NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

TECHNICAL EVALUATION SUMMARY

PRODUCT NAME:
Botulax Powder for Solution for Injection 100 units (Clostridium Botulinum Toxin Type A) (MAL24126017AZ)

ACTIVE INGREDIENT:
Clostridium Botulinum Toxin Type A 100 units

PRODUCT REGISTRATION HOLDER:
Venusys Medical Sdn Bhd

PRODUCT MANUFACTURER:
Hugel Inc., 23 Geodudanji 1-gil, Dongnae-myeon, Chuncheon-si, Gangwon-do, Korea

APPROVAL DATE:
2 December 2024 (DCA 403)

1.0 BACKGROUND INFORMATION

- Botulax contains Clostridium botulinum toxin type A. Botulinum toxin type A is a toxin produced by Clostridium botulinum and is known to cause muscle relaxation by blocking the transmission of acetylcholine.

1.1 Approved Indication

1. Benign essential blepharospasm in adult patients aged between 18 and 75
2. Temporary improvement of glabellar lines ranging from moderate to severe associated with corrugators muscle and/or procerus muscle activities in adults aged between 18 and 65
3. Muscle spasticity: Post stroke upper limb spasticity for adult patients aged 20 or above.
4. Treatment for pediatric cerebral palsy patients with dynamic equinus foot deformity by spasticity aged between 2 and 10.
5. Temporary improvement of lateral canthal lines (crow's feet lines) ranging from moderate to severe associated with orbicularis oculi muscles activity in adults aged between 19 and 65.

1.2 Approved Posology

1. Blepharospasm

For blepharospasm, reconstituted Botulax (see Dilution Table) is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25-2.5 units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient (usually defined as an effect that does not last longer than two months). However, there appears to be little benefit obtainable from injecting more than 5.0 units per site. Some tolerance may be found when this product is used in treating blepharospasm if treatments are given more frequently than every three months, and is rare to have the effect be permanent. The cumulative dose of Botulax treatment in a 30-day period should not exceed 200 units.

2. Glabellar lines

Reconstitute this product with 0.9 % preservative-free, sterile saline to make 100 units/2.5 mL (4 units/0.1 mL). Using a 30-gauge needle, inject a dose of 0.1 mL into each of 5 sites, 2 in each corrugators muscle and 1 in procerus muscle, for a total of 20 units.



In order to reduce the complication of ptosis, avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes. 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. In order to prevent exudation below the orbital ridge, be sure to firmly place the thumb or index finger below the orbital ridge, prior to injection. The needle should be toward the upper center during 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 supercilia 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.

3. Muscle spasticity
Accurate dosage and number of injecting site may vary depending on the size, number, and location of relevant muscles, degree of stiffness, weakening of local muscle, and response of patient from previous treatment. Muscle stress showed clinical improvement between 3-5 weeks after injection. The amount administered in the clinical trial is shown below.

Injection site	Dosage	No. of sites
Flexed wrist		
Flexor carpi radialis	15 - 60 U	1-2 sites
Flexor carpi ulnaris	10 - 50 U	1-2 sites
Clenched fist		
Flexor digitorum superficialis	15 - 50 U	1-2 sites

Flexor digitorum profundus	15 - 50 U	1-2 sites
Flexed elbow		
Biceps	100 - 200 U	Up to 4 sites

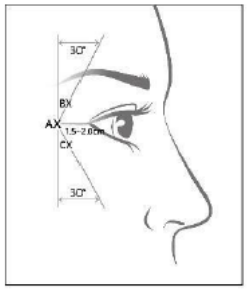
In the clinical trial, the administered amount did not exceed maximum dose 360 units, and it was injected in each muscle. A 24-30 gauge sterile syringe and a proper length needle were used for dosing, depending on the depth of the muscular tissues. The location of muscle as an injection site were selected by using electric stimulation, needle electromyography or ultrasound.

4. Dynamic equinus foot deformity by spasticity of pediatric cerebral palsy
Administer the medial and lateral heads of the rigid gastrocnemius muscle. In the case of bilateral palsy, inject to both legs at a dose of 6 units/kg body weight (3 units/kg for each leg). In the case of unilateral palsy, inject to the rigid leg at a dose of 4 units/kg body weight.

The maximum dose/injection cannot exceed 200 units and after administration, the subject's status is observed for 30 minutes to detect the occurrence of acute adverse events.

5. Lateral Canthal Lines (crow's feet lines)
Lateral canthal lines arise from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. The strong contraction of orbicularis oculi causes lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients

Inject 0.1 ml (4U) into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscles.



As shown in the figure, the first injection site should be at least 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim (marked as AX). The next injection site (marked as BX and CX) is 1.0-1.5 cm above and below from the first injection site at an approximately 30° angle medially. The safety and efficacy of improvement of lateral canthal lines (crow's feet lines) were evaluated for 16 weeks with single dose.

6. Dilution method

Prior to injection, reconstitute this 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

Diluent added (0.9% Sodium Chloride Injection)	Resulting dose (U/0.1mL)
1.0mL	10.0U
2.0mL	5.0U
4.0mL	2.5U
8.0mL	1.25U

Note: These dilutions are calculated for an injection volume of 0.1mL. A decrease or increase in 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 Method of administration

Intramuscular (IM)

1.4 Pharmacological Aspects

Pharmacodynamic Properties:

Mechanism of action

Clostridium botulinum neurotoxin type A blocks the peripheral release of the neurotransmitter acetylcholine at presynaptic cholinergic nerve terminals of neuromuscular junctions by cleaving SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within the nerve endings, thereby leading to denervation of the muscle and a flaccid paralysis.

After injection, there is an initial rapid high-affinity binding of toxin to specific cell surface receptors. This is followed by transfer of the toxin across the plasma membrane by receptor-mediated endocytosis. Finally, the toxin is released into the cytosol with progressive inhibition of acetylcholine release. Clinical signs manifest within 2-3 days, with peak effect seen within 4 weeks of injection. Recovery occurs usually within 3-4 months after injection when nerve terminals sprout again and reconnect with the endplate.

Pharmacokinetic Properties:

Due to the very small amount of product that is administered, pharmacokinetic studies are very difficult to perform and, due to the well-characterised nature of the product, are not expected to be informative. Therefore, pharmacokinetic studies have not been conducted for Botulax.

Pharmacokinetic studies have been performed using other botulinum toxins: distribution studies in rats indicate slow muscular diffusion of 125I-botulinum neurotoxin A complex in the gastrocnemius muscle after injection, followed by rapid systemic metabolism and urinary excretion. The amount of radiolabeled material in the muscle declined with a half-life of approximately 10 hours.

At the injection site, the radioactivity was bound to large protein molecules, whereas in the plasma it was bound to small molecules, suggesting rapid systemic metabolism of the substrate. Within 24 hours of dosing, 60 % of the radioactivity was excreted in the urine. The toxin is probably metabolised by proteases and the molecular components recycled through normal metabolic pathways. Classical absorption, distribution, biotransformation and elimination (ADME) studies on the active substance have not been performed due to the nature of this product.

It is believed that at therapeutic doses, low systemic distribution of botulinum toxin occurs in patients. Clinical studies using single fibre electromyographic techniques have shown increased electrophysiologic neuromuscular activity in muscles distant to the injection site, with no associated clinical signs or symptoms.

2.0 SUMMARY REPORT

2.1 Quality

2.1.1 Drug Substance

- The active substance of botulinum toxin is produced from Botulinum toxin, Type A bacteria CBFC26 strain. The chemical structure is approximately 900kDA.

- The manufacturing process uses Human Serum Albumin (HSA) 20% as a stabilizer. The HSA used in the formulation is registered in Malaysia.
- Process validation (3 consecutive batches) demonstrated that the processes were able to consistently produce drug substance that maintain process parameters and quality attributes within the defined limits as per the pre-defined criteria.
- Stability data submitted support the storage condition of -70°C for 24 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 Drug Product

- Process validation (3 consecutive batches) have been conducted and confirmed that the manufacturing process can consistently produce drug product according to pre-defined specifications.
- The proposed shelf life of 36 months stored at 2-8°C is supported by 3 commercial scale batches' stability study. An in-use stability study following reconstitution with normal saline was conducted on three batches and the results support the proposed in-use stability of 24 hours at 2-8°C.
- GMP Compliance of the same drug substance and drug product manufacturer was verified by Ministry of Food and Drug Safety, Republic of South Korea.
- Botulax is a white lyophilized powder presented in a Type I borosilicate glass vial closed with a grey chlorobutyl rubber stopper and sealed with a white polypropylene flip-off cap with aluminum over seal. The product should be a colorless and transparent liquid after reconstitution with saline solution. Vials are filled to 100U per vial. The units are specific to Botulax and are not interchangeable with other botulinum toxin preparations.
- The product has passed the evaluation on analytical protocol and method validation in accordance with the ICH Q2 guidelines.

2.2 Non-Clinical

- Single dose and repeat dose toxicity studies were conducted in Sprague dawley rats and beagle dogs. Embryo-fetal development study was performed in Sprague-Dawley Rats. Toxicity studies were conducted in compliance with OECD GLP.
- The muscle paralysis effect of Botulax was not significantly different from Botox in the muscle paralysis effectiveness study.
- In the single dose toxicity study, LD50 was 129.5 units/kg for both male and female rats and at least 200 units/kg for dogs. In the repeat dose toxicity study, NOAEL was estimated to be not less than 30 units/kg in the beagle dog and 1.5 units/kg in the rats.
- In the developmental study, all pregnant rats administered with Botulax showed the inhibited weight increase, muscle paralysis, and perineal contamination. However, it is not considered that such findings might be resulted from the inherent toxicity of Botulax, because such findings have been observed in other drug products containing the

Clostridium botulinum toxin type A. Fetuses showed the decreased number of metatarsi (delayed ossification) and the decreased weight of fetuses. However, as it does not lead to any alterations in fetal death rate, these consequences are considered as secondary effects rather than direct effects. These findings were not different from the previous reports.

- Results from these studies confirmed that Botulax has the same effectiveness and safety levels as those shown by the previously approved products.

2.3 Clinical Efficacy

- The pivotal clinical studies to support the proposed indications were non-inferiority studies comparing Botulax versus Botox.

Table 1: Summary of Clinical Studies Conducted

<table>
<tr><th>Study Type & Design (N)</th><th>Objective (s) of the Study</th><th>Results</th></tr>
<tr><td colspan="3">Blepharospasm</td></tr>
<tr><td>HG-06-01
Phase III, double-blinded, randomized, active control comparative, parallel-designed study

N = 174 subjects (92 BOTULAX and 82 Botox)</td><td>To evaluate the safety and efficacy of BOTULAX in comparison to Botox for the treatment of blepharospasm in adults 18-75 years old</td><td>Primary endpoint: Efficacy rate at 4 weeks after drug administration
(when symptoms improved by more than 1 Grade, evaluated using Scott’s scale)

Pre-specific non-inferiority margin of the difference: lower limit of 95% one sided confidence interval is equivalent to or higher than -10%.

Result:
<table>
<tr><th></th><th>Efficacy rate, n (%)</th><th>95% CI</th></tr>
<tr><td>Botulax</td><td>91/92 (98.91%)</td><td>(97.13, 100.00)</td></tr>
<tr><td>Botox</td><td>82/82 (100.00%)</td><td>(100.00, 100.00)</td></tr>
<tr><td>Difference</td><td>-1.09</td><td>(-2.87, -0.01)</td></tr>
</table>
Conclusion:
The efficacy of Botulax in treatment of essential blepharospasm was not inferior to that of the comparator, Botox.</td></tr>
<tr><td>HG Ext 08-01
Phase III, double-blinded, randomized, active control comparative, multicenter study

N = 131 subjects (63 BOTULAX and 68 Botox)</td><td>To evaluate the duration of the effect of Botulax after the second dose in patients with essential blepharospasm</td><td>Primary endpoint: Duration of effect (days)
(the number of days elapsed between the 2nd dose of the study drug (the test drug or comparator) and the administration of Botox Inj. or other comparable surgical intervention due to recurrence of blepharospasm symptoms)

Result:
<table>
<tr><th></th><th>Mean ± standard error (days)</th><th>p-value</th></tr>
<tr><td>Botulax (n = 63)</td><td>136.94 ± 4.52</td><td rowspan="2">0.6855</td></tr>
<tr><td>Botox (n = 68)</td><td>142.75 ± 4.70</td></tr>
</table>
Conclusion:
There was no statistically significant difference between the test drug and the active comparator, with regard to the duration of the effect after the 2nd dose in patients with essential blepharospasm.</td></tr>
<tr><td colspan="3">Glabellar lines</td></tr>
</table>

<table>
<tr><th>Study Type & Design (N)</th><th>Objective (s) of the Study</th><th>Results</th></tr>
<tr><td>HG-11-01
Phase III, double-blinded, randomized, active control comparative, multicenter study

N = 249 subjects (122 BOTULAX and 127 Botox)</td><td>To evaluate safety and efficacy for improvement of glabellar lines of Botulax inj. compared with Botox inj. in patients 18-65 years old with moderate to severe glabellar lines</td><td>Primary endpoint: Responder rate at Week 4 by physician’s rating line severity at maximum frown
(Proportion of subjects attaining grade 0 or 1 by physician’s rating line severity)

Pre-specific non-inferiority margin of the difference: lower end of the two sided 95% confidence interval greater than -14.57

Result:
<table>
<tr><th></th><th>Responder rate, n (%)</th><th>95% CI</th></tr>
<tr><td>Botulax</td><td>109/122 (89.34%)</td><td>(83.87, 94.82)</td></tr>
<tr><td>Botox</td><td>104/127 (81.89%)</td><td>(75.19, 88.59)</td></tr>
<tr><td>Difference</td><td>7.45</td><td>(-1.24, 16.15)</td></tr>
</table>
Conclusion:
Botulax inj. was not inferior to Botox inj. to improve moderate to severe glabellar lines.</td></tr>
<tr><td colspan="3">Post stroke upper limb spasticity</td></tr>
<tr><td>HG-13-01
Phase III, double-blinded, randomized, active control comparative, multicenter study

N = 186 subjects (94 BOTULAX and 92 Botox)</td><td>To compare the efficacy and safety of BOTULAX versus BOTOX in treatment of adults ≥ 20 years old with post stroke upper limb spasticity</td><td>Primary endpoint: Change from baseline at Week 4 for wrist flexor muscle tone as measured on the Modified Ashworth Scale (MAS)

Pre-specific non-inferiority margin of the difference: upper limit of the two sided 95% confidence interval was ≤ 0.5

Result:
<table>
<tr><td>Wrist flexor muscle tone</td><td>Botulax (n = 94)
Mean ± SD</td><td>Botox (n = 92)
Mean ± SD</td><td>Difference (95% CI)</td></tr>
<tr><td>Baseline</td><td>2.30 ± 0.48</td><td>2.38 ± 0.49</td><td rowspan="3">- 0.06 (-0.23, 0.12)</td></tr>
<tr><td>Week 4</td><td>0.85 ± 0.55</td><td>0.98 ± 0.54</td></tr>
<tr><td>Change</td><td>- 1.45 ± 0.61</td><td>- 1.40 ± 0.57</td></tr>
</table>
Conclusion:
BOTULAX is non-inferior to the comparator, BOTOX in the treatment of post stroke upper limb spasticity.</td></tr>
<tr><td colspan="3">Dynamic Equinus Foot Deformity in Children with Cerebral Palsy</td></tr>
<tr><td>HG-11-02
Phase III, double blinded, randomized, active control comparative, multicenter

N = 143 subjects (73 BOTULAX and 70 Botox)</td><td>To evaluate the safety and efficacy of Botulax versus Botox for improving equinus deformity in children with cerebral palsy aged 2-10 years.</td><td>Primary endpoint: Responder rate at 12 weeks after administration of the investigational product.
(Rate of subjects whose Physician’s Rating Scale (PRS) score increase at ≥ 2 points compared to that at baseline)

Pre-specific non-inferiority margin of the difference: Lower limit of two sided 95% confidence interval was greater than -24.0</td></tr>
</table>

<table>
<tr><th>Study Type & Design (N)</th><th>Objective (s) of the Study</th><th>Results</th></tr>
<tr><td></td><td></td><td>Result:
<table>
<tr><th></th><th>Responder rate, n (%)</th><th>95% CI</th></tr>
<tr><td>Botulax</td><td>44/73
(60.27%)</td><td>(49.05, 71.5)</td></tr>
<tr><td>Botox</td><td>43/70
(61.43%)</td><td>(50.03, 72.83)</td></tr>
<tr><td>Difference</td><td>-1.15</td><td>(-17.16, 14.85)</td></tr>
</table>
Conclusion:
BOTULAX was non inferior to BOTOX in the treatment of equinus deformity in children with cerebral palsy.</td></tr>
<tr><td colspan="3">Moderate to Severe Crow’s Feet Lines</td></tr>
<tr><td>HG-BOTCFL-III1
Phase I/III, double blinded, randomize, active control, comparative, multicenter

N = 240 subjects (119 BOTULAX and 121 Botox)</td><td>To evaluate the safety and efficacy of Botulax versus Botox in subjects with moderate to severe Crow’s feet lines aged 19-65 years</td><td>Primary endpoint: Improvement rate of crow’s feet lines when smiling as widely as possible, according to the investigator’s evaluation after 4 weeks

Pre-specific non-inferiority margin of the difference: Lower limit of the 95% confidence interval was greater than -18.0

Result:
<table>
<tr><th></th><th>Improvement rate, n (%)</th><th>95% CI</th></tr>
<tr><td>Botulax</td><td>83/119
(69.75%)</td><td>(61.49, 78.00)</td></tr>
<tr><td>Botox</td><td>82/120
(68.33%)</td><td>(60.01, 76.66)</td></tr>
<tr><td>Difference</td><td>1.41</td><td>(-10.31, 13.14)</td></tr>
</table>
Conclusion:
BOTULAX was non inferior to BOTOX in treatment of moderate to severe Crow’s feet line</td></tr>
</table>

- Four out of five non-interventional post-marketing surveillance (PMS) studies conducted has been completed (HG-10-01, HG-13-02, HGPV-16-01, HGPV-16-02). The fifth PMS (HG-BOTCFL-PMS-01) for Crow’s feet lines has recently completed and report is expected to be available by end of Dec 2024. PMS and re-examination studies on Botulax Inj. did not show any noteworthy findings in terms of its safety and efficacy.

2.4 Clinical Safety

- Across pediatric and adult studies, adverse events occurring from Botulax treatment were consistent with the known adverse events for Botulinum Toxin Type A and were comparable with the Botox group.
- Out of all the subjects tested in both the Botulax and Botox group, none was positive for anti-drug antibodies.

3.0 CONCLUSION

Drug Control Authority (DCA) on the 403th meeting on 2nd December 2024 has decided to approve the registration of this product with the following indication:

1. Benign essential blepharospasm in adult patients aged between 18 and 75
2. Temporary improvement of glabellar lines ranging from moderate to severe associated with corrugators muscle and/or procerus muscle activities in adults aged between 18 and 65
3. Muscle spasticity: Post stroke upper limb spasticity for adult patients aged 20 or above.
4. Treatment for pediatric cerebral palsy patients with dynamic equinus foot deformity by spasticity aged between 2 and 10.
5. Temporary improvement of lateral canthal lines (crow's feet lines) ranging from moderate to severe associated with orbicularis oculi muscles activity in adults aged between 19 and 65.