NATIONAL PHARMACEUTICAL REGULATORY DIVISION (NPRA) MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY FOR NEW REGISTRATION APPLICATION

PRODUCT NAME:
NABOTA Powder 100 Units for Solution for Injection (MAL23086028AZ)

ACTIVE INGREDIENT:
Clostridium Botulinum Toxin Type A

PRODUCT REGISTRATION HOLDER:
Hyphens Pharma Sdn Bhd.

PRODUCT MANUFACTURER:
Daewoong Pharmaceutical Co., Ltd.
Gyeonggi-do, Republic of Korea

APPROVAL DATE:
3 August 2023 (DCA 387)

1.0 BACKGROUND INFORMATION

- This is an application to register new product containing *Clostridium botulinum* neurotoxin type A.
- Botulinum toxin type A is a neurotoxin produced by *Clostridium botulinum* and is known to cause muscle relaxation by blocking the transmission of acetylcholine. Botulinum toxin, Type A via intramuscular injection inhibits the release of acetylcholine, (ACh) from presynaptic motor neurons at the neuromuscular junction, (NMJ) to cause flaccid muscle paralysis.
- DCA has registered the following botulinum toxin type A products:

No.	Name of product	Active ingredient	MAL No.	Marketing authorisation holder
1	Botox (Botulinum Toxin Type A) IM Injection	Clostridium botulinum toxin type A-haemagglutinin complex, 100 U/vial	MAL19970915ARZ	Allergan Malaysia Sdn Bhd
2	Dysport Powder For Injection	Clostridium botulinum toxin type A-haemagglutinin complex, 500U/vial	MAL20000731AZ	EP Plus Group Sdn Bhd
3.	XEOMIN powder for solution for injection 100 LD50 units	Clostridium botulinum toxin type A-haemagglutinin complex free, 100U/vial	MAL16015034AZ	MERZ PHARMA GMBH & CO. KGAA (GERMANY)
4.	XEOMIN powder for solution for injection 50 LD50 units	Clostridium botulinum toxin type A-haemagglutinin complex free, 50U/vial	MAL16015033AZ	
5.	Neuronox ® Powder for Solution for Injection 50 units	Clostridium Botulinum Toxin Type A haemagglutinin	MAL20046092AZ	SUNWARD PHARMACEUTICAL SDN. BHD.
6.	Neuronox ® Powder for Solution for Injection 100 units		MAL20046093AZ	
7.	Neuronox ® Powder for Solution for Injection 200 units		MAL20046094AZ	

1.1 Proposed Indication:

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 20 years to 65 years

1.2 Proposed Posology

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).

1.3 Route of Administration

Intramuscular

1.4 Pharmacological Aspects

Pharmacotherapeutic group: Other muscle relaxants, peripherally acting agents – Botulinum toxin (M03AX01)

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.

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.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Active Substance

The active substance of botulinum toxin is produced from Botulinum toxin, Type A bacteria which is a covalently bonded dimer of two complexes consisting of neurotoxin,

NTNH (non-toxic, non-hemagglutinin) protein, and HA (hemagglutinin) proteins. The chemical structure is approximately 900kDA.

Process validation (3 consecutive batches) demonstrated that the process were able to consistently produce drug substance that maintain process parameters within the defined limits as specified pre-defined criteria.

GMP Compliance for drug substance manufacturer was verified by Ministry Of Food and Drug Safety, Republic Of Korea.

Stability data were submitted to support the storage condition of -70°C for 36 months, according to ICH Q5C "*Quality Of Biotechnological Products: Stability Testing Of Biotechnological/Biological Products*" and should be protected from light during long term storage

2.1.2 Finished Product

Process validation (3 consecutive batches) have been conducted and confirmed that the manufacturing process can consistently produce drug product according to pre-specified specifications.

GMP Compliance of the drug product manufacturer was verified by Ministry of Food And Drug Safety, Republic Of Korea

The proposed shelf life of 36 months stored at 2-8°C is supported by 3 commercial scale batches. In use stability studies were conducted on three batches following reconstitution in sterile sodium chloride. Results demonstrate that the product is stable for over a period of 72 hours.

NABOTA is a white to yellowish vacuum-dried powder presented in a Type 1 glass vial and closed with a rubber stopper sealed with flip off crimp closure.

NON-CLINICAL STUDIES

- The non-clinical studies were conducted to characterize the pharmacological action and determine the safety profile in single and repeat dose studies.
- The pharmacology studies was conducted against BOTOX in single and maximum tolerated dose in rats and beagle dogs.

- All the toxicology studies were conducted in Organisation for Economic Co-operation and Development (OECD) GLP compliant laboratory except the repeat dose study conducted in dogs.

2.2 CLINICAL STUDIES

2.3.1 Efficacy

- One Phase I/ Phase III clinical study conducted to support the indication of temporary improvement in the appearance of moderate to severe glabellar lines. Phase 1, patients with glabellar lines were treated with NABOTA to assess the safety. In the Phase III portion of the study, the efficacy and safety was compared with BOTOX. BOTOX was chosen as the comparator as it is identical in dosage with NABOTA and is most commonly prescribed for treatment of glabellar lines.

- NABOTA was deemed non-inferior to BOTOX when the lower limit of the 97.5% one sided CI of the improvement margin between the two groups was greater than the non-inferiority threshold (-15%).

Study Type & Design (N)	Objective of the study	Results
Won.C.H., et al Comparative trial of a novel botulinum neurotoxin type A versus onabotulinumtoxinA in the treatment of glabellar lines: A multicentre, randomized, double blind, active controlled study: ***International Journal of Dermatology*** **2015 (54): 227-234** Multi-centre, randomized, double-blind, active drug controlled, phase I/III clinical trial Ratio: 1:1 Phase I: 20 subjects Phase III: 265 subjects	**STAGE 1 (PHASE I)** • To identify the **safety** of NABOTA in adult patients for treatment of moderate-to-severe glabellar line after administration of 20U by 28 days observation. **STAGE 2 (PHASE III)** • To assess the glabellar line i**mprovemen**t and the safety of NABOTA 20U or BOTOX ® Injection 20U at **4 weeks post dose** in adult patients for treatment of moderate-to-severe glabellar line and to **verify NABOTA is clinically not inferior to BOTOX ® Injection**	Phase I: No grade 3 or more adverse drug reactions were reported NABOTA group. Primary endpoint Phase III: The improvement rate (percentage of grade 0 (none) and grade 1(mild) in the control group. **DWP450 (N=133)** Week 4 Response, n(%) 125(93.98) Two-sided 95% Confidence Interval (89.94, 98.03) Difference between Treatment groups Lower limit of one-sided 97.5% Confidence Interval Non-inferiority (Margin=-15.0%) **Conclusion:** As the lower limit of the 97.5% one-sided confidence interval (– 1.53%) surpassed the – 15% threshold, the study concluded that NABOTA was not inferior to BOTOX in patients with moderate to severe glabellar lines.

2.3 Safety

- The percentage of adverse events was similar between the NABOTA group (20%) compared to the control group (18.05%) with no differences in the frequency of adverse event. All the reactions were mild to moderate in severity.
- No new safety concerns were identified and the adverse reactions were similar to those previously reported
- Periorbital adverse events, including ptosis and elevation of one or both sides of the lateral portion of the eyebrow were the most frequent in both treatment groups.
- There were no antidrug antibody detected in either the NABOTA or BOTOX group.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 387th meeting on 3 August 2023 has decided to approve the registration of this product with the following indication:

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 20 years to 65 years