▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – NUCEIVA (PRABOTULINUMTOXINA) POWDER FOR SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

NUCEIVA (prabotulinumtoxinA) 100 Units powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 Units prabotulinumtoxinA produced by *Clostridium botulinum*.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

NUCEIVA is a white to yellowish vacuum dried powder in a colorless and transparent vial. When reconstituted in sodium chloride (solution for) injection, it is a clear and transparent solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NUCEIVA is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Once reconstituted, NUCEIVA should only be used to treat a single patient, during a single session.

The units of biological activity of NUCEIVA (prabotulinumtoxinA) are specific to the preparation and assay method utilized.

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

Dilution Technique
NUCEIVA is supplied in a single use 100 Unit vial. Prior to intramuscular injection, reconstitute each vacuum-dried vial of NUCEIVA with only sterile, preservative-free 0.9% Sodium Chloride Injection, USP to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL and a total treatment dose of 20 Units in 0.5 mL (see Table 1).

Draw up the proper amount of 0.9% Sodium Chloride Injection, USP diluent in the appropriate size syringe and 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 diluent by rotating the vial.

Table 1. Dilution Instructions for NUCEIVA Vials (100 Units)

Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL
2.5 mL	4 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP

NUCEIVA should be administered within 24 hours after reconstitution. During this time period, unused reconstituted NUCEIVA should be stored in a refrigerator between 2° to 8°C (36°F to 46°F) in the original carton to protect from light for up to 24 hours until time of use. Do not freeze reconstituted NUCEIVA. Discard any remaining solution after administration.

Method of Administration

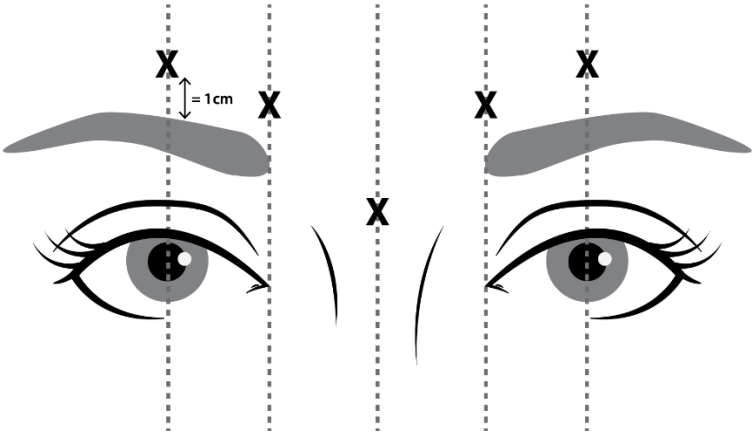
For intramuscular use.

Draw at least 0.5 mL of the properly reconstituted NUCEIVA into a sterile syringe. Attach the syringe to a 30–33-gauge injection needle and expel any air bubbles in the syringe barrel. Confirm the patency of the needle. Inject a dose of 0.1 mL (4 Units) intramuscularly into each of five sites: the inferomedial and superior middle of each corrugator, and one in the mid-line of the procerus muscle for a total dose of 20 Units (See Figure 1). Care should be taken to ensure that NUCEIVA is not injected into a blood vessel.

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

- Physical manipulation (such as rubbing) of the injection site in the immediate post-administration period should be avoided
- 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 1cm above the bony supraorbital ridge

Figure 1. Injection Points



Lack of Response

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.

Retreatment

Retreatment with NUCEIVA should be administered no more frequently than every three months. Consideration of the cumulative dose is necessary when treating adult patients with NUCEIVA for glabellar lines if other botulinum toxin products are or have been used.

The efficacy and safety of repeat injections beyond 12 months have not been evaluated.

4.3 CONTRAINDICATIONS

NUCEIVA is contraindicated in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components listed in section 6.1 List of excipients.

NUCEIVA is contraindicated in the presence of infection or inflammation at the proposed injection sites.

NUCEIVA is contraindicated in patients with generalised disorders of muscle activity (e.g., myasthenia gravis, Lambert-Eaton syndrome, amylotrophic lateral sclerosis).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lack of Interchangeability between Botulinum Toxin Products

THE UNITS OF BIOLOGICAL ACTIVITY OF NUCEIVA (PRABOTULINUMTOXINA) ARE SPECIFIC TO THE PREPARATION AND ASSAY METHOD UTILIZED. BOTULINUM TOXIN UNITS ARE NOT INTERCHANGEABLE FROM ONE PRODUCT TO ANOTHER. DOSES RECOMMENDED ARE DIFFERENT FROM OTHER BOTULINUM TOXIN PREPARATIONS.

Spread of Toxin Effect

Postmarketing safety data from other approved botulinum toxins suggest that botulinum toxin effects may be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, blurred vision, and breathing difficulties. 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 related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and spasticity. NUCEIVA is not approved for the treatment of spasticity or any conditions other than glabellar lines. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech, or respiratory difficulties occur.

Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) were excluded from the clinical studies of NUCEIVA. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from typical doses of NUCEIVA.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported for botulinum toxin products. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of NUCEIVA should be discontinued and appropriate medical therapy immediately instituted. The use of NUCEIVA in patients with a known hypersensitivity to any botulinum neurotoxin or to any of the components in the formulation could lead to a life-threatening allergic reaction (see **4.3 Contraindications**).

Immunogenicity

Antibodies to botulinum toxin type A may develop during treatment with botulinum toxin. Some of these antibodies may be neutralising which may lead to treatment failure of botulinum toxin type A.

Cardiovascular System

There have been reports following administration of botulinum toxins 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.

Albumin and Transmission of Viral Diseases

This product contains 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 and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

Dysphagia and Breathing Difficulties

Treatment with botulinum toxin products, including NUCEIVA, can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this has been a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins, including NUCEIVA, may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports from other botulinum toxin products of serious breathing difficulties, including respiratory failure.

NUCEIVA is not approved for the treatment of cervical dystonia.

Patients treated with botulinum toxin products, including NUCEIVA, may require immediate medical attention should they develop problems with swallowing, speech, or breathing. These reactions can occur within hours to weeks after injection with botulinum.

Ophthalmic Adverse Reactions in Patients Treated with Botulinum Toxin Products

Dry eye has been reported with the use of botulinum toxin products in the treatment of glabellar lines. Reduced tear production, reduced blinking, and corneal disorders may occur with use of botulinum toxins, including NUCEIVA. If symptoms of dry eye (e.g., eye irritation, photophobia, or visual changes) persist, consider referring patients to an ophthalmologist.

Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received botulinum toxin injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the

administration of botulinum toxin products to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of botulinum toxin products.

Bleeding Disorders

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

Pre-existing Conditions at the Injection Site

Caution should be used when NUCEIVA treatment is used when excessive weakness or atrophy is present in the target muscle(s).

Caution should be used when NUCEIVA treatment is used in patients who have marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or when subjects do not respond to 20 Units of botulinum toxin (e.g., the inability to substantially lessen glabellar lines even by physically spreading them apart). Do not exceed the recommended dosage and frequency of administration of NUCEIVA.

Use in the elderly

There were 154 subjects ≥ 65 years old included in the safety analysis as a result of pooling the 3 phase III studies and the two Phase II long term studies. Age did not appear to impact overall safety, however there seemed to be a slightly higher frequency of AEs of special interest that were considered related in the elderly population vs the adult population. These included (in alphabetical order) blepharospasm (1 in each population, 0.6% vs. <0.1%), eyelid ptosis (2 in the elderly, 1.3% vs. 16 adults, 1.1%), vision blurred (2 in the elderly, 1.3% vs. 1 adult, <0.1%), and speech disorder (1 in each population, 0.6% vs. <0.1%).

Paediatric use

There is no relevant use of NUCEIVA in the paediatric population. No data available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug interaction studies have been conducted with NUCEIVA (prabotulinumtoxinA). However, the potential for certain drugs to potentiate the effects of NUCEIVA warrant consideration given the potential risks involved and should be used with caution.

- Aminoglycosides or other agents interfering with neuromuscular transmission
- Anticholinergic drugs
- Botulinum neurotoxin products
- Muscle relaxant

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of NUCEIVA on human fertility is unknown. No animal fertility studies have been conducted with prabotulinumtoxinA. Intramuscular doses of 4 U/kg (males) and 8 U/kg (females) of a similar drug did not affect rat fertility. Decreased fertility occurred with higher doses, which also resulted in signs of toxicity. The relevance of these findings to human fertility is not known.

Use in pregnancy (Pregnancy Category B3)

There are no adequate data from the use of botulinum toxin type A in pregnant women.

In an embryofetal developmental study, intramuscular doses up to 4 U/kg prabotulinumtoxinA were administered to pregnant rats once daily during the period of organogenesis. No adverse embryofetal toxicities were observed. However, adverse embryofetal development effects have been seen in rat and rabbit studies with other botulinum toxins (lower fetal weights, delayed ossification, abortions and embryofetal development lethality). These adverse embryofetal development effects occurred in the context of maternotoxicity.

NUCEIVA is not recommended during pregnancy and in women of childbearing potential not using contraception.

Use in lactation

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

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin effect [see Warnings and Precautions].

Treatment emergent adverse events represent untoward changes in health irrespective of a causal association after exposure to a medicinal product. Table 2 presents treatment-emergent adverse events occurring at an incidence of >1% in the 1659 subjects with exposure to NUCEIVA in the overall pooled population from the single and multiple dose trials in the development program, along with those subjects in the control groups.

As also presented in Table 2, a subtotal of 922 healthy subjects (ranging in age from 19 to 83) had exposure to NUCEIVA in two multi-center, open label, 1-year repeat dose safety trials. Both trials evaluated repeat treatments of 20 units of NUCEIVA for the treatment of moderate to severe glabellar lines. All subjects received NUCEIVA and could receive up to 4 treatments (i.e.,

maximum total of 80 Units). Of the 922 subjects enrolled, the median number of treatments was three. The adverse event profile in the multiple dose trials was similar to that reported in single dose trials.

Table 2. Treatment Emergent Adverse Events Where Preferred Term is ≥1% - Safety Population

	Controls		NUCEIVA		
System Organ Class and Preferred Term	**Pooled Placebo (N=211) n (%)**	**BOTOX (N=246) n (%)**	**Pooled Single Dose (N=737) n (%)**	**Pooled Multiple Dose (N=922) n (%)**	**Pooled All (N=1659) n (%)**
All AEs in ≥1% of subjects	46 (21.8)	69 (28.0)	167 (22.7)	243 (26.4)	410 (24.7)
Nervous System Disorders	**28 (13.3)**	**25 (10.2)**	**91 (12.3)**	**129 (14.0)**	**220 (13.3)**
Headache	28 (13.3)	25 (10.2)	91 (12.3)	129 (14.0)	220 (13.3)
Infections and Infestations	**16 (7.6)**	**39 (15.9)**	**65 (8.8)**	**105 (11.4)**	**170 (10.2)**
Bronchitis	1 (0.5)	3 (1.2)	3 (0.4)	15 (1.6)	18 (1.1)
Gastroenteritis viral	3 (1.4)	0	3 (0.4)	5 (0.5)	8 (0.5)
Influenza	2 (0.9)	5 (2.0)	5 (0.7)	14 (1.5)	19 (1.1)
Nasopharyngitis	3 (1.4)	28 (11.4)	26 (3.5)	17 (1.8)	43 (2.6)
Oral Herpes	0	4 (1.6)	4 (0.5)	2 (0.2)	6 (0.4)
Sinusitis	5 (2.4)	1 (0.4)	7 (0.9)	26 (2.8)	33 (2.0)
Upper respiratory tract infection	3 (1.4)	1 (0.4)	13 (1.8)	20(2.2)	33 (2.0)
Urinary tract infection	1 (0.5)	1 (0.4)	6 (0.8)	19 (2.1)	25 (1.5)
Eye Disorders	**0**	**4 (1.6)**	**12 (1.6)**	**13 (1.4)**	**25 (1.5)**
Eyelid ptosis	0	0	12 (1.6)	12 (1.3)	24 (1.4)
Eyelid sensory disorder	0	4 (1.6)	0	1 (0.1)	1 (<0.1_
Vascular Disorders	**2 (0.9)**	**4 (1.6)**	**4 (0.5)**	**14 (1.5)**	**18 (1.1)**
Hypertension	2 (0.9)	4 (1.6)	4 (0.5)	14 (1.5)	18 (1.1)
Respiratory, Thoracic and Mediastinal Disorders	**1 (0.5)**	**6 (2.4)**	**5 (0.7)**	**10 (1.1)**	**15 (0.9)**
Cough	0	3 (1.2)	2 (0.3)	8 (0.9)	10 (0.6)
Oropharyngeal pain	1 (0.5)	4 (1.6)	3 (0.4)	2 (0.2)	5 (0.3)
Injury, Poisoning and Procedural Complications	**1 (0.5)**	**3 (1.2)**	**4 (0.5)**	**9 (1.0)**	**13 (0.8)**
Contusion	1 (0.5)	3 (1.2)	4 (0.5)	9 (1.0)	13 (0.8)
Investigations	**0**	**0**	**6 (0.8)**	**0**	**6 (0.4)**
White blood cell count increased	0	0	6 (0.8)	0	6 (0.4)

	Controls		NUCEIVA		
System Organ Class and Preferred Term	**Pooled Placebo (N=211) n (%)**	**BOTOX (N=246) n (%)**	**Pooled Single Dose (N=737) n (%)**	**Pooled Multiple Dose (N=922) n (%)**	**Pooled All (N=1659) n (%)**
General Disorders and Administration Site Conditions	**0**	**3 (1.2)**	**2 (0.3)**	**3 (0.3)**	**5 (0.3)**
Pyrexia	0	3 (1.2)	2 (0.3)	3 (0.3)	5 (0.3)

Note: At each level of summarisation, a subject was counted once if the subject reported one or more events. Preferred terms with frequency ≥1% in any NUCEIVA or control grouping are presented. "n" = the number of subjects at each level of summarisation; (%) = percentage of subjects. AEs were coded using MedDRA Version 17.0. AEs are sorted in descending order of frequency of System Organ Class based on the total of the NUCIEVA Pooled All. Within each System Organ Class, Preferred Terms are sorted in alphabetical order.

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In general, most adverse reactions occur within the first week following injection of NUCEIVA and while generally transient, may have a duration of several months or longer.

Table 3 presents adverse reactions, undesirable effects in which there is some basis to believe there is causal relationship between the drug and the occurrence, occurring at an incidence of less than 1%. These terms are categorised as uncommon (≥ 1/1,000 to <1/100) or rare (≥ 1/10,000 to <1/1,000).

Table 3 – Summary of Adverse Reactions Occurring at less than 1%

System Organ Class	Preferred Term	Frequency
Infections and infestations	Upper respiratory tract infection	Rare
Psychiatric disorders	Depression	Rare
Nervous System Disorders	Dizziness, migraine, muscle tone disorder, speech disorder	Uncommon
	Dysaesthesia, head discomfort, hypoaesthesia, paraesthesia, sensory disturbance	Rare
Eye disorders	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

System Organ Class	Preferred Term	Frequency
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	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

Adverse reactions are monitored during the post-approval use of NUCEIVA. The undesirable effects being reported are consistent with those observed in the clinical trials. Additional rare adverse reactions include hypersensitivity reactions, nausea, and dyspnea.

Application related undesirable effects have been reported following administration of NUCEIVA. As is expected for any injection procedure, localized pain, infection, inflammation, tenderness, swelling, erythema, pruritus, paraesthesia, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses, including syncope and hypotension, which may require appropriate medical therapy.

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. Suitable resuscitation facilities, including access to adrenaline (epinephrine), should be available.

Antibody formation

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing 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 in the studies described below, with the incidence of antibodies in other studies, or to other products may be misleading.

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 presence of anti-botulinum antibodies in subjects receiving NUCEIVA was evaluated in 1,414 subjects in two single dose Phase III studies (EV-001 and EV-002) and two repeat dose Phase II studies (EV-004 and EV-006). There were no cases of seroconversion using the vacuum dried formulation of NUCEIVA being commercialised which included 2,231 NUCEIVA treatments. In the EV-004 repeat dose study, which used the lyophilised product formulation that will not be commercialized and included 1,087 treatments, there were two cases of seroconversion; however, no neutralizing antibodies were identified.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 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 (generalized 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 generalized and profound neuromuscular paralysis. No cases of ingestion of botulinum toxin type A have been reported.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Therapeutic class: Neuromuscular blocking agent.

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 docking and release of acetylcholine from vesicles situated within the nerve terminals.

After injection, there is an initial high-affinity binding of toxin to specific cell surface receptors on cholinergic nerve terminals. Bound toxin is then internalised by endocytosis, and the catalytic light chain is translocated across the vesicular membrane into the cytosol where it cleaves SNAP-25. Progressive inhibition of acetylcholine release follows and clinical signs usually manifest within 2–3 days.

Recovery after intramuscular injection takes place normally within 12 weeks.

Clinical trials

Five clinical trials were completed; 3 randomized, controlled, single dose Phase III studies (EV-001, EV-002 and EVB-003) of 150 days duration; and 2 open label, multiple dose, long-term Phase II studies (EV-004 and EV-006) of 1 year duration.

Two randomized, multi-center, double-blind, placebo-controlled trials (EV-001 [NCT02334423] and EV-002 [NCT02334436]) of identical design were conducted to evaluate NUCEIVA for use in the temporary improvement of the appearance of moderate to severe glabellar facial lines. These trials enrolled 654 subjects, randomized 3 to 1 to a single treatment with NUCEIVA (n=492) or placebo (n=162).

The trials enrolled healthy adults (ranging in age from 18 to 81) with glabellar lines of at least moderate severity at maximum frown. The trials excluded subjects who had ptosis, deep dermal scarring, or an inability to substantially lessen glabellar lines even by physically spreading the glabellar lines apart. Injection volume was 0.1 mL/injection site, for a dose/injection site in the active treatment groups of 4 Units. Subjects were injected intramuscularly at five sites, one in the procerus muscle and two in each corrugator supercilii muscle, for a total dose in the active treatment groups of 20 Units.

The primary efficacy endpoint was measured at Day 30 and was defined as the proportion of subjects achieving ≥2-grade improvement from baseline at maximum frown, as assessed independently by both the investigator and the subject using the Glabellar Line Scale (GLS). The

GLS is a 4-point grading scale (0=none, 1=mild, 2= moderate, 3=severe). The results of these two efficacy trials are presented below (See Table 4).

The mean age was 51 years, with 68 subjects (10%) ≥ 65 years of age. Most of the subjects were women (91%), and a majority of the subjects were white (84%).

Table 4. Trials EV-001 and EV-002: Composite Investigator and Subject Assessment of Glabellar Line Severity at Maximum Frown at Day 30 – Responder Rates (% of Subjects Achieving ≥ 2-Grade Improvement from Baseline)

Trial	≥2 point Improvement Composite*		≥2 point Improvement Investigator		≥2 point Improvement Subject	
	NUCEIVA	Placebo	NUCEIVA	Placebo	NUCEIVA	Placebo
EV-001	N=246 67.5%	N=84 1.2%	N=246 77.5%	N=84 1.2%	N=246 76.7%	N=84 3.6%
EV-002	N=246 70.4%	N=78 1.3%	N=246 82.5%	N=78 2.7%	N=246 76.3%	N=78 4%

P-value <0.001 for all 3 comparisons

*A composite endpoint is when both the investigator and subject independently agreed that a ≥2 point improvement had occurred on the GLS at maximum frown.

The EVB-003 study was a multicenter, randomized, double-blind, active and placebo controlled, single dose study of 150 days duration comparing NUCEIVA to an active control (Botox®) and placebo for treatment of moderate to severe glabellar facial lines at maximum frown. This trial enrolled 540 subjects, randomized 5:5:1 to a single treatment with NUCEIVA (n=245), active control (n=246) or placebo (n=49).

The trial enrolled healthy adults (ranging in age from 22 to 79) with glabellar lines of at least moderate severity at maximum frown. Unique to this study, subjects were only eligible to participate if they also felt that their glabellar lines had an important impact on their psychological wellbeing. The trial excluded subjects who had ptosis, deep dermal scarring, or an inability to substantially lessen glabellar lines even by physically spreading the glabellar lines apart. The injection volume and treatment method in the NUCEIVA treatment group was the same as EV-001 and EV-002.

The mean age was 49 years, with 40 subjects (7.4%) ≥ 65 years of age. Most of the subjects were women (88.1%), and a majority of the subjects were white (71.1%).

The primary efficacy endpoint was defined as the proportion of subjects classified as responders on Day 30, and the definition of a responder was a subject with a GLS score of 0 or 1 (i.e., none or mild) at maximum frown by Investigator assessment.

The study met the primary end point of superiority to placebo and non-inferiority to Botox. The percentage of responders at Day 30 for NUCEIVA was 87.2% (83.0, 91.5) and 82.8% (78.1, 87.5) for the Botox group, while the percentage of responders for the placebo group was 4.2% (0.0, 9.9).

Table 5 – 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

Secondary efficacy endpoints included the proportion of subjects with a ≥1 point improvement on GLS as assessed by the investigator at maximum frown on Day 2 and Day 150. On Day 2, the responder rates were 54.2% and 12.2% for NUCEIVA and placebo respectively (absolute difference 41.9%, p<0.001). On Day 150, the responder rates were 38.7% and 8.3% (absolute difference 29.3%, p<0.001). Another secondary endpoint included the assessment of a ≥1 point improvement on the Subject Satisfaction Scale (i.e., satisfied or very satisfied) at Day 30. The percentages of responders were 91.3% and 6.3% for NUCEIVA and placebo respectively (absolute difference 85%, p<0.001).

A further 922 healthy adult subjects (ranging in age from 19 to 83) participated in the two multicenter, open label, multiple dose, long-term Phase II safety studies, EV-004 [NCT02184988] and EV-006 [NCT02428608]. The primary objective of these studies was to demonstrate the safety of multiple treatments of 20 Units of NUCEIVA over the course of 1 year for the treatment of moderate to severe glabellar lines. All subjects received treatment with NUCEIVA and could receive up to 4 NUCEIVA treatments (i.e., maximum total of 80 Units). Of the 922 subjects enrolled, the median number of treatments was three. Efficacy and safety profile results were consistent with the single dose trials.

The mean age was 50.8 years, with 84 subjects (9.1%) ≥ 65 years of age. Most of the subjects in these studies were women (91.2%), and a majority of the subjects were white (82.0%).

5.2 PHARMACOKINETIC PROPERTIES

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

Genotoxicity

No genotoxicity studies have been conducted with prabotulinumtoxinA.

Carcinogenicity

No long term carcinogenicity studies in animals have been conducted with prabotulinumtoxinA.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Albumin (0.5 mg)

Sodium chloride (0.9 mg)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials of NUCEIVA should be stored in a refrigerator between 2° to 8°C in the original carton to protect from light.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours

6.5 NATURE AND CONTENTS OF CONTAINER

NUCEIVA is supplied in a clear vial (Type I glass) fitted with a stopper (chlorobutyl rubber) and a seal (aluminum).

NUCEIVA is a white to yellowish vacuum dried powder. When reconstituted in sodium chloride (solution for) injection, it is a clear and transparent solution.

Pack size of one 100 Unit vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

NUCEIVA is a 900 kDa botulinum toxin type A, produced from fermentation of *Clostridium botulinum*. Each vial of NUCEIVA contains 100 Units of prabotulinumtoxinA, albumin (0.5 mg), and sodium chloride (0.9 mg) in a sterile, vacuum-dried form without a preservative.

The primary release procedure for NUCEIVA uses an animal-based potency assay to determine the potency relative to a reference standard. The assay is specific to NUCEIVA. One Unit of NUCEIVA corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. Due to specific details of this assay, Units of biological activity of NUCEIVA cannot be converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method.

CAS number

93384-43-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4: Prescription Only Medicine

8 SPONSOR

PPD Australia Pty Ltd
Level 5, 412
St Kilda Road
Melbourne AUSTRALIA

9 DATE OF FIRST APPROVAL

13 January 2023

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	New Product Information