

PACKAGE INSERT

1. Name of the medicinal product

NABOTA® Powder 100 Units for Solution for Injection

2. Qualitative and quantitative composition

Each vial contains:

- Active ingredient: Clostridium botulinum toxin type A – 100 Units
- Stabilizing agent: Human serum albumin – 0.5mg
- Isotonic agent: Sodium chloride – 0.9mg

3. Pharmaceutical form

It appears as a white to yellowish, vacuum-dried powder for injection in a colourless and transparent vial. It should become clear transparent liquid when dissolved in the diluent (physiological saline solution).

4. Clinical particulars

4.1 Therapeutic indications

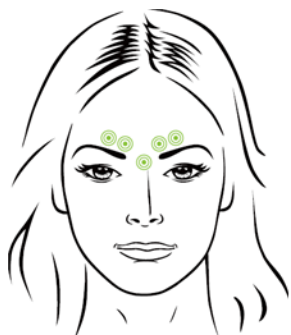
Temporary improvement in the appearance of moderate to severe glabellar lines (vertical lines between the eyebrows) associated with corrugator muscle and/or procerus muscle activities, in adults aged 20 to 65.

4.2 Posology and method of administration

NABOTA® should only be given by physicians with the appropriate qualifications and experience in the treatment of patients and the use of required equipment. The relevant anatomy, and any alterations to the anatomy due to prior surgical procedures, must be understood prior to administering NABOTA® and injection into vulnerable anatomic structures must be avoided considering information described in the Section 4.4.

Glabellar lines

Reconstitute by diluting with preservative-free, sterile saline solution to make 100U/2.5mL (4U/0.1mL). Using a sterile 30-gauge needle, inject a dose of 0.1mL into each of the 5 injection sites: 2 injections in each corrugator muscle and 1 injection in the procerus muscle for a total dose of 20 Units.



In order to reduce the complication of ptosis, injections near the levator palpebrae superioris muscle must be avoided, particularly in patients with larger brow-depressor complexes (depressor supercilii). Injections into inner corrugators muscle and central eyebrow should be placed at least 1 cm above the bony supraorbital ridge.

Careful attention should be paid to avoid injection of this product into the blood vessel. The thumb or index finger should be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection and careful attention should be paid to inject accurate volume.

Glabellar facial lines arise from the activity of corrugator muscle and orbicularis oculi muscle. These muscles move the brow medially, and the procerus muscle and depressor supercilii muscle pull the brow inferiorly. This creates a frown or “furrowed brow”. The location, size, and use of the muscles vary markedly among individuals. An effective dose for facial lines is determined by gross observation of the patient’s ability to activate the superficial muscles injected.

Each treatment lasts approximately three to four months. More frequent injection of this product is not recommended because the safety and efficacy are not established.

Typically, the initial doses of botulinum toxin induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.

Preparation and Dilution Technique

Prior to injection, reconstitute the product with a preservative-free, sterile saline. 0.9% sodium chloride injection is the recommended diluent. Draw up the proper amount of diluent in the syringe of appropriate size. Since this product is denatured by bubbling or similar violent agitation, the diluent should be injected gently into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time of reconstitution on the label. This product should be administered within 24 hours after reconstitution. During this period, reconstituted product should be stored in a refrigerator (2-8°C). Reconstituted product should be clear, colourless and free of particulate matter. Parental drug products should be inspected visually for particulate matter and discoloration prior to administration. Because this product and the diluent do not contain any preservative, one vial of this product should be used for a single patient.

Dilution Table

Volume of Diluent Added (0.9% Sodium Chloride Injection)	Resulting dose (Units per 0.1mL)
1.0mL	10.0 Units
2.0mL	5.0 Units
4.0mL	2.5 Units
8.0mL	1.25 Units

Note: These dilutions are calculated for an injection volume of 0.1mL. A decrease or increase in the dose is also possible by administering a smaller or larger injection volume – from 0.05mL (50% decrease in dose) to 0.15mL (50% increase in dose).

4.3 Contraindications

- Patients who are hypersensitive to any ingredient in the formulation of this product
- Patients who have neuromuscular junctional disorders (e.g. myasthenia gravis, Lambert-Eaton syndrome, or amyotrophic lateral sclerosis). The diseases may be exacerbated due to the muscle relaxation activity of this drug product.
- Pregnant women, women of childbearing potential or nursing mothers.

4.4 Special warnings and precautions for use

Administer with care to the following patients:

- Patients under treatment with other muscle relaxants (e.g. tubocurarine chloride, dantrolene sodium, etc.) – Muscle relaxation may be potentiated or risks of dysphagia may be increased.
- Patients under treatment with drugs with muscle relaxation activity, e.g. spectinomycin HCl, aminoglycoside antibiotics (gentamicin sulfate, neomycin sulfate, etc.), polypeptide antibiotics (polymyxin B sulfate, etc.), tetracycline antibiotics, lincomycin antibiotics (lincoamides), muscle

relaxants (baclofen etc.), anti-cholinergic agents (scopolamine butylbromide, trihexylphenidyl HCl, etc.), benzodiazepine and other similar drugs (diazepam, etizolam, etc.), and benzamide drugs (thiapride HCl, sulpiride, etc.). Muscle relaxation may be potentiated or risks of dysphagia may be increased.

Special warnings

Since the active ingredient of this drug product is Clostridium botulinum toxin type A which is derived from Clostridium botulinum, the information in this section should be fully understood and the recommended dosage and administration methods should be strictly followed. Physicians administering this drug product should sufficiently understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures, and standard electromyographic techniques. The recommended dosages and administration frequencies should not be exceeded.

A. Distant Spread of Toxin

The effects of botulinum toxin products may spread from the area of injection and produce negative symptoms. The symptoms may include asthenia, generalized muscle weakness, dysphonia, dysarthria, stuttering, urinary incontinence, breathing difficulties, dysphagia, diplopia, blurred vision, and ptosis. 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 spastic cerebral palsy, but symptoms can also occur in adults treated for spastic cerebral palsy and other conditions. Cases of the above adverse reactions have occurred at doses comparable to those used to treat cervical dystonia and at lower doses.

B. Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported in other botulinum toxin products. These reactions include anaphylaxis, urticarial, soft tissue oedema and dyspnoea. One fatal case of anaphylaxis has been reported in which lidocaine was used as a diluent, and consequently, the causal agent was not reliably determined. If such a reaction occurs, further injection of this drug product should be discontinued and appropriate medical therapy should be immediately instituted.

C. Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis or motor neuropathy) or neuromuscular junction disorders (e.g. myasthenia gravis or Lambert-Eaton syndrome) may be at increased risk of clinically significant systemic effects, including severe dysphagia and respiratory compromise from typical doses of this product. Published medical literatures with other botulinum toxin products have reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where patients have shown serious hypersensitivity to systemic effects of typical clinical doses. In some cases, dysphagia lasted several months and placement of a gastric feeding tube was required.

D. Dysphagia

Dysphagia is a commonly reported adverse event following treatment of cervical dystonia patients with all botulinum toxins. In these patients, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube.

There are also rare case reports where subsequent to the finding of dysphagia, a patient developed aspiration pneumonia and died.

E. Cardiovascular System

There have also been reports of adverse reactions with other botulinum toxin products, involving cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease.

F. Retrobulbar Haemorrhages / Ocular Penetrations

During administration of other botulinum toxin products for treatment of strabismus, retrobulbar haemorrhages sufficient to compromise retinal circulation have occurred owing to penetration of the needle into areas surrounding the eyes. It is recommended that appropriate instruments to decompress the orbit be accessible. Ocular (globe) penetrations by needles have also occurred. An ophthalmoscope to diagnose this condition should be available. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past-pointing. Covering the affected eye may alleviate these symptoms.

G. Blepharospasm

Reduced blinking from injection of botulinum toxin into orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. In the use of other botulinum toxin products for treatment of blepharospasm, one case of corneal perforation in an aphakic eye requiring corneal grafting has occurred because of this effect. Careful testing of corneal sensation in eyes previously operated upon should be conducted and injection into the lower lid area should be avoided to reduce the risk of ectropion. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

H. Lack of Interchangeability between Botulinum Toxin Products

Since the potency units of botulinum toxin are specific to individual products, they are not interchangeable with other botulinum toxin products. Therefore, units of biological activity of botulinum toxin cannot be compared nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

I. Injections In or Near Vulnerable Anatomic Structures

Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received botulinum toxin injected directly into the salivary glands, the oro-lingual-pharyngeal region, oesophagus and stomach. Some patients had pre-existing dysphagia or significant debility. (Safety and effectiveness have not been established for indications pertaining to these injection sites). Pneumothorax associated with injection procedure has been reported following the administration of botulinum toxin near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

J. Pulmonary Effects of Botulinum Toxin in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Over-activity associated with a Neurologic Condition

In patients with upper limb spasticity and respiratory disorder, upper respiratory tract infections and reduced lung function (decrease in Forced Vital Capacity [FVC] $\geq 15\%$) were reported more frequently when administered with other botulinum toxin products, compared to placebo. Reduced lung function (decrease in Forced Vital Capacity [FVC] $\geq 15\%$) were also reported in patients with respiratory disorder treated with other botulinum toxin products for detrusor over-activity associated with a neurologic condition.

K. Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with botulinum toxin, compared to placebo. In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with botulinum toxin compared to placebo. In the clinical study to confirm the therapeutic benefits in 195 patients who received treatment for upper limb spasticity, upper respiratory tract infections with 2 cases of the test group (treated with NABOTA) and 1 case of the control group were reported.

L. 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.

Precautions for use

A. This drug product contains albumin, a derivative of human blood. When a drug product derived from human blood or plasma is administered into human body, the potential of infectious diseases by transmissible agents cannot be completely excluded. It may include pathogenic agent that is still unknown. In order to minimize the risks of such infection by transmissible agents, particular cares are given to the albumin manufacturing process, including virus removal and/or inactivation processes, in addition to careful screening of donors and appropriate testing of donation units.

B. Due to the nature of the disease being treated, the effects of this drug product on the ability to drive or to operate machines cannot be predicted.

C. Glabellar line

Reduced blinking from botulinum toxin injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders.

Patients with skin disorders such as skin disease, infection and scars at the injection site, patients with the history of treatment of glabella part (including forehead) such as face lifting and permanent implant, patients with the history of facial nerve paralysis or the symptoms of eyelid ptosis, patients whose Glabellar lines cannot be satisfactorily improved with physical method since the lines are not flattened even using hands were excluded from the phase III safety and efficacy test and, therefore, should be warned. Injection of this product should not be more frequent than every three months and minimum effective dose should be used.

4.5 Interaction with other medicinal products and other forms of interaction

- The effects of botulinum toxin products are generally potentiated by concomitant use of aminoglycoside antibiotics or other drugs that interfere with neuromuscular transmission, e.g. tubocurarine-type muscle relaxants. Concomitant use of aminoglycosides or spectinomycin is contraindicated. Polymyxin, tetracycline and lincomycin should be carefully used in patients injected with this product.
- The effects of administering different botulinum neurotoxin serotypes at the same time or within several months of each other are unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin product prior to the resolution of the effects of a previously administered botulinum toxin.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women.

Administration of this product is not recommended during pregnancy or lactation.

4.7 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate carcinogenic potential.

4.8 Undesirable effects

General

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events have been reported in other botulinum toxin and a causal relationship to the botulinum toxin injected is unknown: skin rash (including erythema multiforme, urticaria and psoriasiform eruption), pruritus, and allergic reaction.

In general, adverse reactions occur within the first week following injection and, while generally transient may have a duration of several months. Localized pain, tenderness, bruising, traction, swelling, hot feeling or hypertonia at injection site or adjacent muscles may be associated with the injection. Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may also occur due to spread of toxin. When injected to patients with blepharospasm or cervical dystonia, some muscles distant from the injection site can show increased electrophysiological jitter (rapid variation in a waveform) which is not associated with clinical weakness or other types of electrophysiological abnormalities.

Glabellar lines

Safety of this product was evaluated in multicentre, comparative, double-blinded, randomized studies which included 268 patients aged 20 to 65, with moderate to severe Glabellar lines in Korea. 135 subjects and 133 subjects were received single treatment with NABOTA® and comparator (Botox®, control), respectively. Adverse reactions were observed in 20.00% of test group, and in 18.05% of control group. Most of the adverse reactions were mild, and none was severe. Adverse reactions reported more than 1% in the test group of this drug, listed in the order of frequency are: ptosis (2.22%), raised eyebrows (1.48%), and vertigo (1.48%).

Adverse drug reactions reported commonly in the test group were listed in the table, below

System Organ Class	Frequency	Adverse drug reaction
Nervous system disorders	Common	Dizziness
Gastrointestinal disorders	Uncommon	Nausea
Eye disorders	Common	Extraocular muscle disorder, Eyelid ptosis
Skin and subcutaneous tissue disorder	Uncommon	Pruritus, Skin tightness

Additional 5 controlled studies were conducted in the US, Canada and the EU. During the clinical studies, 1659 received with this product including 922 subjects received multiple dose, 246 received treatment with comparator (Botox®, control) and 211 received treatment with Placebo. The frequency of any adverse events in pooled test group of this drug was 38.4% and 41.9% and 30.3% were observed in pooled control group and pooled placebo group, respectively. Most subjects experienced adverse events that were assessed as mild or moderate in severity. An adverse event assessed as severe was reported by 1.9%, 2.0% and 0.9% in the pooled test group, pooled control group and pooled placebo group, respectively. 93% of severe adverse events were assessed as not related to study drug. 1 report of headache, and 2 reports of migraine in a single subject were assessed as possibly related to this drug. Adverse reactions reported more than 1% in the pooled test group, listed in the order of frequency are: Headache (13.3%), Nasopharyngitis (2.6%), Upper respiratory tract infection (2.0%) Sinusitis (2.0%), Urinary tract infection (1.5%), Eyelid ptosis (1.4%), Influenza (1.1%), Bronchitis (1.1%) and Hypertension (1.1%).

Adverse drug reactions reported commonly in the test group were listed in the table, below

System Organ Class	Frequency	Adverse drug reaction
Infections and infestations	Rare	Upper respiratory tract infection
Psychiatric disorders	Rare	Depression
Nervous system disorders	Common	Headache
	Uncommon	Dizziness, migraine, muscle tone disorder, speech disorder

System Organ Class	Frequency	Adverse drug reaction
	Rare	Dysaesthesia, head discomfort, hypoaesthesia, paraesthesia, sensory disturbance
Eye disorders	Common	Eyelid ptosis
	Uncommon	Asthopenia, blepharospasm, brow ptosis, eyelid oedema, eye swelling, vision blurred
	Rare	Diplopia, dry eye, eyelid sensory disorder
Ear and labyrinth disorders	Rare	Vertigo
Vascular disorders	Rare	Flushing
Respiratory, thoracic and mediastinal disorders	Rare	Epistaxis
Gastrointestinal disorders	Rare	Diarrhea
Skin and subcutaneous tissue disorders	Uncommon	Pruritis
	Rare	Dermal cyst, erythema, photosensitivity reaction, skin mass, skin tightness
Musculoskeletal and connective tissue disorders	Rare	Muscle twitching, musculoskeletal pain, myalgia, neck pain
General disorders and administration site conditions	Common	Application site bruising, influenza like illness, injection site bruising, injection site pain, injection site swelling
	Rare	Injection site: erythema, injection site paresthesia, injection site pruritis, pain, tenderness
Investigations	Rare	Intraocular pressure test
Injury, poisoning and procedural complications	Uncommon	Contusion
	Rare	Post-procedural swelling, procedural headache

4.9 Overdose

Signs and symptoms of overdose are not apparent immediately after injection. Should accidental injection or oral intake occur, the person should be medically supervised for up to several weeks for signs and symptoms of systemic weakness or muscle paralysis.

An antitoxin may be used in the event of immediate knowledge of overdose or wrong administration. The antitoxin will not reverse any botulinum toxin-induced muscle weakness effects already appeared by the time of antitoxin administration.

If the muscles of the oropharynx and oesophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be required until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

Antibodies to botulinum toxin type A may develop during frequent treatment with botulinum toxin. Some of the antibodies formed are neutralising which may lead to treatment failure of botulinum toxin type A.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other muscle relaxant, peripherally acting agents

ATC Code: M03AX01

5.1.1 Mechanism of action

This product blocks neuromuscular transmission by binding to receptor site on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When injected intramuscularly at therapeutic doses, this product produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extra junctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by this product.

5.1.2 Clinical efficacy

Phase I/III Clinical Trial on Moderate to Severe Glabellar Line

The clinical trial was designed to conduct phase 1 (Step 1: A single-center, randomized, double-blind, active controlled) and phase 3 (Step 2: A multi-center, randomized, double-blind, active controlled) to evaluate this drug for the use in the temporary improvement of moderate to severe glabellar lines at maximum frown in healthy adults. In step 1, patients with such glabellar lines were treated with NABOTA to assess the safety and in step 2 (Phase 3) the efficacy and safety was compared with comparator (Botox®) and was confirmed that NABOTA is non-inferior compared to the comparator.

To prove that 20 units of NABOTA is non-inferior to comparator in efficacy for treatment of glabellar lines and is equivalent to comparator in safety, an active-controlled, double-blind, parallel group phase 3 clinical trial was conducted. Allergan's Botox® was selected as the comparator as it is identical in dosage with NABOTA, enabling effective comparison in efficacy and safety, and is the most prescribed drug for the treatment of glabellar lines. The primary endpoint was the investigator's assessment of glabellar line severity at maximum frown at week 4 post dose. Based on the primary endpoint, the responder rate is summarized, below.

Responders for the Primary Endpoint	BOTOX	NABOTA
Number	117/132	123/131
Percentage	88.6%	93.9%
(% CI)	(83.2, 94.1)	(89.8, 98.0)

In conclusion the test groups' results are non-inferior to the results of the comparator group.

Phase III Clinical Trial on Moderate to Severe Glabellar Line in the US, Canada and the EU

2 multi-center, randomized, double blind placebo-controlled Phase III clinical trials (EV-001 and EV-002) were conducted to evaluate this drug 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. Based on the primary endpoint, the responder rate is summarized, below.

Responders for the Primary Endpoint	EV-001		EV-002	
	Placebo	NABOTA	Placebo	NABOTA
Number	1/83	162/240	169/240	1/75
Percentage	1.2%	67.5%	1.3%	70.4%
(% CI)	(0.0, 9.8)	(61.2, 73.4)	(0.0, 7.2)	(64.2, 76.1)

In a supportive Phase III trial (EVB-003), the primary efficacy endpoint was the proportion of responders if they had a GLS score of 0 or 1 at maximum frown on Day 30 by Investigator, and it was evaluated with a superiority of this drug versus Placebo and a non-inferiority design with a comparator (Botox®). Based on the primary endpoint, the responder rate is summarized, below.

Responders for the Primary Endpoint	Placebo	BOTOX	NABOTA
Number	2/48	202/244	205/235
Percentage	4.2%	82.8%	87.2%
(% CI)	(0.0, 9.8)	(78.1, 87.5)	(83.0, 91.5)

In the conclusion, results of the 3 controlled single dose studies provide evidence of the effectiveness of this product for the treatment of moderate to severe glabellar lines.

5.1.3 Clinical safety

Pharmacological Characteristic Adverse Events

Clostridium botulinum toxin type A is a toxin produced by bacterium Clostridium botulinum which is known to cause muscle relaxation by blocking the transmission of acetylcholine and is currently available as a focal muscle relaxant. Headaches and eyelid ptosis are the most reported adverse events and it has been also reported to cause injection site pain, facial pain, erythema, focal muscle weakness, oedema on injection site, ecchymosis, localized numbness, nausea and *etc* to 1~3% of the patients.

The safety evaluation result of this during the clinical trials is provided in the Section 4.8.

5.1.4 Paediatric population

Safety and effectiveness in children and adolescents were not investigated for improvement of Glabellar lines.

5.2 Pharmacokinetic properties

Not applicable.

NABOTA is a very potent neurotoxin that is directly injected into the targeted muscle where it exerts its desired paralytic pharmacological effect and therefore is considered a localized treatment. Intramuscular injection of a low therapeutic dose of 20U is not expected to be present in peripheral circulation. Nor are there any sensitive bio-analytical methods for evaluating metabolism, distribution and mass balance.

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 NABOTA® 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). No maternal or embryofetal toxicities were observed at doses up to 4 unit/kg (12 times the MRHD of 20 units, based on unit/kg comparison). Effects on peri-/postnatal development have not been evaluated.

6. Patient Information

Patients should be encouraged to consult with their doctor about any and all concerns over effectiveness and/or risks of this product. Careful attention should be paid to potential signs or symptoms of adverse reactions. Call your doctor or get immediate medical help if you experience any unusual symptoms

after treatment with this product, including difficulty in swallowing, speaking or breathing, or muscle weakness. Such adverse reactions may happen hours to weeks after injection of this product.

7. Pharmaceutical particulars

7.1 List of excipients

Human serum albumin
Sodium chloride

7.2 Incompatibilities

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

7.3 Shelf-life

36 months

7.4 Special precautions for storage

Store at 2-8°C in hermetic container.

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.

7.5 Nature and contents of container

Vial (Type I glass) fitted with a stopper (chlorobutyl rubber) and a seal (aluminium).
Each box contains 1 vial.

7.6 Special precautions for disposal and other handling

Unopened vials of this drug product should be stored in a refrigerator (2-8°C) for up to 24 hours after reconstitution. For safe disposal, all vials including expired vials or equipment directly contacted with the drug should be disposed as medical waste. If inactivation is required (e.g. spillages), use of diluted hypochlorite solution (0.5% of 1%) before disposal as medical waste is recommended.

For the instruction for the reconstitution, please refer to the section “Preparation and Dilution Technique” in the “4.2 Posology and method of administration”

8. Name and Address of the Manufacturer

Daewoong Pharmaceutical Co., Ltd
35-14, Jeyakgongan 4-Gil,
Hyangnam-Eup, Hwaseong-Si,
Gyeonggi-Do, Republic of Korea

9. Date of revision of the text

June 07, 2023