NEW DRUG APPROVAL

Brand Name	Daxxify™
Generic Name	daxibotulinumtoxinA-lanm
Drug Manufacturer	Revance Therapeutics, Inc

New Drug Approval

FDA approval date: September 07, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 761127

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Frown lines, or glabellar lines, are vertical lines that appear between the eyebrows. They are caused by small muscles between your eyebrows and in your forehead, an area called the glabella. Frowning and squinting contract those muscles, and over time this repeated action can cause permanent wrinkles. For people who want to lessen the lines they already have or prevent lines from forming at all, the most common treatment is to inject the muscles with a botulinum toxin (i.e., Botox ® or Dysport ® are approved medications for the treatment of glabellar lines).

Glabellar frown lines are generally created by the frontalis, the procerus, and the corrugator supercilii muscles (CSM), and are not only esthetically unattractive but also may result in the individual appearing older than they are or giving a negative facial expression. The CSM has two distinct belly components and depresses the medial eyebrow, forming vertical lines on the glabella. The procerus muscle originating from the nasal bone is intermingled with the frontalis muscle at the insertion point, and this muscle forms a horizontal or curved line on the radix below the glabella by pulling down the medial side of the eyebrow. Based on the anatomical features contributing to glabellar frown lines, the general botulinum neurotoxin (BoNT) injection procedure has been performed in the CSM and procerus muscles.

Efficacy

Two randomized, double-blind, multi-center, placebo-controlled clinical trials, Studies GL-1 and GL-2 were conducted to evaluate Daxxify™ for use in the temporary improvement of moderate-to-severe glabellar lines in adults. The 2 trials enrolled a total of 609 subjects (≥18 years old) with glabellar lines of at least moderate severity at maximum frown. A total of 405 subjects were randomized and 406 were treated with 40 Units of Daxxify™ and 204 subjects were randomized and 203 were treated with an equal volume of placebo. Subjects were excluded if they had eyelid ptosis, deep dermal scarring, excessive dermatochalasis or an inability to lessen glabellar lines by physically spreading them apart.

Efficacy was determined through the assessment by investigators and subjects of frown wrinkle severity at maximum frown using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The primary efficacy endpoint (treatment success) was defined as achieving a score of 0 or 1 (none or mild) and an improvement of at least 2 points from baseline for both the investigators and subject's assessments at Week 4. The percentages of subjects with treatment success at Week 4 are presented in Table 1.

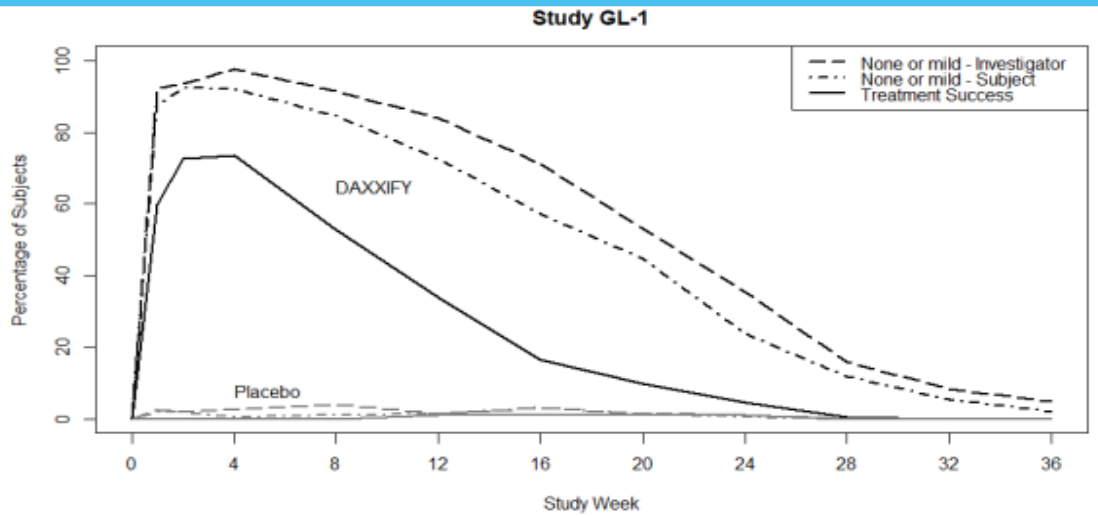
Table 1: Percentage of Subjects Achieving a Score of None or Mild and ≥ 2-Grade Improvement from Baseline

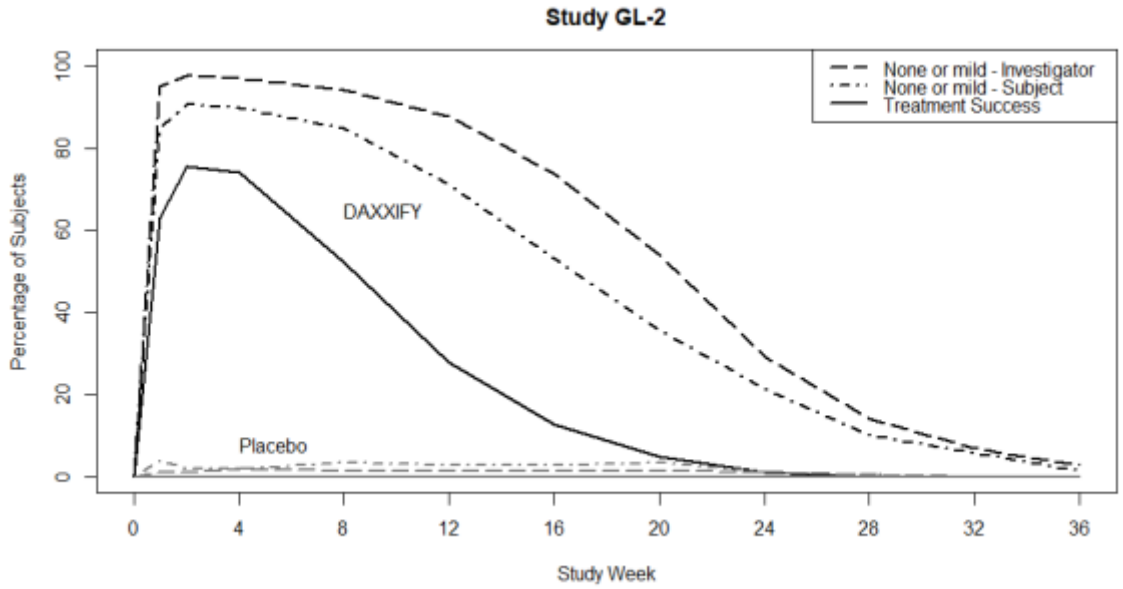
on the Investigator and Subject Assessment of Glabellar Line Severity at Maximum Frown at Week 4						
	STUDY GL-1			STUDY GL-2		
	Daxxify™ (N=201) n (%)	Placebo (N=102) n (%)	Treatment Difference and 95% Confidence Interval	Daxxify™ (N=205) n (%)	Placebo (N=101) n (%)	Treatment Difference and 95% Confidence Interval
Treatment Success[a]	148 (74%)	0 (0%)	74% (68%, 80%)	152 (74%)	0 (0%)	74% (68%, 80%)
Individual Components						
Investigator Assessment	172 (86%)	1 (1%)	---	187 (92%)	2 (2%)	---
Subject Assessment	152 (76%)	0	---	156 (77%)	0	---

[a] A score of 0 or 1 (none or mild) and ≥ 2-Grade Improvement from Baseline on both the Investigator and Subject Assessment

Figure 1 shows the proportion of subjects, over 36 weeks, rated as 0 or 1 (none or mild) by the investigator, 0 or 1 by the subject, and 0 or 1 with at least a 2-point improvement from their baseline based on both the investigator and subject ratings. Subjects were followed through at least Week 24 and then were discontinued from the study when both the investigator and subject scores returned to baseline. Subjects who returned to baseline levels prior to Week 36 were counted as non-responders following study discontinuation.

Figure 1: Proportion of subjects rated as 0 or 1 (none or mild) by investigator, 0 or 1 by the subject, and 0 or 1 with at least 2-point improvement from their baseline (based on both the investigator and subject ratings) in Study GL-1 and Study GL-2





Treatment Success is defined as a score of 0 or 1 (none or mild) and ≥ 2-grade improvement from baseline on both the investigator and subject assessment.

Safety

ADVERSE EVENTS

In the two randomized, placebo-controlled, Phase 3 clinical trials that assess the use of Daxxify™ for the temporary improvement in the appearance of moderate to severe glabellar lines, GL-1 and GL-2, 406 subjects received a single dose treatment of 40 Units Daxxify™ and 203 subjects received placebo.

Table 2: Most Common Adverse Reactions ≥1% and More Frequent than Placebo in Pooled Double-Blind, Placebo-Controlled Trials for Glabellar Lines

Adverse Reaction	Daxxify™ N=406 n (%)	Placebo N=203 n (%)
Headache	26 (6%)	4 (2%)
Eyelid ptosis	9 (2%)	0 (0%)
Facial paresis*	5 (1%)	0 (0%)

* Facial paresis, including facial asymmetry

Injection site reactions were reported in 6% of subjects treated with Daxxify™ and in 6% of subjects treated with placebo (these reactions included injection site pain, injection site erythema, injection site oedema, injection site bruising, injection site hematoma, injection site papule, injection site pruritus).

Injection site reactions were the most common adverse reactions, reported in 9% of subjects [including injection site pain (4%), injection site erythema (3%), injection site oedema (3%), injection site bruising (1%), injection site papule.

WARNINGS & PRECAUTIONS

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, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, 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 the spread of toxin effects. The risk of symptoms is greatest in children treated for spasticity, but symptoms can occur in adults treated for spasticity and other conditions, and particularly in those patients who have underlying conditions that would predispose them to these symptoms.

Lack of Interchangeability between Botulinum Toxin Products:
The potency Units of Daxxify™ are specific to the preparation and assay method utilized. They are not interchangeable with other preparation of botulinum toxin products therefore, Units of biological activity of Daxxify™ cannot be compared to or converted to Units of any other botulinum toxin products assessed with any other specific assay method.

Serious Adverse Reactions with Unapproved Use:
Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received botulinum toxin injections for unapproved uses. In these cases, the adverse reactions may have resulted from the administration of botulinum toxin products to the site of injection and/or adjacent structures. In some cases, patients had pre-existing dysphagia or other significant disabilities.

Hypersensitivity Reactions:
Serious and/or immediate hypersensitivity reactions have been reported for botulinum toxin products. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, discontinue further injection of Daxxify™ and immediately institute appropriate medical therapy. The use of Daxxify™ in patients with a known hypersensitivity to any botulinum toxin preparation, Daxxify™ or any of its formulation components could lead to a life-threatening allergic reaction.

Cardiovascular System:
There have been reports following administration of botulinum toxins of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease.

Pre-Existing Neuromuscular Disorders:
Monitor patients with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) for increased neuromuscular compromise following botulinum toxin treatment. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from typical doses of Daxxify™.

Dysphagia and Breathing Difficulties:
Treatment with botulinum toxin products, including Daxxify™, can result in swallowing or breathing difficulties. These reactions can occur within hours to weeks after injection with botulinum toxin. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a

consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory mechanisms may be involved.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin products. Dysphagia may persist for several months. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Treatment with botulinum toxins, including Daxxify™, may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post-marketing reports from other botulinum toxin products of serious breathing difficulties, including respiratory failure. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders.

Pre-existing Conditions at the Injection Site:
Use caution when administering Daxxify™ to patients with surgical alterations to the facial anatomy, marked facial asymmetry, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, inflammation at the injection site(s), pre-existing eyelid or eyebrow ptosis, when excessive weakness or atrophy is present in the target muscles, or the inability to substantially lessen glabellar lines even by physically spreading them apart.

Ophthalmic Adverse Reactions:
Dry eye has been reported with the use of botulinum toxin products in the treatment of glabellar lines. Reduced tear production, reduced blinking, and corneal disorders may occur with use of botulinum toxins, including Daxxify™. If symptoms of dry eye (e.g., eye irritation, photophobia, or visual changes) persist, consider referring patient to an ophthalmologist.

CONTRAINDICATIONS

Daxxify™ is contraindicated in patients with:

- Known hypersensitivity to any botulinum toxin preparation, Daxxify™ or any of the components in the Daxxify™ formulation.
- Infection at the injection sites.

Clinical Pharmacology

MECHANISMS OF ACTION

Daxxify™ blocks cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine. When injected into skeletal muscle, Daxxify™ is internalized into the nerve terminal, translocates into the neuronal cytosol where it cleaves SNAP25, a protein necessary for synaptic vesicle membrane docking and subsequent release of acetylcholine which produces a dose dependent decrease of muscle function. Recovery of activity is gradual and results from the degradation of neurotoxin light chain in the neurons with a contribution from the formation of axonal sprouts. Muscle reinnervation occurs, leading to a slow reversal of the pharmacological effects of Daxxify™.

Dose & Administration

ADULTS

0.1 mL (8 Units) by intramuscular injection into each of five sites, for a total dose of 40 Units.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For injection: 50 Units or 100 Units sterile lyophilized powder in a single-dose vial.