EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

NABOTA

Date: November 2024

Unit: Technical Assessment Unit

Assessment report
NABOTA

Administrative information:

Invented name of the medicinal product:	NABOTA Injection 100 unit
INN (or common name) of the active substance(s):	Clostridium botulinum Toxin Type A- 100 unit.
Marketing Authorization holder	Daewoong pharmaceutical Co.Ltd., 35-14, Jeyakgondan 4-gil, Hyangnam-eup, Hwaseong-si,Gyeonggi-do-Republic of Korea.
Applied Indication(s):	**1.Glabellar lines** 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 between 20 to 65. **2.Focal upper limb spasticity** Upper limb spasticity associated with stroke in adults over 18 years of age.
Pharmaceutical form(s) and strength(s):	- Powder for solution for I.M injection - Strength:100 U/2.5 ml (4 U/0.1 mL)
Route of administration	I.M. Injection
Approved Pack(s):	Carton box contains borosilicate (Type 1) glass vial (highly resistant borosilicate with transparent nonporous Si-O-C-H layer) and closed with a chlorobutyl Stopper with fluoro-polymer laminate. The rubber stopper is sealed to the vial with a polypropylene cap and aluminum flip-off crimp closure with insert leaflet.

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 3.1.2022 after providing all the required documents according to "the Checklist for documents of new biological products registration file".
- Full CTD along with detailed SOPs were provided.

List of abbreviations

I.M	Intramuscular
CTD	Common Technical Document
SOP	Standard Operation Procedure
DP	Drug Product
DS	Drug Substance
USP	United States Pharmacopeia
WCB	Working Cell Bank
COA	Certificate of Analysis
PV	Pharmacovigilance
HA	Haemagglutinin
NTNH	Non-toxic, non-haemagglutinin
NIBC	National Institute for Biological Standard and Control
HDPE	High-density polyethylene
QbD	Qualities by Design

Table of contents

1. General introduction about the product including brief description of the AI, its mode of action and indications

- NABOTA (Botulinum toxin, Type A) Drug substance (NABOTA DS) is a covalently bonded dimer of two complexes consisting of neurotoxin, NTNH (non-toxic, non-haemagglutinin) protein, and HA (haemagglutinin) proteins (HA50, HA33, HA20, and HA17)
- NABOTA DP vacuum dried powder is composed of 100 units of Botulinum Toxin, Type A (active ingredient), 0.5 mg of human serum albumin (stabilizing agent), and 0.9 mg of sodium chloride (isotonic agent). NABOTA DP is reconstituted with commercially available, preservative free, 0.9% sodium chloride compliant with the United States Pharmacopeia (USP) and/or European Pharmacopoeia (Ph. Eur.) to form a clear, transparent solution as per the directions for use.
- NABOTA DP is reconstituted with 2.5 mL of sterile sodium chloride injection 0.9 % w/v (non-preserved saline solution) to give a final concentration of 4 U/0.1 mL per injection (consistent with the proposed indication). The 0.9% sterile saline is not provided with the product.
- The time for reconstitution of the vacuum dried NABOTA DP is within 60 seconds. In-use stability studies conclude that the product is stable after reconstitution with 0.9% sterile, non-preserved (w/v) saline (normal saline) solution for 72 hours at 2°C to 8°C.
- Therapeutic 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 aged between 20 to 65.

2. Quality aspects:

2.1 Introduction

As mentioned in the aforementioned section

2.2 Drug Substance (Active ingredient)

- **General information**

Botulinum toxin, Type A, is a neurotoxin produced by Clostridium botulinum, and is known to play a role in relaxing muscles by blocking the release of the neurotransmitter called acetylcholine.

The toxin is a two-chain polypeptide, a heavy chain joined by a bond to a light chain. The light chain is a protease enzyme that attacks fusion proteins at a neuromuscular junction, preventing the vesicles containing acetylcholine from anchoring to the pre-synaptic membrane, hence inhibiting their release. The toxin therefore interferes with nerve impulses by inhibiting the release of acetylcholine into the neuromuscular junction, causing a flaccid paralysis of muscles.

- **Manufacture, process controls and characterization:**

- **Manufacturer:**
  Daewoong pharmaceuticals Co.Ltd., Hyangnam factory,35-14, Jeyakgondan 4-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do-Republic of Korea.

- **Description of Manufacturing Process and Process Controls:**

  The manufacturing process for the production of NABOTA (Botulinum Toxin, Type A) Drug Substance (NABOTA DS) is carried out in eleven steps, including two purification steps. Cells from a single thaw of an aliquot of the Working Cell Bank (WCB) are used for the seed expansion. This involves two seed culture steps and a main culture step in a 10 L anaerobic fermenter. After this cultivation, acid precipitation is used to concentrate and harvest the toxin complex from the main culture fluid using sulfuric acid. The toxin complex is then solubilized from the precipitated toxin complex in sodium phosphate buffer. Then enzymes are added and after centrifugation, supernatant is collected and pellet is removed. And collected supernatant is precipitated with hydrochloric acid then clarified by centrifugation. After this harvest step, the toxin complex is purified and the nucleic acids are removed by anion exchange chromatography at pH 6.5. The toxin complex is then precipitated in ammonium sulfate and the neurotoxin product is separated from impurities by anion exchange chromatography and subsequently is filtered with a 0.22 µm filter in order to remove the microbes prior to filling and storage at ≤ - 70°C.

- **Control of Materials:**
  - An overview of the raw materials of biological origin used in the manufacture of NABOTA substance along with the testing and acceptance criteria is well described in the file.
  - All submitted COAs of raw materials used in fermentation and downstream Processing are complying with the acceptance criteria.

- **Controls of Critical Steps and Intermediates:**

  - Overview of In-Process Controls during Each Manufacturing Stage are full described in MA file.
  - Overall, the proposed controls appear adequate to ensure consistent quality of the DS.

- **Process Validation**

  - Validation process is made on three batches through in specific stages.

  - The details pertaining to process performance qualification or PV study of the 3 batches at commercial scale are provided.

All results for the 3 batches were found to comply with the pre-set specifications and acceptance criteria.

➢ **Manufacturing Process Development**

The manufacturing process for the NABOTA DS was developed by Daewoong Pharmaceutical Co., Ltd. It consists of 11 steps, including 2 purification steps. The current process for manufacturing the NABOTA DS begins with cells from a single thaw of an aliquot of the WCB being used for the seed expansion. This involves 2 seed culture steps and a main culture step in a 10 L anaerobic fermenter. After this cultivation, acid precipitation is used to harvest and concentrate the toxin complex from the main culture fluid using sulfuric acid. The toxin complex is then solubilized from the precipitated toxin complex in sodium phosphate buffer and precipitated with hydrochloric acid then clarified by centrifugation. After this harvest step, the toxin complex is purified and the nucleic acids are removed by anion exchange chromatography at pH 6.5.

- **Characterization**

Botulinum Toxin, Type A is composed of dimer structures consisting of neurotoxin, NTNH (non-toxic, non-haemagglutinin) protein covalently bonded with HA (haemagglutinin) proteins (HA50, HA33, HA20, and HA17). The molecular weight of the dimer structure is observed to be approximate 900 kDa.

➢ **Specification**

- The parameters for controlling the quality of DWP-450 DS are derived by taking into consideration the European Pharmacopoeia (Ph. Eur.) for Botulinum toxin type A for injection.
- Method verification was performed for (the bacterial endotoxins, the electrophoresis, the nucleic acid, the protein concentration, the SEC-HPLC, the specific activity, Total viable count test and the western blot

- All acceptance limits for the analytical methods indicated in the Ph. Eur. Monograph and MA file.
- SOPs were provided with the MA file.

➢ **Batch analysis**

- Nine batches are provided in the MA file and all batches met the acceptance criteria.

- The results were within the predefined specifications in place at the time of testing and confirm consistency of manufacturing process.

➢ **Reference Standards or Materials**

- An internationally certified standard is not registered at the NIBSC (National Institute for Biological Standard and Control) or elsewhere, so in house reference standard was developed and qualified by Daewoong Pharmaceutical Co., Ltd.

➢ **Container closure system**

- DWP-450 (Botulinum toxin, Type A) Drug substance (DWP-450 DS) is stored in a ready-to-use, sterile, 1.8 mL external thread, round, translucent, polypropylene tube with a translucent, high-density polyethylene (HDPE) screw cap. The materials of the DWP-450 DS container closure system meet the requirements of United States Pharmacopeia (USP). The DWP-450 DS is stored in this container closure system at ≤ -70°C**.**

- Screening leachable report and a toxicological risk assessment for leachable are provided in MA file.

➢ **Stability of drug substance**

Approved Shelf Life: 3 years

Approved Storage Conditions: Deep freeze≤ -70°C.

2.2.3 Drug product:

➢ **Description and Composition of the Drug Product:**

Description of the dosage form:

Botulinum toxin, Type A Drug product (NABOTA) is a sterile, white to yellowish, preservative free, vacuum dried powder. Upon reconstitution of NABOTA DP with 2.5 mL of 0.9% sterile saline, it yields a clear and transparent solution with a final concentration of 4 U/0.1 mL per injection. The 0.9% sterile saline is not provided with the product. Each vial of NABOTA DP contains 100 units of vacuum dried *Clostridium botulinum* Toxin, Type A as the active ingredient, 0.5 mg of human serum albumin, and 0.9 mg of sodium chloride.

➢ **Pharmaceutical Development**

Formulation Development

The NABOTA (Botulinum toxin, Type A) Drug substance (NABOTA DS), is produced from stocks of the working cell bank via fermentation and tested to confirm that it meets specifications as defined in the European Pharmacopoeia (Ph. Eur.). The purified neurotoxin is stored frozen at -70˚C until used to formulate the NABOTA DP.

- The NABOTA DP is a formulation of the toxin, 0.5% human serum albumin (HSA) and 0.9% sodium chloride (NaCl). The NABOTA DP is sterile filtered into individual glass vials at 100 U

(Units)/vial; vacuum dried, and stored refrigerated (2˚C to 8˚C). The NABOTA DP Type A has similar formulation, to that have been approved for marketing (BOTOX®, Dysport®, and Xeomin®).

Manufacturing Process Development

- Daewoong Pharmaceutical Co., Ltd. built a new finished NABOTA DP manufacturing facility that was completed in 2016 and is the current commercial manufacturing site. The current NABOTA DP manufacturing facility (Building C) is located adjacent to the original NABOTA DP (Building A) manufacturing facility and has the capacity to manufacture 34,500 vials per batch for the purpose of global commercial distribution.
- In addition, qualities by design (QbD) studies have been performed by the NABOTA DP manufacturer (Daewoong Pharmaceuticals Co., Ltd.), in the current manufacturing facility ('Building C') at the proposed commercial batch size of 34,500 vials. - Details of quality by design studies have been discussed in the MA file.

Compatibility

- NABOTA (Botulinum toxin, Type A) Drug product (NABOTA DP) is provided as a sterile, vacuum dried product that is reconstituted with sterile sodium chloride injection 0.9% (saline solution) prior to administration. The container closure vial and stoppers are heat sterilized in house prior to be being filled with NABOTA DP.
- The container closure system is composed of components that are standard for parenteral use. The container closure system 10 mL TopLyo® vial with chlorobutyl rubber stopper is used from clinical development, process validation, aseptic process simulations, and long-term and accelerated stability studies. This container closure is suitable for its intended use as the primary packaging for NABOTA DP.
- Leachable study, Container Closure Integrity Studies, Dye Leak Test, Microbial Challenge Test and Aseptic Simulations: full described in MA file.

- **Manufacture of the drug product:**

- **Description of manufacturing process and process controls along with manufacturers and responsibilities.**

Manufacturer:

- Manufacturer release of drug product, primary and secondary packaging is Daewoong pharmaceuticals Co.Ltd., Hyangnam factory,35-14, Jeyakgondan 4-gil, Hyangnam-eup,Hwaseong-si,Gyeonggi-do-Republic of Korea.

- **Control of critical steps and intermediates**

- Details on identified critical steps and process controls during manufacturing process of product (DP) are provided in MA file.
- The manufacturing process for NABOTA DP does not give rise to pharmaceutical intermediates

- **Process validation and / or evaluation**

- A Process validation data protocol is provided in the file including evaluation of results of product analysis for three commercial batches.
- The results of all production steps are valid.

- **Product specification:**

- The specifications for the finished product comprise tests for appearance, identity, potency, general tests and microbial safety tests
- Detailed SOPs, validation protocols & reports are provided for the in-house methods
- Justification of the drug product specifications at the release and during stability studies are provided.
- All the excipients used in the manufacture of DWP-450 (Botulinum toxin, Type A) Drug product (DWP-450 DP) is compendial excipients.
- Human Serum Albumin, which is used as stabilizing agent, is a material of human origin. This material is controlled by a supplier in compliance with United States Food and Drug Administration regulations and the European Union Legislation related to the quality and safety of human plasma.

➢ **Reference Standards or Materials**

- There is no international official reference standard available at (NIBSC) for Botulinum toxin, Type A that can be used to establish a reference standard. Thus, a specific lot of NABOTA DP was qualified as a reference standard to be used in the testing and release of NABOTA DP.

Container closure system

- The primary container closure for NABOTA (Botulinum toxin, Type A) drug product (NABOTA DP) consists of a 10 mL, Type 1 borosilicate glass vial and closed with chlorobutyl stopper with fluoro-polymer laminate complying with the United States Pharmacopeia (USP).
- The rubber stopper is sealed to the vial with a polypropylene cap and aluminum flip-off crimp closure with the United States Pharmacopeia (USP) and/or European Pharmacopoeia (Ph. Eur.)
- Secondary packaging: The assembled capped, stoppered, and labelled vial is inserted into a secondary carton made of heavy paper stock with the Package Insert.

➢ **Stability of the drug product**

Based on available stability data

- **Approved Shelf Life:** 3 Years.
- **Approved Storage Conditions:**

Before reconstitution: Should be stored in a refrigerator (2-8°C)

After reconstitution: Reconstituted product may be stored in a refrigerator (2-8‘C) for up to 24 hours

3. Non–clinical aspect

- Botulinum toxin is a potent neurotoxin that is produced from spore-forming anaerobic bacteria called *Clostridium botulinum* and is known to inhibit the release of acetylcholine, needed to transfer electrical impulses from the nerves to the muscles in order for the muscles to contract, therefore, it acts as muscle relaxant. Of the seven known immunologically distinct serotypes of botulinum toxin (A to G), only types A and B have been developed for routine commercial use.

- **Pharmacology:**

No safety pharmacology studies have been conducted with DWP-450 DP; this is acceptable and in accordance with ICH S6 (R1) guideline. Effects to the core organ systems are expected to be the same as seen with Botox. This includes a concern to the effect that some types of Botulinum Toxin Type A undergo retrograde axonal transport and may affect the Central Nervous System (CNS). Breathing difficulties and respiratory impairment, which can be life threatening, have been reported for Botulinum toxin, Type A.

- **Toxicology (including TKs):**

In none of the single and repeated dose studies, severe systemic effects or apparent organ toxicity have been detected but all observed effects were either directly related to the pharmacological action of the neurotoxin (impaired in limb function, decreased gastrocnemius weights with muscle fibre atrophy and the testicular and epididymal findings) or effects on body weight and food intake
- The toxicity profile of NABOTA and BOTOX was similar Judged by mortality, body weight and food consumption decreases, and histopathological findings, but the toxicity of DWP-450 appeared to less severe than BOTOX.
- In pregnant rats, daily IM injections up to 4 Units/kg during the period of organogenesis did not induce significant test article-related toxicological effects on the dams and on embryo-fetal development.

Overall conclusion: *the application* ***is approvable from a non-clinical point of view.***

4.Clinical aspect:

Clinical Pharmacology conclusion:

- A 100U vial of NABOTA® DP contains estimated 3 to 4 nanograms of drug substance; a single treatment of glabellar lines uses 20U/dose.
- The pharmacokinetic studies cannot be conducted with this molecule and the regulatory agencies have generally exempted this class of product from having to conduct such studies.
- No pharmacodynamics studies were conducted *in vitro* or clinically such as receptor binding or attempts to correlate pharmacodynamic effects to dose or plasma concentrations, based on the understanding that there are no sensitive analytical methods to support this.

Clinical Efficacy conclusion:

- For a Phase I/III Study on Moderate to Severe Glabellar Lines of Daewoong Nabota: in the PPS, the primary endpoint, were 93.89% (95% CI: 89.79, 97.99) for the NABOTA® group and 88.64% (95% CI: 83.22, 94.05) for the BOTOX® group, it was demonstrated that the NABOTA® group was not inferior to the BOTOX® group.
- In the FAS and PPS, there were no statistically significant differences between the groups in the secondary endpoints.
- For a Phase III Study on Treatment for Post Stroke Upper Limb Spasticity of Daewoong Nabota: In the PPS, the changes in MAS score of wrist flexor muscle tension based on the investigator's assessment at Week 4.
- Also, since the upper limit of the one-sided 97.5% CI the two groups, And There was non-inferiority of the two groups.

In the FAS and PPS, there were no statistically significant differences between the groups in the secondary.

Clinical Safety conclusion:

A Phase I/III Study on Moderate to Severe Glabellar Lines:

- In the phase I study on glabellar lines, the incidences of AEs were 10.0% the two groups.

The incidence of AEs did not show any statistical significance between the two group (p=1.0000).

- In Step 2 (phase III), the incidences of AEs were 20.00% in the NABOTA® group and 18.05% in the BOTOX® group, therefore there was no statistical significance between the two groups (p=0.6835).
- Most of the AEs were mild in severity.

A Phase III Study on Treatment for Post-Stroke Upper Limb Spasticity:

- In the phase III study on post-stroke upper limb spasticity in Korea, the incidence of AEs in the NABOTA® group was 19.59% and the AEs with a high incidence by PT were pain in extremity, upper respiratory tract infection and gastritis each occurring in (2.06%, 1 event).
- The incidence of AEs did not show any statistical significance between the two groups.

For EU/US clinical studies:

- Adverse events were assessed as both of **special interest and as study drug related** were **eyebrow ptosis**, **eyelid ptosis**, **blurred vision**, **dysphagia**, **speech disorder**, **blepharospasm**, **presbyopia, muscle twitching** and **diplopia**. All were **mild or moderate in severity**; none was assessed as serious.
- Adverse Events Identified as **Possible Hypersensitivity Reactions.**
- Two subjects had events that were considered to be clinically important; one subject had a new onset of complete **right bundle branch block** at the EOS visit and one subject had **atrial bigeminy** at the IT D30 visit that was resolved at the EOS visit.
- By system organ class, the most common class of serious adverse events across all treatment groups was **neoplasms**, reported by 0.7% of All DWP-450 subjects, 0.5% of pooled Placebo subjects, and 0.4% of BOTOX subjects. None of the serious adverse events were assessed as related to study drug.
- The incidence of hypersensitivity **reactions was 4%** and four adverse events that led to **study discontinuation** in 4 DWP-450 subjects.
- **Clinical Immunogenicity conclusion:**
- The immunogenicity assessment is regarded as not fit for purpose since the assays are insensitive, poorly validated, generate results for NAbs which are substantially lower than reported in the literature, and provide no realistic estimation of ADA rates for DWP-450 alone or in comparison with Botox.

5. Benefit/ Risk discussion:

- In conclusion, the overall benefit/risk of Nabota is favorable in the treatment of Glabellar lines indication and Focal upper limb spasticity.

6. General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.