CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761225
PDUFA Goal Date	April 6, 2023
OSE RCM #	2022-2295
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	April 4, 2023
Subject	Evaluation of Need for a REMS
Established Name	Letibotulinumtoxin A
Trade Name	Letbyo
Name of Applicant	Hugel Inc.
Therapeutic Class	Acetylcholine release inhibitor and neuromuscular blocking agent
Formulation(s)	Single-use 50 unit vial and 100 unit vial Reconstituted to 4 units/0.1 mL
Dosing Regimen	0.1 mL (4 Units) by intramuscular injection into each of five sites, for a total dose of 20 Units

This memorandum (memo) by the Division of Risk Management (DRM) serves as an update to the March 22, 2022 REMS determination review to evaluate whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Letbyo (letibotulinumtoxinA) is necessary to ensure the benefits outweigh its risks.

Hugel Inc. (hereafter referred to as the Applicant) originally submitted a Biologics Licensing Application (BLA) 761225 on March 31, 2021 for letibotulinumtoxinA with the proposed indication 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] The risks associated with letibotulinumtoxinA-wlbg (hereafter referred to as letibotulinumtoxinA) include the serious risk of distant toxin spread that can cause life threatening swallowing and breathing difficulties. DRM completed a REMS Determination Review on March 22, 2022 and concluded that a REMS is not necessary to ensure the benefits letibotulinumtoxinA outweigh its risks.[2] A Complete Response (CR) Letter was issued to the Applicant on March 31, 2022 due to deficiencies related to facility inspection, microbiology, and product quality.[3]

On October 6, 2022, the Applicant resubmitted the application in response to the CR Letter.[4] The resubmission was determined by the Agency to be a Class 2 resubmission[5] and is the subject of this memo. The Applicant did not submit any new efficacy or safety data.

The recommended regulatory action is pending due to a recent facilities inspection; however, there are no deficiencies related to efficacy or safety. The clinical reviewer recommends approval of letibotulinumtoxinA on the on the basis of the efficacy and safety information available.[6,7] The benefit-risk profile is unchanged from our previous REMS Determination review.[2] DRM conclusions remain the same, a REMS is not necessary to ensure the benefits of letibotulinumtoxinA outweigh its risks for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients.

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/s/

LINDSEY W CRIST
04/04/2023 07:07:33 AM

JACQUELINE E SHEPPARD
04/04/2023 08:37:30 AM

CYNTHIA L LACIVITA
04/04/2023 08:51:59 AM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
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Application Type	BLA
Application Number	761225
PDUFA Goal Date	March 31, 2022
OSE RCM #	2021-987
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 22, 2022
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Established Name	Letibotulinumtoxin A
Trade Name	Letbyo
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Letbyo (letibotulinumtoxinA) is necessary to ensure the benefits outweigh its risks. Hugel Inc. submitted a Biologics Licensing Application (BLA) 761225 on March 31, 2021 for letibotulinumtoxinA with the proposed indication 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 risks associated with letibotulinumtoxinA include the serious risk of distant toxin spread that can cause life threatening swallowing and breathing difficulties. The Applicant did not submit a proposed REMS or risk management plan with this application; however, proposed labeling includes the class wide boxed warning for distant spread of the effects of botulin toxin and a Medication Guide.

The recommended regulatory action at this time is a Complete Response due to outstanding deficiencies, none of which are related to safety or efficacy. Based on the available clinical data, DRM and the Division of Dermatology and Dentistry agree that a REMS is not necessary to ensure the benefits of letibotulinumtoxinA outweigh its risks. The benefit for the temporary improvement in the appearance of moderate to severe glabellar lines was demonstrated as letibotulinumtoxinA resulted a statistically significant difference in the primary endpoint compared to placebo in the three phase 3 pivotal trials. A serious risk of all agents in this class is the risk of distant toxin spread that may lead to life-threatening or fatal swallowing or breathing difficulties. The safety profile of letibotulinumtoxinA is similar to other BLAs for botulinum toxins approved for the same indication. Healthcare providers who prescribe and administer botulinum toxin products are likely aware of the risks associated with these products as these products are commonly used for the treatment of glabellar lines. Final labeling negotiations will occur after the Applicant responds to the Complete Response; however, labeling will include the class wide boxed warning for distant toxin spread and a Medication Guide to communicate the risk to patients similar to the other approved botulinum toxin products.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Letbyo (letibotulinumtoxinA) is necessary to ensure the benefits outweigh its risks. Hugel Inc. (hereafter referred to as the Applicant) submitted a Biologics Licensing Application (BLA) 761225 on March 31, 2021 for letibotulinumtoxinA with the proposed indication 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] This application is under review in the Division of Dermatology and Dentistry (DDD). The Applicant did not submit a proposed REMS or risk management plan with this application. The proposed labeling includes the class wide boxed warning for distant spread of the effects of botulin toxin and a Medication Guide.[1]

2 Background

2.1 PRODUCT INFORMATION

LetibotulinumtoxinA, a new molecular entity[a], is a botulinum toxin proposed for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. Botulinum toxin products block cholinergic transmission at the neuromuscular junction by inhibiting the release of acetylcholine resulting in a dose-dependent decrease of muscle function. Recovery of function occurs gradually resulting in a slow reversal of the pharmacologic effects of letibotulinumtoxin A.[2] The botulinum toxin products are not interchangeable.

LetibotulinumtoxinA is proposed to be supplied as a single-use 50 Unit or 100 Unit vial. Prior to intramuscular injection, letibotulinumtoxinA requires reconstitution to a final concentration of 4 Units/0.1 mL. The proposed dosage regimen is a total dose of 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each (two injections in each corrugator muscle and one injection in the procerus muscle). LetibotulinumtoxinA should be administered no more frequently than every 3 months.[2,b] LetibotulinumtoxinA has been available in Korea since 2019 and is licensed in 22 other countries.[3]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761225 relevant to this review:

- **03/31/2021:** BLA 761225 submission for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients was received.[1]

- **09/14/2021:** A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no major safety issues have been identified at this stage of review and a REMS for letibotulinumtoxinA will likely not be required.

- **12/13/2021:** A Late Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency discussed Chemistry, Manufacturing, and Controls (CMC) review issues. The Agency informed the Applicant no issues related to risk management have been identified to date.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug*

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Glabellar lines, commonly known as frown lines, are a common aesthetic concern of aging adults.[4,c] Glabellar lines are vertical lines that develop between the eyebrows upon frowning and may be present at rest. The lines result from repeated contractions of the corrugator and procerus muscles over an extended period of time. The presence of these facial lines at rest may cause patients to unintentionally appear angry or concerned.[5,6] Treatments to improve or lessen the appearance of glabellar lines may be of interest to some patients as the lines may affect their self-perception and confidence.[5] In 2018, 17.7 million cosmetic procedures were performed in the United States and 15.9 million were minimally-invasive procedures.[7] Botulinum toxin type A is the most common cosmetic minimally-invasive procedure with over 7.4 million procedures in 2018.[7,d] Minimally invasive cosmetic procedures with botulinum toxin type A products may improve patient satisfaction with their appearance and patient-reported outcome measures for self-esteem and quality of life.[8-10]

3.2 Description of Current Treatment Options

Non-surgical treatment options most often used for facial rejuvenation treatment include neuromodulators (botulinum toxins) and dermal fillers. The current botulinum toxins are approved for the temporary improvement in the appearance of moderate to severe glabellar lines are listed below. See Appendix 10.2 for Table 1 for a summary of approved products:

- Botox Cosmetic (onabotulinumtoxinA)
- Dysport (abobotulinumtoxinA)
- Xeomin (incobotulinumtoxinA)
- Jeuveau (prabotulinumtoxinA)

Botulinum toxin products have the potential to spread beyond the injection site and lead to adverse events in tissues adjacent to the target muscle (local spread) or it can spread more widely and lead to adverse events in tissues remote to the injection site (distant spread). Symptoms potentially suggestive of distant spread of toxin include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, blurred vision and breathing difficulties. Swallowing and breathing difficulties can be life-threatening and there have been reports of deaths.[2]

The Agency required REMS for Botox Cosmetic, Dysport, and Xeomin due to post-marketing reports of distant toxin spread with botulinum toxin products. The REMS for each of these products consisted of a

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Medication Guide, communication plan, and a timetable for submission of assessments. The goal of the REMS for these products was to minimize the risks of medication errors due to the lack of interchangeability of the licensed botulinum toxins and to inform prescribers and patients about the potential risk of distant spread of toxin beyond the injection site. In 2012, it was determined the REMS for these products could be eliminated because the communication activities were complete and there were no new safety signs based on the post-marketing safety data.[11] Currently, the risks associated with botulinum toxin agents are communicated through labeling (see Appendix 10.2, Table 1). There is a class wide boxed warning for the risk of distant toxin spread and a Medication Guide remains a part of labeling.

In addition to the botulinum toxins, there are several facial fillers approved by the FDA.[12] The majority of fillers have a temporary effect similar to the botulinum toxins. The serious, but rare, side effects of these dermal fillers include scarring, blurred vison, partial vision loss, and blindness if the product is injected into a blood vessel particularly in the eye region. The risk associated with dermal fillers used near the eyes makes botulinum toxins the primary non-surgical treatment for use in the glabellar regions.

4 Benefit Assessment

The clinical development program for letibotulinumtoxinA consists of three phase 3 trials, BLESS I: CPH-301-201030 (NCT 02677298); BLESS II: CPH-302-201030 (NCT 02677805); and BLESS III: CPH-302- 201040 (NCT 03985982) to assess the efficacy and safety of letibotulinumtoxinA for the treatment of glabellar lines. The pivotal trials were identical in study design: multicenter, randomized, double-blind, and placebo-controlled. Eligible subjects were men and women 18-75 years with moderate to severe glabellar frown lines at maximum frown [severity score of 2 or 3 on the 4-point Facial Wrinkle Scale (FWS) as determined by both the investigator and the subject][e] At the time of the original BLA submission, data was available for the randomized, double-blind, placebo-controlled period for all three pivotal studies. Data from the long-term open label extension for BLESS III was submitted as part of the 120 Day Safety Update.

Across the pivotal studies for the first treatment, 1276 subjects were randomized 3:1 to receive letibotulinumtoxinA (N=957) or placebo (N=319). Subjects were injected intramuscularly at 5 sites for a total dose in the active treatment group of 20 Units. After completion of the first cycle, eligible subjects could enter the open-label extension and receive up to three additional retreatments.[f] Subjects were

[e] The Facial Wrinkle Scale is a 4-point scale of 0-3 to determine severity of glabellar lines at maximum frown and at rest. Score assessment is based on the following definitions: 0= no lines or minimal lines, 1=mild lines, 2=moderate lines, 3=severe lines. FWS was the primary efficacy outcome for the pivotal studies. Scores were assessed by both the investigator and subject using the FWS instrument corresponding to the glabellar line scale – investigator (GLS-I) or GLS-subject (GLS-S).

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

eligible for retreatment at 12 weeks after a treatment cycle if their glabellar lines at maximum frown had relapsed to a FWS score of 2 or 3 as determined by both the investigator and subject and no infection, inflammation or pregnancy was present. If not eligible at 12 weeks, re-evaluation occurred every 4 weeks until week 48.

The primary endpoint for all three trials was measured at Week 4 and was defined as the proportion of subjects with a FWS score of 0 or 1 and an improvement of at least 2 points on FWS score at maximum frown compared to baseline, assessed independently by both the investigator and subject. Among the 1276 subjects randomized, 1272 subjects received treatment, and 1271 subjects[g] were included in the full analysis set, including 954 subjects who received letibotulinumtoxinA and 317 who received placebo.[2,13] In the three pivotal studies, there was a statistically significant higher proportion of responders in the letibotulinumtoxinA group compared to placebo (See Table 1).

Table 1. Primary Endpoint Results for the Full Analysis Set[2,13]

	BLESS I		**BLESS II**		**BLESS III**	
	Letibotulinum-toxinA (N = 528)	Placebo (N = 175)	Letibotulinum-toxinA (N = 160)	Placebo (N = 53)	Letibotulinum-toxinA (N = 266)	Placebo (N = 89)
Treatment Success						
Multi-Component Assessment n (%)	246 (46.6%)	0 (0%)	78 (48.8%)	1 (1.9%)	172 (64.7%)	0 (0%)
Treatment Difference and 95% Confidence Interval*	47% (42.7%, 51.4%)		45% (36%, 54.3%)		65% (59.3%, 71.2%)	
P-value**	<0.0001		<0.0001		<0.0001	
Individual Components						
Investigator Assessment n (%)	348 (65.9%)	1 (0.6%)	120 (75%)	1 (1.9%)	209 (78.6%)	1 (1.1%)
Subject Assessment n (%)	290 (54.9%)	0 (0%)	83 (51.9%)	1 (1.9%)	183 (68.8%)	0 (0%)

* Mantel-Haenszel estimate and confidence limits for the common risk difference by using the Mantel-Haenszel weights for study center.

** P-values are based on the CMH general association test stratified on study center.

Source: Statistical reviewer analysis (Unireview)

The clinical reviewer concluded the Applicant provided adequate evidence to support approval of letibotulinumtoxinA for the indication of temporary improvement in the appearance of moderate to severe glabellar lines.[h,13]

[g] Although 1272 subjects received treatment, one subject was excluded from the full analysis set and primary efficacy analysis as they had mild glabellar lines at baseline and did not meet the inclusion criteria. This subject was included in the safety population and analysis.

[h] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

5 Risk Assessment & Safe-Use Conditions

The safety population for letibotulinumtoxinA is comprised of data from the three pivotal, phase 3 trials. A total of 1272 subjects were treated, 955 with letibotulinumtoxinA and 317 with placebo. In the open-label period, a total of 1177 subjected were exposed to letibotulinumtoxinA. According to the trial protocols, subjects were allowed to receive up to four treatments. Overall, a total of 1246 subjects received 1 treatment, 1160 subjects received 2 treatments, 994 subjects received 3, and 546 subjects received 4 treatments.[14]

The Agency excluded 110 subjects (44 subjects in the letibotulinumtoxinA group and 7 subjects in the placebo group) from the safety analysis due to protocol noncompliance identified at a site in the BLESS III trial. Therefore, the final safety analysis set included a total of 1221 subjects, 911 treated with letibotulinumtoxinA and 310 treated with placebo.[2,14]

The most common adverse reactions reported in more than one subject in the letibotulinumtoxinA group compared to placebo were headache (17/911, 2%), brow ptosis (3/911, <1%), eyelid ptosis (3/911, <1%), and blepharospasm (2/911, <1%).[2] The adverse reaction profile was similar in the open-label extension periods of the trials.

5.1 DEATHS

There were no deaths reported in the clinical development program.[13-16]

5.2 SERIOUS ADVERSE EVENTS

In the double-blind period of the three pivotal trials, 10 subjects (1.1%) treated with letibotulinumtoxinA reported one or more serious adverse events[i] (SAE) compared to 1 subject (0.3%) treated with placebo. In the open label period, a total of 21 (1.9%) subjects reported one or more SAEs. None of the SAEs were considered treatment related.[13,14]

5.3 ADVERSE EVENT OF SPECIAL INTEREST

5.3.1 Spread of Toxin Effect

Events indicative of spread of toxin were adverse events of interest (AESI) in the clinical development program. Based on the clinical reviewer analysis, TEAEs indicative of local spread of toxin during the placebo-controlled period of the pivotal trials included eyelid ptosis (N=3, 0.3%), brow ptosis and heaviness (N=3, 0.3%), blurred vision (N=1, 0.1%) in the letibotulinumtoxinA group compared to no

[i] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

events in the placebo group. Events suggestive of distant toxin spread in the placebo-controlled period of the pivotal trials included bradycardia (N=1, 0.1%), dysarthria (N=1, 0.1%), and constipation (N=1, 0.1%) in the letibotulinumtoxinA group and muscular weakness (N=1, 0.3%) and dysphagia (N=1, 0.3%) in the placebo group.

In the open-label period, events indicative of local spread of toxin included eyelid ptosis (N=6, 0.5%), brow ptosis (N=1, 0.1%), blurred vision (N=1, 0.1%), photophobia (N=1, 0.1%), and diplopia (N=1, 0.1%). In the open-label period, events indicative of distant spread of toxin included one event each of dyspnea and constipation.

The clinical reviewer concluded that none of the events potentially indicative of distant spread of toxin were considered related to study medication or injection procedures.[j,13] The proposed label includes the class-wide boxed warning for distant spread of toxin effect and a Medication Guide that would communicate the risk to patients.

6 Expected Postmarket Use

LetibotulinumtoxinA for cosmetic use is likely to be prescribed and administered by plastic surgeons and dermatologists in the outpatient setting. These specialties constitute up to 70% of the physician population providing cosmetic procedures.[17] Botulinum toxin type A is one of the most common cosmetic minimally-invasive procedure. If approved, letibotulinumtoxinA would be the fifth botulinum toxin A product approved for the temporary improvement in the appearance of moderate to severe glabellar lines. Approved products have a similar risk profile; therefore, healthcare providers who are likely to prescribe and administer letibotulinumtoxinA should be familiar with risks and appropriate administration technique.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a proposed REMS or risk management plan with this application; however, proposed labeling includes the class wide boxed warning for distant spread of the effects of botulin toxin and a Medication Guide.

[j] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

8 Discussion of Need for a REMS

The clinical reviewer recommends approval of letibotulinumtoxinA based on the efficacy and safety information currently available.[13,18]

Glabellar lines, commonly known as frown lines, are a common aesthetic concern of aging adults. Some people seek interventions to improve these aesthetic concerns. Botulinum toxin type A treatments are a common minimally invasive cosmetic procedure for improving wrinkle appearance. If approved, letibotulinumtoxinA would be the fifth agent approved for the temporary improvement in the appearance of moderate to severe glabellar lines.

The benefit of letibotulinumtoxin A was demonstrated in three, phase 3 pivotal trials, BLESS I: CPH-301-201030; BLESS II: CPH-302-201030; and BLESS III: CPH-302-201040. In all three trials, there was a statistically significant higher proportion of responders in the letibotulinumtoxinA group compared to placebo.

There were no deaths in the clinical development program. Similar to all botulinum toxin A products in this class, letibotulinumtoxinA has the serious risk of distant toxin spread that may lead to life-threatening or fatal swallowing or breathing difficulties. The clinical reviewer concluded that none of the events reported in the trials that were potentially indicative of distant spread of toxin were related to study medication or injection procedure. No serious adverse events were considered treatment related. The clinical reviewer concluded that the safety profile appears similar to other botulinum toxin A products and no new safety signals for this botulinum toxin A product were identified.

Previously, REMS were required for botulinum toxin A products due to post-marketing reports of distant toxin spread. The REMS for these products were released in 2012 as the communication activities were complete and there were no new safety signs based on post-marketing safety data. The risks of botulinum toxin A products are communicated through labeling. There is a class wide boxed warning for the risk of distant toxin spread and a Medication Guide remains a part of labeling. If approved, labeling for letibotulinumtoxinA is proposed to include the class wide boxed warning and risks will be communicated to patients in a Medication Guide similar to other agents in the class.

The recommended regulatory action at this time is a Complete Response due to outstanding deficiencies, none of which are related to safety or efficacy. Based on the available safety and efficacy data, the prescribing community's familiarity with the risks associated with botulinum toxin A products, and the lack of any new or unique safety considerations compared to other approved products in this class, this reviewer concludes that a REMS is not necessary to ensure the benefits outweigh the risks. Final labeling negotiations will occur after the Applicant responds to the Complete Response; however, labeling will include the class wide boxed warning for distant toxin spread and a Medication Guide to communicate the risk to patients.

9 Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with botulin toxins are well documented. If approved, letibotulinumtoxinA would join the other botulin toxins approved for this indication. There are no new or unique risks associated with letibotulinumtoxinA compared to the other agents in this class. In general, healthcare providers who prescribe and perform cosmetic procedures for facial rejuvenation should be familiar with the risks and proper administration of botulinum toxin products.

Should DDD have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10 Appendices

10.1 References

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10.2 TABLE 1. BOTULINUM TOXINS INDICATED FOR THE TREATMENT OF GLABELLAR LINES

Product Trade Name (Generic) Initial Approval Year	Indication	Dosage for glabellar lines	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
Botox Cosmetic (OnabotulinumtoxinA) 1989	Moderate to severe glabellar lines; Moderate to severe lateral canthal lines; Moderate to severe forehead lines	0.1 mL (4 Units) into each of 5 sites, for a total dose of 20 Units	Spread of toxin effect; lack of interchangeability between botulinum toxin products; serious adverse reactions including some with fatal outcomes (excessive weakness, dysphagia, aspiration pneumonia) with unapproved uses; hypersensitivity reactions; cardiovascular adverse events including arrhythmia, myocardial infarction, some with fatal outcomes; increased risk of clinically significant effects with pre-existing neuromuscular disorders; dysphagia and breathing difficulties; caution with pre-existing conditions at the injection site; corneal exposure and ulceration in patients treated for blepharospasm; dry eye;	Boxed Warning for Distant Spread of Toxin; Medication Guide REMS consisting of a Medication Guide, Communication Plan, and timetable of assessments released in 2012

			spatial disorientation, double, vision, or past-pointing in patients treated with strabismus; contains albumin - remote risk for transmission of Creutzfeldt-Jakob disease (CJD)	
Dysport (abobotulinumtoxinA) 2009	Cervical dystonia, moderate to severe glabellar lines, spasticity	Total dose of 50 Units, divided in five equal aliquots of 10 Units each intramuscularly	Spread of toxin effect; lack of interchangeability between botulinum toxin products; hypersensitivity reactions; dysphagia and breathing difficulties; caution with administering to patients with surgical alterations to facial anatomy or other pre-existing conditions near the injection site; dry eyes with treatment of glabellar lines; patients with pre-existing neuromuscular disease may be at increased risk of clinically significant adverse events; contains albumin - remote risk for transmission of CJD	Boxed Warning for Distant Spread of Toxin Medication Guide REMS consisting of a Medication Guide, Communication Plan, and timetable of assessments released in 2012
Xeomin (incobotulinumtoxinA) 2010	Chronic sialorrhea, upper limb spasticity, cervical dystonia, blepharospasm; Moderate to severe glabellar lines	Total recommended dose is 20 Units per treatment session divided into five equal intramuscular injections of 4 Units each	Spread of toxin effect; lack of interchangeability between botulinum toxin products; hypersensitivity reactions; dysphagia and breathing difficulties; corneal exposure and ulceration and ectropion in patients treated for blepharospasm; risk of ptosis in patients treated for glabellar lines; contains albumin - remote risk for transmission of CJD	Boxed Warning for Distant Spread of Toxin Medication Guide REMS consisting of a Medication Guide, Communication Plan, and timetable of assessments released in 2012

Jeaveau (prabotulinumtoxinA-xvfs) 2019	Moderate to severe glabellar lines	0.1 mL (4 Units) by intramuscular injection into each of five sites, for a total dose of 20 Units	Spread of toxin effects; lack of interchangeability among other botulinum toxin products; serious adverse reactions including some with fatal outcomes (excessive weakness, dysphagia, aspiration pneumonia) with unapproved uses; hypersensitivity reactions; cardiovascular adverse events including arrhythmia, myocardial infarction, some with fatal outcomes; increased risk of clinically significant effects with pre-existing neuromuscular disorders; dysphagia and breathing difficulties; caution with pre-existing conditions at the injection site; ophthalmic adverse reactions; contains albumin - remote risk for transmission of CJD	Boxed Warning for Distant Spread of Toxin; Medication Guide

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/s/

LINDSEY W CRIST
03/22/2022 07:31:53 AM

JACQUELINE E SHEPPARD
03/22/2022 02:18:59 PM

CYNTHIA L LACIVITA
03/22/2022 08:45:36 PM