleared.

NUCEIVA contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dose; this means it is essentially 'sodium-free'.

3. How to use NUCEIVA

Unit doses for NUCEIVA are not interchangeable with those used for other preparations of botulinum toxin.

NUCEIVA should only be injected by physicians with appropriate qualifications and expertise in the treatment of glabellar lines at maximum frown.

The usual dose of NUCEIVA is 20 Units. You will be injected with the recommended volume of 0.1 millilitre (ml) (4 Units) of NUCEIVA into each of 5 injection sites.

Improvement of severity of the lines between the eyebrows generally occurs within a few days of treatment.

The interval between treatments will be decided by your doctor.

How NUCEIVA is injected

NUCEIVA is injected into your muscles (intramuscularly), directly into the affected area above and between the eyebrows.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. In general, side effects occur within the first few days after injection and are temporary. Most side effects are of mild to moderate severity.

If you have any difficulty in breathing, swallowing or speaking after receiving NUCEIVA contact your doctor immediately.

If you get hives, swelling, including swelling of the face or throat, wheezing, feeling faint or shortness of breath, contact your doctor immediately.

The chance of having a side effect is described by the following categories:

Common (May affect up to 1 in 10 people)	Headache, muscle imbalance resulting in elevated or asymmetrical eyebrows, eyelid drooping, injection site bruise
Uncommon (May affect up to 1 in 100 people)	Sensory disturbance, head discomfort, dry eye, eyelid swelling, eye swelling, muscle twitching, injection site: redness, pain, tingling

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store NUCEIVA

Keep out of the sight and reach of children.

Unopened vial

Do not use NUCEIVA after the expiry date which is stated on the vial and the carton after EXP.

6. Contents of the pack and other information

What NUCEIVA contains

- The active substance is: 100 Units botulinum toxin type A.
- The other ingredients are human albumin and sodium chloride.

What NUCEIVA looks like and contents of the pack

NUCEIVA is presented as a white powder for solution for injection in a transparent glass vial. Each pack contains 1 vial.

Marketing Authorisation Holder

Evolus Pharma Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

Manufacturers

PCI Pharma Services
Biotec House, Central Park,
Western Avenue,
Bridgend Industrial Estate
Bridgend,
CF31 3RT, United Kingdom

For any information about this medicine, please contact the the Marketing Authorisation Holder

This leaflet was last revised in {month YYYY}.

THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:

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

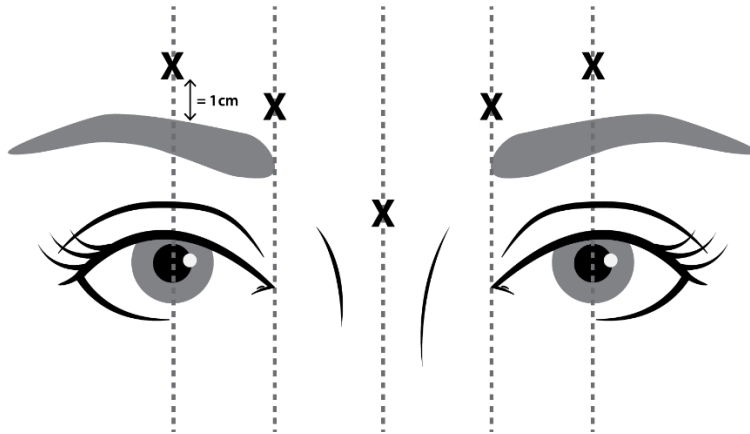
Reconstitution should be performed in accordance with good clinical practice, particularly with respect to aseptic technique. NUCEIVA is reconstituted with sodium chloride 9 mg/ml (0.9%) solution for injection . 2.5 mL of sodium chloride 9 mg/ml (0.9%) solution for injection is drawn up into a syringe in order to obtain a reconstituted solution for injection at a concentration of 4 Units/0.1 mL.

Amount of diluent added to 100 Unit vial (sodium chloride 9 mg/ml (0.9%) solution for injection)	Resulting dose (Units per 0.1 mL)
2.5 mL	4.0 U

The central part of the rubber cap should be cleaned with alcohol. Inject the diluent slowly into the vial with a needle through the rubber stopper and gently rotate the vial avoiding bubble formation. The vial has to be discarded if the vacuum does not pull the diluent into the vial. Once reconstituted, the solution for injection should be visually inspected prior to use to verify it is a clear, colourless solution free of particulate matter.

Reconstituted NUCEIVA (100 Units/2.5 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.

Figure 1: Injection Points



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

- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.

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

Immediately after use, unused reconstituted NUCEIVA solution for injection in the vial and/or the syringe must be inactivated, prior to disposal, with 2 mL of dilute sodium hypochlorite solution at 0.5% or 1% available chlorine. Following inactivation, dispose of in accordance with local requirements. Used vials, syringes and materials should not be emptied and must be discarded into appropriate containers and disposed of according to local regulations.

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, 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 operator injures himself (cuts, pricks himself), proceed as above and take the appropriate medical steps according to the dose injected.

These instructions for use, handling and disposal should be strictly followed.