PACKAGE INSERT

1. Name of the medicinal product

NABOTA Powder for Solution for Injection 100units/vial

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 below 65 years of age.

4.2 Posology and method of administration

For intramuscular use only.

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.

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

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.

Elderly patients
NABOTA is not recommended for use in patients over 65 years of age.

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. Parenteral 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 treatment only during a single session.

Dilution Table

Volume of Diluent Added (0.9% Sodium Chloride Injection)	**Resulting dose (Units per 0.1mL)**
2.5mL	4.0 Units

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.
- Infection or inflammation at the proposed injection sites.

4.4 Special warnings and precautions for use
General
Localised pain, inflammation, paraesthesia, hypoaesthesia, tenderness, swelling/oedema, erythema, localised infection, bleeding and/or bruising have been associated with the injection. Needle-related pain and/or anxiety have resulted in vasovagal responses, including transient symptomatic hypotension and syncope.
Caution should be taken when the targeted muscle shows pronounced weakness or atrophy.
There is a risk of eyelid ptosis following treatment.
Caution should be taken if complications have resulted with previous botulinum toxin injections.
Continued concomitant use of aminoglycosides or spectinomycin is contraindicated.

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. 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. Spread of Toxin Effect

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

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. Bleeding disorders

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

E. 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.

F. 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.

G. 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.

H. 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.

<u>Precautions for use</u>
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. NABOTA 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.
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
- No interaction studies have been performed.
- 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. Continued 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.
An effect of this drug to maternal condition and embryofetal development was assessed as this drug (0.5, 1, 4U/kg) was intramuscularly injected to pregnant rats during the period of organogenesis (days 6 to 16 of gestation). As a result, stooped toes, paralytic gait, curling of toes were observed from mother rats and osteopenia from fetus of 4U/kg dose group, statistically not significant.
It is not known whether botulinum toxin is excreted in human milk.

Administration of this product during pregnancy or lactation is contraindicated as described in section 4.3.

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

4.7 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 (test group 135, control group 133) in Korea. 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%).
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%).

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.

Admission to hospital should be considered in patients presenting with symptoms of botulinum toxin type A poisoning (generalised weakness, ptosis, diplopia, swallowing and speech disorders, or paresis of the respiratory muscles).

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

<u>Phase I/III Clinical Trial on Moderate to Severe Glabellar Line in Korea</u>

The clinical trial was designed to conduct phase 1 (Step 1) and phase 3 (Step 2) on moderate to severe glabellar line patients. 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.

A total of 268 subjects enrolled to evaluate efficacy of the product in the step 2 studies (phase 3).

In the demographic characteristic studies, no statistically significant differences were found in any parameters and no imbalance was identified.

As a result of analysis of efficacy endpoints, the improvement rate was 93.89% in the test group and 88.64% in the comparator group after administration. And no statistically significant differences were found between the groups in the improvement of glabellar lines and subject's satisfaction survey results at resting state 4, 8, 12 and 16 weeks after administration.

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.

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 rates in test group and placebo groups were, respectively, 67.5% and 1.2% in EV-001; 70.4% and 1.3% in EV-002; and 87.2% and 4.2.% in EVB-003 ($p<0.001$). In addition, non-inferiority of this drug compared to comparator in EVB-003 were confirmed as there was no statistically significant differences in the improvement rate of test group (87.2%) and comparator group (82.8%).Additionally, the effectiveness of this drug at rest was evaluated as the secondary endpoint during the studies. The result shows that the absolute difference between pooled test group and placebo groups in the percentages of responders for the composite endpoint of a ≥2 point improvement on the GLS at rest on Day 30 was 25.0% ($p<0.001$).

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 drug during the clinical trials is provided in the Section 4.8.

5.1.4 Paediatric population

Safety and effectiveness in children and adolescents below the age of 18 years 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.

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
Chemical and physical in-use stability has been demonstrated for 72 hours at 2 to 8°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless 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.

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
20 February 2023