Letybo®: Amount of Neurotoxin Protein

RELEVANT PRESCRIPTION INFORMATION LABEL INFORMATION

The information provided relates to a use for Letybo® that is not approved by the US Food and Drug Administration (FDA).

CLINICAL DATA

A search of the published medical literature was conducted regarding Letybo® and the nanogram (ng) quantification in its indicated 20 Unit dose for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

The relevant citations referenced in this communication are listed below. The hyperlinks to publicly available abstracts are included. Findings were focused on empirical quantifications of protein content and do not report or correlate clinical outcomes.

Letybo® is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. Hugel Inc. and BENEV Inc. do not endorse the use of Letybo® in a manner not consistent with the approved label.

Some references cited in this response may discuss other botulinum toxin products either alone or in conjunction with Letybo®. Units of biological activity of Letybo® cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method.

CITATIONS

1. Letybo® Prescribing Information, 2024.
2. Hong JY, Kim JH, Jin JE, Shin SH, Park KY. Practical Application of Novel Test Methods to Evaluate the Potency of Botulinum Toxin: A Comparison Analysis among Widely Used Products in Korea. *Toxins (Basel)*. 2021;13(12):833. Published 2021 Nov 23. doi:10.3390/toxins13120833 https://pmc.ncbi.nlm.nih.gov/articles/PMC8707463/
3. Frevert J, Ahn KY, Park MY, Sunga O. Comparison of botulinum neurotoxin type A formulations in Asia. *Clin Cosmet Investig Dermatol*. 2018;11:327-331. Published 2018 Jul 5. doi:10.2147/CCID.S160723 https://pmc.ncbi.nlm.nih.gov/articles/PMC6039073/

The objective of the Hong et al. 2021[2] study was to comparatively evaluate widely used botulinumtoxinA (BoNT-A) products using various assay methods. The total BoNT-A protein levels were measured using a colorimetric enzyme-linked immunosorbent assay (ELISA). The total mean amount of BoNT-A protein contained in 100-Unit vials of LetibotulinumtoxinA was (4.64±0.21 ng; N= 13). By this quantification, it follows that 20 U of LetibotulinumtoxinA contains 0.928 ng of BoNT/A protein.

Frevert et al. 2018[3] also reported quantifications of different BoNT-A products using a sensitive ELISA assay. The total mean amount of BoNT-A protein contained in 100-Unit vials of LetibotulinumtoxinA was (844±43 pg; N= 2). By this quantification, it follows that 20 U of LetibotulinumtoxinA contains 169 pg of BoNT/A protein.

Measurement of Total BoNT/A Protein Amounts by Sandwich ELISA[2]

Sandwich ELISA was carried out to determine the total amounts of botulinum toxin proteins, either active or inactive, present in each vial of the indicated products, which is required to calculate the toxin efficacy value corresponding to the same toxin dose across the samples. Sandwich ELISA colorimetric detection methods were used to objectively quantify the total amount of BoNT/A proteins present in each product vial. Considering batch variations, the BoNT/A samples of 5–6 different batches were included in this study.

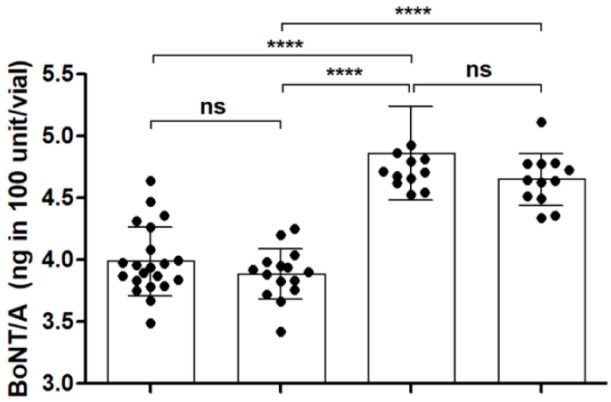

Figure 1 | Graph summarizing the total amounts of BoNT/A protein present in each of the 100 unit vials indicated. Each dot represents one 100 unit vial of the products. n = 21 for Prabotulinumtoxin A, n = 15 for Onabotulinumtoxin A, n = 13 for Neubotulinumtoxin A, and n = 13 for Letibotulinumtoxin A. The bars represent average ± standard deviation (SD).
**** p-value < 0.0001; ns = non-significant.

The overall amount of BoNT/A protein within a 100-unit vial of each product was detected via the sandwich ELISA (Figure 1). The total amount of BoNT/A protein contained in prabotulinumtoxin A (3.98 ± 0.28 ng) was similar to that of onabotulinumtoxinA (3.88 ± 0.20 ng), and the total amount of BoNT/A protein in neubotulinumtoxin A (4.86 ± 0.37 ng) was similar to that of letibotulinumtoxin A (4.64 ± 0.21 ng). The difference in the protein amounts between pra/onabotulinumtoxin A and neu/letibotulinumtoxin A was statistically significant ($p < 0.0001$).

Comparison of Botulinum Neurotoxins Type A Formulations in Asia[3]

Highly sensitive sandwich ELISA was used to quantify the amount of BoNT/A protein in Botulax®, Meditoxin®, Nabota®, Relatox® and Xeomin® (Table 2). Xeomin® was independently analyzed in parallel as a control and found to have a mean toxin content of 416 pg/vial, comparable to reports from another batch. The variation from previously published values is due to intervial variability during the manufacturing process.

Botulax® and Nabota® contained 844 and 754 pg of neurotoxins, respectively, which are nearly twice the neurotoxin content of Xeomin® (416 pg) in an equivalent 100 U vial. Meditoxin and Relatox contained 575 and 578 pg of neurotoxins, respectively.

Tabel 2. Determination of content of botulinum neurotoxin type A protein in products by ELISA[3]

Product name	Batch name	Dosage	Amount of neurotoxin protein per 100 units (pg)
Botulax®	HUA 15133	100 U/vial (Lyo)	844 ± 43‡
Meditoxin®/Neuronox®	FAA 1587	100 U/vial (Lyo)	575 ± 6
Nabota®	084962	100 U/vial (Lyo)	754 ± 11‡
Relatox®	0615	100 U/vial (Lyo)	578 ± 48
Xeomin®	31149	100 U/vial (Lyo)	416 ± 6

Notes: Innotox® (not reported in this table) contains the surfactant polysorbate,25 which can interfere with antibody–antigen binding during ELISA and lead to inaccurate and low concentrations. Innotox's toxin content, therefore, could not be accurately measured using standard ELISA, which is validated for experimental conditions without polysorbate. *Calculation based on claim that Xeomin contains only the active neurotoxin (=100%); ‡Value above standard curve.

LetibotulinumtoxinA (Hugel Inc., Seoul, Korea; also known as Botulax® or Letybo®)
BotulinumtoxinA (Medytox Inc., Seoul, Korea; also known as Meditoxin® or Neuronox®)
PrabotulinumtoxinA (Daewoong Pharmaceutical Co. Ltd., Seoul, Korea; also known as Nabota®)
BotulinumtoxinA (Microgen, Russia; also known as Relatox®)
IncobotulinumtoxinA (Merz Pharmaceuticals GmbH, Reinheim, Germany; also known as Xeomin®)

Abbreviations: ELISA, enzyme-linked immunosorbent assay; Lyo: lyophilized

Approved Indication for Letybo®

Letybo® (letibotulinumtoxinA-wlbg) is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients[1].

Important Safety Information:

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing safety data from other approved botulinum toxins suggest that botulinum toxin effects may be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, blurred vision and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. In unapproved uses and approved indications, symptoms consistent with spread of toxin effects have been reported at doses comparable to or lower than the maximum recommended total dose. LETYBO is not approved for any conditions other than glabellar lines. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory difficulties occur.

Letybo is contraindicated in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the LETYBO formulation and/or have an infection at the injection site.

The potency Units of Letybo® are specific to the preparation and assay method utilized. Letybo® is not equivalent to other preparations of botulinum toxin products, and therefore, Units of biological activity of Letybo® cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

This response contains information that is not included in the approved Product Information label. Hugel Inc. and BENEV Inc. do not endorse the use of its products in a manner not consistent with the approved label. For approved products, please refer to the full Prescribing Information for additional information. The Prescribing Information label for Letybo® is available at: bit.ly/3UbRZtP