Letybo® for Frontalis (Forehead): Evidence-based Treatment and Dosing

Relevant Prescription Information Label Information

The information provided relates to a use for Letybo® (letibotulinumtoxinA-wlbg) 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 treatment of frontalis.

The relevant citations referenced in this communication are listed below. The hyperlinks to publicly available abstracts are included. Findings were limited to consensus statements, which may not be reflective of findings from controlled studies or to outcomes in a broader population, and should be considered when evaluating the data.

Some references cited in this response may discuss additional treatment areas that were not specified in this Medical Information Request.

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.

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. Liu S, Cong L, Pongprutthipan M, et al. Use of LetibotulinumtoxinA for Aesthetic Treatment of Asians: A Consensus. *Aesthet Surg J*. 2023;43(11):NP962-NP974. doi:10.1093/asj/sjad151 https://pmc.ncbi.nlm.nih.gov/articles/PMC10575620/
3. Choi HS, Wang J, Tauber D, et al. Consensus Recommendations for Treatment of the Upper Face With LetibotulinumtoxinA. Plast Aesthet Nurs (Phila). 2024;44(4):239-250. doi:10.1097/PSN.0000000000000585 https://pubmed.ncbi.nlm.nih.gov/39348312/

Review of Research and Clinical Practice Information

Liu et al. 2023[2] is an expert consensus statement that provides clinical guidance on the aesthetic use of Letybo® (letibotulinumtoxinA-wlbg) for treating wrinkles, contour adjustment, and facial lifting in Asian patients. The publication highlights the importance of understanding facial musculature, patient preferences, and botulinum toxin pharmacology to optimize treatment. It underscores that cultural nuances, such as the preference for natural-looking results among Asian patients, inform injection techniques and dosing strategies. The panel recommends starting with conservative dosing, individualizing treatment plans, and adjusting based on patient feedback to achieve high satisfaction. This guidance is especially relevant for applications including frontalis treatment, where anatomical knowledge and precision are critical.

Choi et al. 2024[3] is an expert consensus that provides guidelines for treating facial lines of the upper face with letibotulinumtoxinA. The members of the consensus provided recommendations for injection sites, dosages, and injection techniques using letibotulinumtoxinA and considered relevant anatomy, patient assessment and selection, and individual variations to evaluate clinical strategies for minimizing complications.

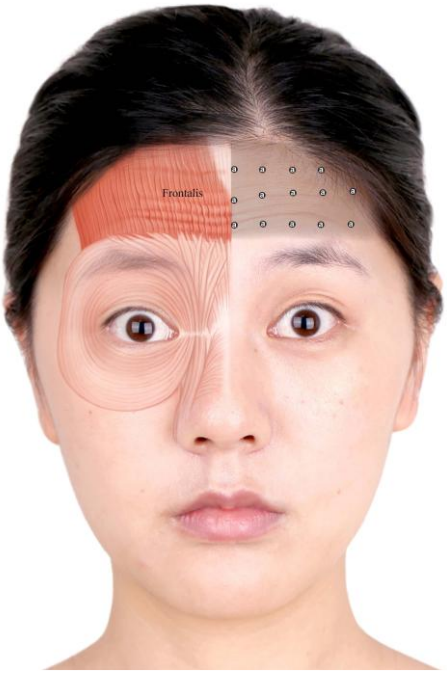
Use of LetibotulinumtoxinA for Aesthetic Frontalis Treatment of Asians: A Consensus[2]

Horizontal Forehead Lines[2]

The frontalis is responsible for forehead wrinkles and brow elevation. To evenly efface the wrinkles while preserving the eyebrow position and some movement of the frontalis, the dose of BTxA should be controlled, and the lower frontalis, a once “forbidden” area because of the risk of brow ptosis, should be carefully addressed. Uneven weakening of the frontalis can potentially result in an exaggeration of previously unidentifiable wrinkles due to overcompensation by the untreated part of the frontalis.

Anatomy[2]

In the view of the upper face, the frontalis muscle is rectangular, originates from the galea aponeurosis, and runs in an inferior direction to insert with the fibers of the orbicularis oculi, procerus, depressor supercilii, and corrugator supercilii near the superciliary arch before finally inserting into the frontal skin above the eyebrow. Transverse forehead lines are formed. The width of the frontalis muscle varies between individuals. In cases in which the lateral border of the frontalis muscle is located lateral to the temporal crest, the elevation of the eyebrow tail may occur due to only medial injection.



Injection Technique[2]: The injection site and depth should be tailored according to the distribution and severity of the horizontal forehead lines. For wrinkles in the lower frontalis
or mild forehead wrinkles, intradermal injection with a lower dose per site facilitates superficial delivery of the toxin, thereby reducing rhytids without brow ptosis.

Figure 1. Anatomy and Injection Points for Frontalis Treatment with Letybo

Table 2: Consensus Recommendations for Anti-wrinkle Treatment With LetibotulinumtoxinA in Asian Patients

Indication	Target Muscle	Injection points (n)	Dose per Injection Point (Units)	Typical total Dose rage (Units)	Perferred Injection Level
Horizontal forehead lines	Frontalis	6-12 (nmd)/ 10-40 (md)	0.5-1 (nmd)/ 0.2-0.25 (md)	4-12 (nmd)/ 2-10 (md)	ID, IM, SC

The dose shown in this table is for females, and the dose for males is 20% to 30% higher than that for females. ID, intradermal; IM, intramuscular; md, microdroplet; nmd, nonmicrodroplet; SC, subcutaneous

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To explore the clinical research and references below, please review the cited publication.

Consensus Recommendations For Treating Horizontal Forehead Lines with LetibotulinumtoxinA[3]: Horizontal forehead lines are an indication for neurotoxin injections and are frequently treated, often in combination with the glabellar region.

Overview and Anatomy[3]: The forehead constitutes the upper third of the face. It is delineated superiorly by the hairline, laterally by the lateral temporal fat pads, and inferiorly by the glabella and frontonasal groove and the eyebrows overlying the supraorbital ridge (Kim et al., s). The frontalis muscle, the dominant musculature of the forehead, is a large, paired, fan-shaped muscle that originates from the galea aponeurotica near the coronal suture. The muscle is associated with the insertion of other facial muscles, such as the procerus muscle, corrugator supercilii muscle, depressor supercilii, and fibers of the orbicularis oculi muscle, at the superciliary arch of the frontal bone. The muscle attaches to the deep layer of the skin on the eyebrow and forehead, with one portion situated on each side of the forehead. The frontalis muscle elevates the eyebrows and conveys emotions of surprise, interest, or concern. Contraction of this muscle causes horizontal wrinkles in the forehead (Abramo et al., 2016). Treating the frontalis muscle is challenging, especially for practitioners with minimal experience. The anatomy of the frontalis muscle varies among individuals, as do the functional aspects related to an individual's habits and facial expressions. Isolated treatment poses challenges because of the risk for eyebrow ptosis and the inability to completely eliminate forehead lines. The potential for providing excessive treatment and the consequent unnatural aesthetic appearance also present a challenge (Carruthers et al., 2003). The goal of treatment in this area is to relax expression lines while minimizing the risk for eyebrow ptosis or complete paralysis of upper facial expressions (Borba et al., 2022). When treating horizontal forehead lines, practitioners must understand the importance of expertise and using precise technique in achieving optimal aesthetic outcomes.

Patient Evaluation[3]: To ensure that only regions with active muscle movement are targeted for injection, the practitioner must assess the degree of medial, central, and lateral brow elevation and the contour of the eyebrow arch. The practitioner should instruct the patient to fully elevate their eyebrows by "making a surprised face" or "looking up at the ceiling without moving the head" and then have the patient relax their forehead and close their eyes. The practitioner should examine the patient's facial asymmetry and any compensated eyebrow ptosis, as a patient may elevate their eyebrow to compensate for the descent of the eyebrow from its normal position. Persistent contractions of the frontalis muscle in the supraorbital region are a sign of this condition. To check the deep ligaments, the practitioner should assess the degree of eyebrow ptosis, both with and without lacing a hand on the patient's forehead (Braccini et al., 2023). The intensity of muscle contraction and the height of the frontalis muscle may differ significantly among individuals. When determining the dose of neurotoxin and injection points, it is important for the practitioner to consider individual variations in muscle function. These variations can be identified through gentle palpation of the forehead while the patient actively raises and lowers their eyebrows (Anido et al., 2017).

Injection Forehead Height[3]: There are various criteria for distinguishing the injection pattern of neurotoxins on the forehead. The consensus panel members recommend using an injection technique based on forehead height. Currently, there is a scarcity of research investigating the quantification of the average height of the forehead. According to Kite & Lucas (2015), when measured from the trichion to the glabella, the average forehead height is 7–8 cm in men and 6–7 cm in women. Choi et al. (2019) found that men had significantly longer foreheads than women (7.22 cm vs. 6.41 cm, $p < .0001$). Individuals with forehead heights ranging from 5.5 to 7.5 cm are categorized as having an average forehead, whereas individuals with forehead heights less than 5.5 cm are categorized as having a short forehead and individuals with forehead heights greater than 7.5 cm are categorized as having a long forehead. The injection technique for this expert panel recommendation is based on women with an average forehead height (5.5–7.5 cm ± 1).

Injection Sites[3]: Figure 1 illustrates the expert panel recommendations for injection sites on the forehead. The panel recommends using a standardized technique for injecting the

forehead. It is important to understand that the forehead is one of the most challenging facial areas for neurotoxin injection and there are factors the practitioner should consider. In a prospective study of 30 adults, Kwon et al. (2023) used three-dimensional skin vector displacement analysis to investigate skin displacement patterns of the forehead and adjacent skin caused by frontalis muscle contraction. The researchers observed three kinds of vectors of forehead skin displacement:

- Vertical (if the average angle of all vectors was = 90 ± 5 degrees from the x-axis [0-degree]),
- Lateral oblique (if the average angle was >95 degrees from the x-axis), or
- Medial oblique (if the average angle was ≤85 degrees from the x-axis).

A total of 19 participants (63.4%) showed forehead skin movement along the vertical direction (mean angle: 90.6 ± 1.19; range: 89.02–94.39), 10 participants (33.3%) showed forehead skin movement along the lateral oblique vector (mean angle: 107.1 ± 6.26; range: 98.86– 119.0), and 1 participant (3.3%) showed forehead skin movement along the medial oblique vector (angle: 76.23). The researchers concluded that to individualize neurotoxin injections, practitioners should consider the vector and symmetry of skin displacement. Patients with vertical or medial oblique vectors should receive central injections. Patients with lateral oblique vectors should receive lateral or medial injections. Moqadam et al. (2017) investigated the shape of forehead lines and their relationship to the morphology of the underlying frontalis muscle using a sample of 31

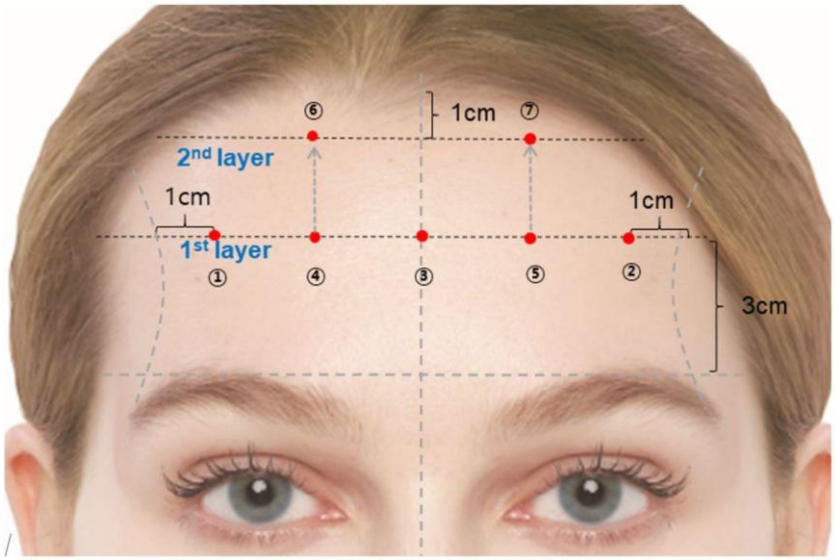

FIGURE 1[3]
Recommended injection points for treating horizontal forehead lines with LetibotulinumtoxinA (letiBoNT-A; Letybo, Hugel, Inc., Chuncheon, South Korea). When injecting the forehead to treat horizontal forehead lines, aesthetic practitioners should envision three hypothetical horizontal lines on the forehead. Position the first line across the tops of both eyebrows. Position the second line 3 cm above the first line. The initial injection points (① and ②) are located on the second line, 1 cm medial to both sides of the temporal crests. The next injection point (③) is located at the intersection of the second line and the facial midline. Injection point ④ is located on the second line midway between points ① and ③. Injection point ⑤ is located on the second line midway between points ② and ③. All five injection points are on the second horizontal line. Position the third horizontal line parallel to the second line and 1 cm below the hairline. Injection point ⑥ is located on the third parallel line directly above point ④. Injection point ⑦ is located on the third parallel line directly above point ⑤. When injecting individuals with a short forehead height (< 5.5 cm), do not use injection points ⑥ and ⑦. When injecting individuals with a long forehead height (>7.5 cm) add two injection points on the third parallel line directly above points ① and ②.

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 patient[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 ats 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