PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] NUCEIVA

prabotulinumtoxinA for injection

Sterile vacuum-dried powder for solution for injection

100 Units per vial

Neuromuscular Blocking Agent

Evolus, Inc.
1027 Garden Street
Santa Barbara, CA 93101

Control No: 208364 **Date of Approval: August 16, 2018**

RECENT MAJOR LABEL CHANGES

Not Applicable (NA)

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

NUCEIVA is indicated for:

- The temporary improvement in the appearance of moderate to severe glabellar lines in adult patients < 65 years of age.

1.1 Pediatrics

Pediatrics (< 18 years of age): **NUCEIVA** is not recommended for use in children.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): The clinical data for subjects ≥ 65 years of age are limited. No specific dose adjustment is required for use in the elderly.

2 CONTRAINDICATIONS

NUCEIVA is contraindicated in patients:

- who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging;
- with infection or inflammation at the proposed injection sites.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- DISTANT SPREAD OF TOXIN EFFECT: The effects of **NUCEIVA** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life-threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.
- The term “Unit” upon which dosing is based, is a specific measurement of toxin activity that is unique to this formulation of Botulinum toxin Type A. Therefore, the Units used to describe **NUCEIVA** activity are different from those used to describe that of other botulinum toxin preparations and the Units representing **NUCEIVA** activity are not interchangeable with other products.
- **NUCEIVA** should only be administered by physicians with the appropriate qualifications and experience in the use of botulinum toxins.
- Follow the recommended dosage and frequency of administration for **NUCEIVA** (See **WARNINGS AND PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **For Intramuscular Use Only**
- **The potency Units of NUCEIVA are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of NUCEIVA cannot be compared to or converted into Units of any other botulinum toxin products assessed with any other specific assay method.**
- **Treatment should be administered at no more than the recommended dose and interval.**
- **Injection intervals of NUCEIVA should be no more frequent than every three months.**

4.2 Recommended Dose and Dosage Adjustment

Glabellar Lines
Four (4) Units should be injected intramuscularly at each of five injection sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units (see Figure 1).

Typically, **NUCEIVA** indices chemical denervation of the injected muscles two days after injection, increasing in effect during the first two weeks.

4.3 Administration

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or “furrowed brow”. The location, size, and use of the muscles can vary among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles.

Physicians administering **NUCEIVA** must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures.

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

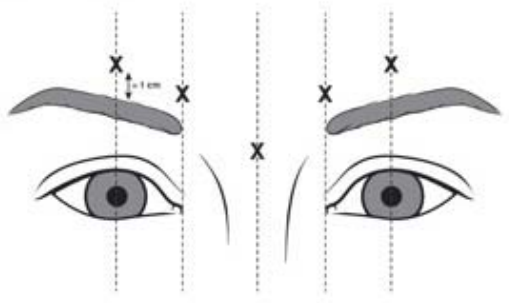
- Avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes.
- Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.
- Do not inject toxin closer than 1 centimeter above the central eyebrow.
- Ensure the injected volume/dose is accurate and where feasible kept to a minimum.
- The use of one vial for more than one injection session or one patient is not recommended because the product and diluent do not contain a preservative.

Following reconstitution (see below), the needle used could remain in the vial and the required amount of solution drawn up with a new sterile syringe suitable for injection, preferably a 1.0mL tuberculin syringe. Draw at least 0.5 mL of the properly reconstituted toxin into the syringe and expel any air bubbles seen in the barrel. Disconnect the syringe and attach a sterile 30 gauge needle.

Inject a dose of 0.1 mL (4 Units) intramuscularly into each of 5 sites, the inferomedial and superior middle of each corrugator and 1 in the mid-line of the procerus muscle for a total dose of 20 Units (see Figure 1).

NUCEIVA vials are for single-use only. Discard remaining solution.

Figure 1.



4.4 Reconstitution

Each 100 Unit vial of **NUCEIVA** is to be reconstituted with 2.5 mL of 0.9% sterile, preservative-free, saline. As per the dilution table below, the 2.5 mL of sodium chloride 0.9% solution for injection is to be drawn into a sterile syringe and mixed in the vial in order to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL.

Table 1. Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Nominal Concentration per mL
100 Unit Vial	2.50 mL	4 Units/0.1 mL

Inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix **NUCEIVA** with the saline by rotating the vial.

Once reconstituted, **NUCEIVA** should be stored in a refrigerator at 2–8°C and used within 24 hours. Do not freeze reconstituted **NUCEIVA**. Discard the vial and needle in accordance with local regulations.

4.5 Missed Dose

NA

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Excessive doses of **NUCEIVA** may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required when excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis. Symptomatic treatment may be necessary.

Symptoms of overdose are not likely to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or paralysis.

In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local Health Department to process a request for antitoxin and also notify the company. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular	Sterile, vacuum-dried powder for reconstitution; 100 Units per vial	Human Serum Albumin, Sodium Chloride

Each vial of **NUCEIVA** contains 100 Units of botulinum type A neurotoxin complex, 0.5 mg of human serum albumin, and 0.9 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

The top and bottom flaps of the **NUCEIVA** cartons have a tamper-evident seal. Vials of the **NUCEIVA** have a holographic film. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. If the tamper-evident seal is not intact and present on both ends of the carton or if you do not see the hologram, do not use the product.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General
Use **NUCEIVA** only as directed. Injection intervals of **NUCEIVA** should be no more frequent than every three months. Indication-specific dosage and administration recommendations should be followed.

Do not use dosage recommendations and potency Units applied to other botulinum toxin products when using **NUCEIVA**. Do not exceed the recommended dosage and frequency of administration of **NUCEIVA**.

The safe and effective use of **NUCEIVA** depends upon proper storage of the product, selection of the correct dose, reconstitution, and injection technique.

Caution should be exercised when administering **NUCEIVA** to patients with neuromuscular junction disorders or when excessive weakness or atrophy is present in the target muscle, and in patients with prolonged bleeding times, surgical alterations to the facial anatomy, marked facial asymmetry, inflammation at the injection site(s), ptosis, excessive dermatochalasis, deep dermal scarring, or thick sebaceous skin.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue. Muscle weakness remote to the site of injection and other serious adverse effects have been very rarely reported in the cosmetic applications. Progressive signs or symptoms of muscular weakness remote to the site of injection may include ptosis and diplopia, as well as other serious adverse effects including swallowing and speech disorders.

Patients with a history of underlying neurologic disorders, dysphagia and/or aspiration are at a greater risk of these effects and should be treated with extreme caution. The botulinum toxin product should be used under specialist supervision in these patients and should only be used if the benefit of treatment is considered to outweigh the risk.

Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders arise.

This product contains human serum albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. The theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No known cases of transmission of viral diseases or CJD have been identified for human serum albumin.

Carcinogenesis and Mutagenesis
Animal studies to evaluate the carcinogenic and genotoxic potential of **NUCEIVA** have not been conducted.

Cardiovascular
There have been reports following administration of other botulinum toxin products of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

Immune
As with all biologic products, an anaphylactic reaction may occur. Necessary precautions should be taken and epinephrine should be available. Serious and/or immediate hypersensitivity reactions such as anaphylaxis and serum sickness have been rarely reported, as well as other manifestations of hypersensitivity including urticaria, soft tissue edema, and dyspnea.

Treatment with botulinum toxins may result in the formation of antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin. The results from some studies suggest that botulinum toxin injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation.

The presence of antibotulinum antibodies in subjects receiving **NUCEIVA** was evaluated in two single dose Phase III studies (EV-001and EV-002) and one repeat dose Phase II study (EV-006). There were no cases of seroconversion with **NUCEIVA**. One subject who had a history of exposure to botulinum toxin and tested positive at baseline did not respond to treatment.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to **NUCEIVA** with the incidence of antibodies to other products may be misleading.

Monitoring and Laboratory Tests
There are no specific requirements for laboratory test monitoring when patients are treated with **NUCEIVA**.

Neurologic
Caution should be exercised when administering **NUCEIVA** to individuals with peripheral motor neuropathy (e.g., amyotrophic lateral sclerosis or other motor neuropathy), facial palsy or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at an increased risk of clinically significant systemic effects such as severe dysphagia and respiratory compromise. There have been rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular junction disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some of these cases, dysphagia has lasted several months and required placement of a gastric feeding tube.

Ophthalmologic
Caution should be exercised when administering **NUCEIVA** to individuals with eye disorders, including dry eye and eyelid oedema.

Risk of ptosis can be mitigated by careful examination of the upper lid for separation or weakness of the levator palpebrae muscle (true ptosis) and evaluation of the range of lid excursion while manually depressing the frontalis to assess compensation.
The potential risk of localized muscle weakness or visual disturbances linked with the use of **NUCEIVA** may temporarily impair the ability to drive or operate machinery.

Skin
Caution should be exercised when administering **NUCEIVA** to patients with inflammation at the injection site(s), deep dermal scarring, or thick sebaceous skin. As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, tenderness, swelling/edema, erythema, localized infection, bleeding and/or bruising have been associated with injections.

7.1 Special Populations

7.1.1 Pregnant Women
There is limited data from the use of Botulinum toxin Type A in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development other than at high doses causing maternal toxicity. The potential risk to pregnant women is unknown. **NUCEIVA should not be used during pregnancy.** If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential risks, including abortion or fetal malformations, which have been observed in rabbits.

7.1.2 Breast-feeding
It is unknown if the drug is excreted in human milk. The excretion of **NUCEIVA** in milk has not been studied in animals. Because many drugs are excreted in human milk precaution should be exercised. The use of **NUCEIVA** during lactation is not recommended.

7.1.3 Pediatrics
Pediatrics (**<18 years of age)**: **NUCEIVA** is not recommended for use in children.

7.1.4 Geriatrics
The clinical data for subjects ≥ 65 years of age are limited. No specific dose adjustment is required for use in the elderly.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse reactions may occur within the first few days following injection and while generally transient may have a duration of several months.

Local muscle weakness represents the expected pharmacological action of botulinum toxin in muscle tissue; however, weakness of adjacent muscles associated with local diffusion and/or injection technique has been reported. Muscle weakness remote to the site of injection and other serious adverse effects have been very rarely reported in the cosmetic application.

As is expected for any injection procedure, localized pain, inflammation, paresthesia, hypoesthesia, tenderness, swelling/oedema, erythema, localized infection, bleeding and/or bruising have been associated with injections. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse events were evaluated in subjects receiving 20 U of NUCEIVA in the glabellar region in three single dose Phase III studies (EV-001, EV-002 and EVB-003; Table 3), and one repeat dose EV-006 study where 570 subjects could receive repeat treatments every 3 months up to a possible maximum total dose of 80 U. The demographics were similar in these studies: mean age was 50.3 years, 89.7% of the subjects were female, and commonly identified races were 83.6% White and 5.3% Black. Most treatment emergent adverse events (TEAEs) were mild to moderate in severity and none considered study drug related were serious.

Table 3. Treatment-emergent adverse events with > 1% incidence following a single dose of 20 Units in the glabellar region

System Organ Class and Preferred Term	Pooled Placebo (N=211) (%)	Pooled Single Dose (N=737) (%)
All AEs in ≥1% of subjects	21.8%	22.7%
Nervous System Disorders	**13.3%**	**12.3%**
Headache	13.3%	12.3%
Infections and Infestations	**7.6%**	**8.8%**
Gastroenteritis viral	1.4%	0.4%
Influenza	0.9%	0.7%
Nasopharyngitis	1.4%	3.5%
Sinusitis	2.4%	0.9%
Upper respiratory tract infection	1.4%	1.8%
Eye Disorders	**0.0%**	**1.6%**
Eyelid ptosis	0.0%	1.6%
Vascular Disorders	**0.9%**	**0.5%**
Hypertension	0.9%	0.5%

In the pooled single dose Phase III studies, all TEAEs with an incidence >1%, included headache, viral gastroenteritis, influenza, nasopharyngitis, sinusitis, upper respiratory tract infection, eyelid ptosis and hypertension. Common TEAEs that were considered study drug related included headache, 7.6% in placebo and 9.4% in the NUCEIVA group, and eyelid ptosis with 0% in placebo and 1.2% in the NUCEIVA group.

Other TEAEs that were less frequent included dysphagia, dysphonia, paresthesia, pyrexia, urinary tract infection, urticaria and increased white blood cell count. Less frequent TEAEs considered study drug related included blepharospasm, blurred vision, diplopia, dry eye, eyebrow ptosis, eyelid edema, muscle twitching and injection site bruising.

In one year, open label, multi-dose Study EV-006, all TEAE's that occurred with an incidence of >1% included headache, bronchitis, nasopharyngitis, sinusitis, upper respiratory tract infection, urinary tract infection, contusion, contact dermatitis, pain in extremity, eyelid ptosis, cough, hypertension and injection site reactions (e.g. bruising/pain/swelling/pruritus). Headache and eyelid ptosis were the only study drug related TEAE's with an incidence of >1%.

The presence of antibotulinum antibodies in subjects receiving **NUCEIVA** was evaluated in two single dose Phase III studies (EV-001and EV-002) and one repeat dose Phase II study (EV-006). There were no cases of seroconversion with **NUCEIVA**. One subject who had a history of exposure to botulinum toxin and tested positive at baseline did not respond to treatment.

8.3 Clinical Trial Adverse Reactions (Pediatrics)

NA

8.4 Post-Market Adverse Reactions

NUCEIVA contains the same active ingredient as other botulinum toxin containing products. Therefore, adverse events observed with these products also have the potential to be associated with the use of **NUCEIVA**.

Adverse reactions reported during post-marketing and not reflected elsewhere in the Product Monograph include the following:

Ear and labyrinth disorders: Vertigo
Eye disorders: Periorbital haematoma
Gastrointestinal disorders: Dry mouth, Nausea
General disorders: Asthenia, Malaise
Immune system disorders: Hypersensitivity
Investigations: Neutralizing antibodies
Nervous system disorders: Amyotrophy, Burning sensation, Dizziness, Dysarthria, Facial paresis, Hypoaesthesia
Renal and urinary disorders: Urinary incontinence
Respiratory, thoracic and mediastinal disorders: Dyspnea
Skin and subcutaneous tissue disorders: Erythema, Excessive granulation tissue.

9 DRUG INTERACTIONS

9.1 Overview

No formal drug interaction studies have been conducted with **NUCEIVA**.

Patients treated concomitantly with botulinum toxins and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents) should be observed closely because the effect of the botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of **NUCEIVA** may potentiate systemic anticholinergic effects such as blurred vision.

The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **NUCEIVA**.

9.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

Table 4. Potential Drug-Drug Interactions

Proper/Common Name of Drug	Source of Evidence	Effect	Clinical Comment
aminoglycoside antibiotics or other medicinal products that interfere with neuromuscular transmission (e.g., curare-like agents, lincosamides, polymyxins, and anticholinesterases).	T	Theoretically, the effect of botulinum toxin may be potentiated.	The effect of botulinum toxin may be potentiated by aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission. Caution should be exercised when **NUCEIVA** is used with aminoglycosides or any other drugs that interfere with neuromuscular transmission.
Different botulinum neurotoxin serotypes	T	Unknown	The effect of administering different botulinum neurotoxin serotypes at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Legend: T = Theoretical

9.3 Drug-Food Interactions

Interactions with food have not been established

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory test have not been established

9.6 Drug-Lifestyle Interactions

Lifestyle interactions have not been established

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

NUCEIVA inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings, causing a flaccid paralysis of muscles. Toxin activity occurs in the following sequence: toxin heavy chain mediated binding to specific surface receptors on nerve endings, internalization of the toxin by receptor mediated endocytosis, pH-induced translocation of the toxin light chain to the cell cytosol and cleavage of SNAP25 leading to intracellular blockage of neurotransmitter (acetylcholine) exocytosis into the neuromuscular junction. This accounts for the therapeutic utility of the toxin in diseases characterized by excessive efferent activity in motor nerves.

Recovery of transmission occurs gradually as the neuromuscular junction recovers from SNAP25 cleavage and as new nerve endings are formed.

10.2 Pharmacodynamics

The primary pharmacodynamic effect of NUCEIVA is due to chemical denervation of the treated muscle resulting in a measurable decrease of the compound muscle action potential, causing a localized reduction of muscle activity.

10.3 Pharmacokinetics

NUCEIVA is not expected to be present in the peripheral blood at measurable levels following intramuscular injection at the recommended doses. Using currently available analytical technology, it is not possible to detect **NUCEIVA** in the peripheral blood following intramuscular injection at the recommended doses.

11 STORAGE, STABILITY AND DISPOSAL

NUCEIVA must be stored under refrigeration at 2–8°C.
Administer **NUCEIVA** within 24 hours of reconstitution. Reconstituted **NUCEIVA** should be clear, colorless and free of particulate matter. Do not freeze after reconstitution.

Do not use after the expiration date on the vial.

12 SPECIAL HANDLING INSTRUCTIONS

All vials, including unused product remaining and expired vials, or equipment used with NUCEIVA should be disposed of carefully as is done with all medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of dilute hypochlorite solution (0.5% or 1%) for five minutes is recommended prior to disposal as medical waste.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: prabotulinumtoxinA for injection

Chemical name: Botulinum toxin Type A (BoNT/A)

Molecular formula and molecular mass: 150 kDa toxin within a 900 kDa protein complex

Structural formula: The drug substance in **NUCEIVA** is purified from *Clostridium botulinum*, Type A and composed of a dimer of 2 covalently bonded complexes consisting of a neurotoxin, non-toxic, non-haemagglutinin protein (NTNH), and haemagglutinin (HA) proteins (HA50, HA33, HA20, and HA17). It has the same structural characteristics, physiochemical, and biological properties as Botulinum toxin, Type A variant. The molecular weight is 900 kDa.

Physicochemical properties: **NUCEIVA** (Botulinum toxin, Type A) is a sterile, preservative free, white to yellowish powder. **NUCEIVA** is composed of 100 units of Botulinum Toxin, Type A (active ingredient), 0.5 mg of human serum albumin (stabilizing agent), and 0.9 mg of sodium chloride (isotonic agent). **NUCEIVA** is reconstituted with a preservative free, 0.9% sodium chloride (USP) to form a clear, transparent solution. See Dosage and Administration and Warnings sections for further details.

One Unit of **NUCEIVA** corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method for performing the assay is specific to **NUCEIVA**. Due to differences in specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for the various mouse LD_{50} assays, Units of biological activity of **NUCEIVA** are not interchangeable with Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of **NUCEIVA** is approximately 28 Units/nanogram of neurotoxin complex.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Two identical multi-center, randomized, double blind placebo-controlled Phase III clinical trials (EV-001 and EV-002) were conducted to evaluate NUCEIVA for the use in the temporary improvement of moderate to severe glabellar lines at maximum frown in healthy adults. The primary endpoint was based on the responder rate on Day 30 using a composite endpoint, where both the investigator and subject independently agreed that a ≥2 point improvement had occurred on a 4-point severity glabellar line scale (none, mild, moderate, severe) at maximum frown.

In a supportive Phase III trial (EVB-003), the efficacy of NUCEIVA was evaluated in a non-inferiority design with a comparator product containing onabotulinumtoxinA. In this study, subject's satisfaction was evaluated as a secondary endpoint using a 5-point satisfaction scale on Day 30.

In these studies, exclusion criteria included the inability to substantially lessen glabellar frown lines by physically spreading them apart or any condition that might have affected neuromuscular function. Subjects received as single dose of 20U, divided into 5 injection sites (4U) in the corrugator and procerus muscles (see Figure 1).

Table 5. **Summary of patient demographics for Studies EV-001, EV-002 and EV-003**

Study #	**Trial designs**	**Dosage, route of administration and duration**	**Study subjects (N)**	**Mean age (range)**
EV-001	Phase III, multi-center, double blind, placebo-controlled	Single dose (20U), administered on Day 0;and study duration of 150 days	Males 24 Females 306	Placebo 50.4 (23, 74) PrabotulinumtoxinA 50.2 (22, 81)
EV-002			Males 34 Females 290	Placebo 50.4 (18, 71) PrabotulinumtoxinA 51.5 (21, 81)
EV-003	Phase III multicenter, double blind, placebo and active controlled		Males 64 Females 476	Placebo 48.4 (26, 71) PrabotulinumtoxinA 48.8 (22, 79) OnabotulinumtoxinA 49.7 years (24, 75)

14.2 Study Results

Based on the composite primary endpoint, the responder rates in the NUCEIVA (prabotulinumtoxinA) and placebo groups were, respectively, 67.5% and 1.2% in EV-001; and 70.4% and 1.3% in EV-002 (Table 6). The absolute differences between groups were 66.3% and 69.1% in EV-001 and EV-002, respectively (both p<0.001).

Table 6. **Responder rates in Studies EV-001 and EV-002 based on ≥ 2 point improvement at maximum frown on Day 30 using a 4-point severity glabellar line scale**

Study	Responder rate (%)	NUCEIVA	PLACEBO
EV-001	**Composite endpoint**	**67.5**	**1.2**
	Absolute difference	66.3	
	95% CI for difference	59.0, 72.4	
	p-value (Exact Test)	<0.001	
	Investigator's assessment	77.5	1.2
	Subject assessment	76.7	3.6
EV-002	**Composite endpoint**	**70.4**	**1.3**
	Absolute difference	69.1	
	95% CI for difference	61.5, 75.1	
	p-value (Exact Test)	<0.001	
	Investigator's assessment	82.5	2.7
	Subject assessment	76.3	4.0

In the EVB-003 Study, the proportion of subjects reporting satisfied or very satisfied with NUCEIVA supported the results of the primary endpoint.

15 MICROBIOLOGY

NA

16 NON-CLINICAL TOXICOLOGY

Carcinogenicity
Long Term Studies in animals have not been performed to evaluate carcinogenic potential of **NUCEIVA**.

Mutagenicity
Genotoxicity studies have not been conducted with **NUCEIVA**.

Fertility and Reproductive Toxicity
No studies have been conducted for **NUCEIVA** to evaluate the potential of fertility impairment.

In an embryo-fetal developmental study, **NUCEIVA** was administered (0.5, 1, or 4 U/kg) intramuscularly to pregnant rats daily during the period of organogenesis (on gestation days 6 to 16). No significant test article-related toxicological effects were evident on embryo-development or in the maternal animals compared to the control group. Clinical signs in dams were consistent with pharmacologically mediated effects of botulinum toxin Type A (paralytic gait and curling of toes on the injected hind limb). No test substance-related toxicological changes on body weights, food consumption, organ weights and necropsy findings were evident in any dosing groups. The no observed adverse effect level (NOAEL) for developmental toxicity was ≤ 4 U/kg, approximately 2-fold the human dose of 20 U based on a body surface area for a 60 kg subject.

Animal Toxicity Studies
In two studies to evaluate the acute and repeat-dose toxicity of **NUCEIVA,** a single or once-weekly (for 4 weeks) intramuscular injection of 4, 8 or 32 U/kg was administered to rats in the hind limb. **NUCEIVA** produced similar pharmacologically mediated effects, including limb paralysis and correlated reductions in food consumption and body weight. At 32 U/kg/dose, these effects were statistically significant and were associated with additional clinical signs of toxicity. Decreased muscle weight and microscopic muscle atrophy of the injected limb as well as local inflammatory responses were observed at doses ≥ 4 U/kg. In male rats, unilateral seminiferous tubule degeneration and atrophy were also observed at doses ≥ 4 U/kg. The maximum tolerated dose for acute and repeat-dose toxicity was ≤ 8 U/kg.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

NUCEIVA
prabotulinumtoxinA for injection

Read this carefully before you start taking **NUCEIVA** and each time you are re-treated. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NUCEIVA.**

Serious Warnings and Precautions

- ***Side effects may occur from misplaced injections of NUCEIVA temporarily paralyzing nearby muscle groups. There have been very rare reports of side effects that may be related to the spread of Botulinum neurotoxin distant from the injection site. These may include excessive muscle weakness, swallowing and breathing difficulties, or accidental swallowing of food or drink into the airway, which can be life threatening or fatal. These symptoms have been reported hours to weeks after injection. Patients who receive the recommended doses may very rarely experience excessive muscle weakness.***

What is NUCEIVA used for?

- **NUCEIVA** is indicated for the temporary improvement in the appearance of moderate to severe frown lines (glabellar lines) in adult patients < 65 years of age.

How does NUCEIVA work?

NUCEIVA is a drug that temporarily reduces movement of muscles that cause wrinkles. Some patients see results as soon as two days after injection.

What are the ingredients in NUCEIVA

Medicinal ingredients: Botulinum toxin Type A
Non-medicinal ingredients: Human serum albumin and sodium chloride

NUCEIVA comes in the following dosage forms: a single-use, sterile vial (100 Units).

NUCEIVA can only be used by health care professionals experienced in the injection of botulinum toxin.

The optimum dosage and number of injection sites in the treated muscle will be chosen by your doctor.

Do not use NUCEIVA if:

- you are allergic or sensitive to any of the ingredients
- you have an infection in the muscles where it would normally be injected
- you have any muscle disorders in other parts of your body, such as myasthenia gravis, Eaton Lambert Syndrome or amyotrophic lateral sclerosis

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUCEIVA. **Talk about any health conditions or problems you may have, including if:**

- you have muscle disorders
- have received any other botulinum toxin product in the last four months
- you have eye disorders including drooping eyes, dry eyes
- have bleeding problems
- you have pre-existing swallowing or breathing difficulties
- you are allergic or sensitive to any botulinum toxin product
- you have an infection at the proposed injection site
- you are scheduled to have surgery using a general anesthetic
- you are taking or are likely to take antibiotics, especially aminoglycoside antibiotics
- you are pregnant or become pregnant while taking this drug
- you are nursing. It is not known whether this drug is excreted in human milk

NUCEIVA is for intramuscular use only.

NUCEIVA should only be injected by a physician with the appropriate qualifications and experience in the treatment and use of botulinum toxin products.

NUCEIVA may cause loss of strength or general muscle weakness, blurred vision, or drooping eyelids within hours to weeks after injection. If this happens, do not drive a car, operate machinery, or do other dangerous activities.

Seek immediate medical attention if swallowing, speech or respiratory problems arise.

Tell your doctor if you experience any difficulties in swallowing food after **NUCEIVA** treatment, as it could be related to the dosage. Difficulty in swallowing food, ranging from very mild to severe, which can persist for 2–3 weeks after injection, or longer has been reported with use of botulinum toxins.

Tell your doctor if you are taking other medicines, including those you have bought at your pharmacy, supermarket or health food shop.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NUCEIVA:

- The effect of **NUCEIVA** may be increased by aminoglycoside antibiotics (e.g., streptomycin, tobramycin, neomycin, gentamicin, netilmicin, kanamycin, amikacin), spectinomycin, polymyxins, tetracyclines, lincomycin, muscle relaxant, or other drugs that interfere with neuromuscular transmission.

How to take NUCEIVA:
NUCEIVA can only be used by health care professionals experienced in the injection of botulinum toxin.

Usual dose:
The optimum dosage and number of injection sites in the treated muscle will be chosen by your doctor.

Overdose:
Symptoms of overdose for this product, as for all botulinum toxins, are related to the dose, the condition being treated and susceptibility of the patient. Symptoms are not apparent immediately after the injection and may include general weakness, drooping eyelid, double vision, swallowing and speech difficulties, and pneumonia.

In case you feel symptoms of overdose please seek medical emergency services immediately or ask your relatives to do so and seek medical attention urgently. Medical supervision for up to several days and assisted ventilation may be necessary.

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

If you think you have taken too much **NUCEIVA**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using NUCEIVA?

These are not all the possible side effects you may feel when taking **NUCEIVA**. If you experience any side effects not listed here, contact your healthcare professional.

The most commonly reported **NUCEIVA** side effects (≥ 1%) were headache, drooping eyelid or brow, injection site reactions (e.g. pain, bruising, itchy skin, swelling), and upper respiratory infection or sinus infection.

Other potential side effects can include allergic reactions (e.g. eyelid edema, wheezing), blurred vision or double vision, temporary facial paralysis close to injection site, and urinary tract infection.

This is not a complete list of side effects. For any unexpected effects while taking **NUCEIVA**, contact your doctor or pharmacist.

If you have troublesome symptoms or side effects that are not listed here or become~~s~~ bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep out of the reach and sight of children.
NUCEIVA must be stored under refrigeration at 2-8°C. Once reconstituted, it can be stored under refrigeration at 2-8°C for up to 24 hours. Do not freeze after reconstitution.

If you want more information about **NUCEIVA:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website <phone number>, or by calling <phone number>.

This leaflet was prepared by EVOLUS, Inc.

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