طبقاً لقرار اللجنة العلمية المتخصصة للمستحضرات الحيوية بدعوة اللجنة العلمية المتخصصة لأمراض النفسية والعصبية بجلستها في ١٤/٩/٢٠٢٢

داليا محمد

NABOTA Injection 100 Units
(Clostridium botulinum toxin type A)

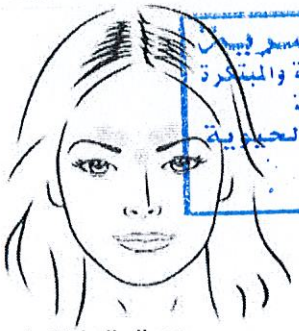
QUALITATIVE AND QUANTITATIVE COMPOSITION
NABOTA Injection 100 Units (Clostridium botulinum toxin type A)
Each vial contains:
- Active ingredient: Clostridium botulinum toxin type A - 100 Units
- Stabilizing agent: Human serum albumin - 0.5 mg
- Isotonic agent: Sodium chloride - 0.9 mg

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

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

2. Focal upper limb spasticity
Upper limb spasticity associated with stroke in adults over 18 years of age.

DOSAGE & ADMINISTRATION



1. Glabella lines
Reconstitute by diluting with preservative-free, sterile saline solution to make 100U/2.5 mL (4U/0.1 mL) Using a sterile 30-gauge needle, inject a dose of 0.1 mL 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.

Glabella 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 interiorly. 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.

2. Treatment of focal spasticity
The exact dosage and number of injection sites may be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, the presence of local muscle weakness, and the patient response to previous treatment. Clinical improvement of spasticity was observed within the 4 weeks, and also assessHed at 8 and 12 weeks after the injection. The injection doses in the clinical study are as follows :

Muscle	Total dose	Number of sites
Biceps brachii	100 - 200 Units	Up to 4 sites
Flexor digitorum profundus	15-50 Units	1-2 sites
Flexor digitorum sublimis	15-50 Units	1-2 sites
Flexor carpi ulnaris	10 - 50 Units	1-2 sites

In the clinical study, the recommended dose was allowed up to 360 Units, and divided among selected muscles.

Sterile 24-30 gauge needle is recommended. Needle length should be determined based on muscle location and depth. Localisation of the involved muscles with techniques such as electromyographic guidance, or nerve stimulation is recommended.

PREPARATION AND DILUTION TECHNIQUE
Prior to injection, reconstitute freeze-dried 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 space of 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, colorless 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.

[DILUTION TABLE]

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

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

PRECAUTIONS

1. Warning

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-v, 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.

B. Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported in other botulinum toxin product. These reactions include anaphylaxis, urticaria, soft tissue edema and dyspnea. 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 product 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. There have also been reports of adverse reactions with other botulinum toxin product, involving cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes Some of these patients had risk factors including cardiovascular disease .

F. During administration of other botulinum toxin product for treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred owing to penetration of the needle into areas surrounding 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 product 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 product. Therefore, units of biological activity of botulinum toxin cannot be compared or converted into units of any other botulinum toxin product assessed with 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 salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach (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 Overactivity 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] £15%) were reported more frequently when administered with other botulinum toxin products, fc*. compared to placebo. Reduced lung functions (decrease.^, in Forced Vital Capacity [FVC] >15%) were also reported in patients treated with other botulinum toxin products for detrusor overactivity 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 NABOTA) and 1 case of the control group were reported.

2. CONTRAINDICATIONS

A. Patients who are hypersensitive to any ingredient in the formulation of this product.

B. 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.

C. Patients with severe respiratory disorders, when used for treatment of cervical dystonia.

D. Pregnant women, women of childbearing potential or nursing mothers.

E. Patients with neurogenic detrusor overactivity who also has acute urinary tract infection and patients with acute anuresis who does not routinely conduct clean intermittent catheterization, when injected into detrusor muscle.

3. ADMINISTER WITH CARE TO THE FOLLOWING PATIENTS

A. 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.

B. 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 (lincosamides), muscle relaxants (baclofen etc.), anti cholinergic agents (scopolamine butylbromide, trihexylphenidil 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.

4. ADVERSE REACTIONS

A. General

There have been spontaneous reports of death . sometimes associated with dysphagia, pneumonia, and'/biyother significant debility or anaphylaxis, after ' treatment with botulinum toxin. There have also been ports 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.

B. Glabella lines

Safety of this product was evaluated in multicenter, comparative, double-blinded, randomized studies which included 268 patients aged between 20 to 65. with moderate to severe glabella lines (test group 135.

control group 133). 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%).

C. **Upper limb spasticity**
In multicenter, double blinded, randomized active controlled trial with 197 post-stroke patients aged over 18 years, more than 6 weeks since stroke onset, safety in upper limb spasticity was evaluated (NABOTA test group (n =99) or Botox control group (n = 98)). Adverse reactions occurred in 19.59% (19/97, 30 cases) of the test group and 19.39% (19/98, 22 cases) of the control group.

Most of the adverse reactions were mild, and none was severe. Adverse reactions reported in this clinical study were 3 cases in the test group of this drug and 4 cases in the control group.

The frequency of adverse reactions reported in the clinical trials is defined as follows:
Very Common (≥ 1/10); Common (≥ 1/100 to <1/10); Uncommon (≥ 1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (<1/10,000).
Adverse reactions reported commonly in treatment of this drug were listed as follows: See Table .

Table. Reported adverse reactions in NABOTA-treated group

System Organ Class	Common
Musculoskeletal and connective tissue disorders	muscular weakness(1.03%, 1 case), pain in extremity(1.03%, 1 case), muscle atrophy(1.03%, 1 case)

5. GENERAL PRECAUTIONS

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. Glabella line
Reduced blinking from botulinum toxin injection of the orbicularis muscle can lead to corneal exposure, specialty in patients with VII nerve disorders. persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. 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 glabella 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 therefore, should be warned. Injection of this product should not be more frequent than every three months and minimum effective dose should be used.

D. Upper limb spasticity
This drug is a treatment of focal spasticity that has only been studied in association with usual standard of care regimens, and is not likely to be effective in improving range of motion at a joint affected by a fixed contracture.

6.DRUG INTERACTIONS

A. 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.

B. The effects of administering different botulinum. ne-urotoxin serotypes at the same time or within several months are unknown. Excessive neuromuscular weakness! may be exacerbated by administration of another botulinum toxin product before the effects of a previously administered botulinuin toxin disappear.

7. PREGNANCY & BREASTFEEDING

There are no adequate and well-controlled studies in pregnant women.
When pregnant mice and rats were injected intramuscularly during the period of organogenesis, the developmental NOEL (No Observed Effect Level) of other botulinum toxin was 4 U/kg. Higher doses (8 or 16 U/kg) were associated with reductions in fetal body weights and/or delayed ossification. In a range finding study in rabbits, daily injection of 0.125 U/kg/day (days 6 to 18 of gestation) and 2 U/kg (days 6 and 13 of gestation) produced severe maternal toxicity, abortions and/or fetal malformations. Higher doses resulted in death of the dams. The rabbit appears to be a very sensitive species to this drug. The patient should be apprised of the potential risks, including abortion or fetal malformations which have been observed in rabbits. It is not known whether botulinum toxin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when this product is administered to a nursing woman. Administration of this product is not recommended during pregnancy or lactation.

8. PEDIATRIC USE

Safety and effectiveness in children and adolescents below the age of 20 years were not investigated for improvement of glabella lines.

The safety and efficacy of upper limb spasticity have not been established in children and adolescents under the age of 18 years.

9. CARCNINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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

Animal Toxicity

In a study of other botulinum toxin product to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 U/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 U/kg (~12X the human dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injection of up to 100 U/kg (~33X the human dose).

10. OVERDOSAGE

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 or 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 esophagus 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.

11. PRECAUTIONS IN STORAGE & HANDLING

Unopened vials of this drug product should be stored in a refrigerator (2-8'C). Reconstituted product may 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 dilute hypochlorite solution (0.5% or 1%) before disposal as medical waste is recommended.

12. 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.

This product blocks neuromuscular transmission by binding to acceptor sites 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.

HOW SUPPLIED

ONE vial x In-house packaging unit

STORAGE & EXPIRY DATE

Store at 2-8°C in hermetic container, 36 months from the date of manufacture

MANUFACTURER

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

Marketing authorization holder in EYGPT :

Egyptian international for medical supplies
EIMS –Egypt

Revision date
December 2015