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	761127
PDUFA Goal Date	September 8, 2022
OSE RCM #	2019-2406
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	August 25, 2022
Subject	Evaluation of Need for a REMS
Established Name	DaxibotulinumtoxinA-lanm
Trade Name	Daxxify
Name of Applicant	Revance Therapeutics, Inc.
Therapeutic Class	Acetylcholine release inhibitor and neuromuscular blocking agent
Formulation(s)	Single Use 50 unit vial and 100 unit vial Reconstituted to 8 units/0.1 mL
Dosing Regimen	0.1 mL (8 units) by intramuscular injection into each of the 5 sites, for a total dose of 40 units

This memorandum (memo) by the Division of Risk Management (DRM) serves as an update to the July 15, 2020 REMS determination review to evaluate whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Daxxify (daxibotulinumtoxinA-lanm) is necessary to ensure the benefits outweigh its risks.

Revance Therapeutics, Inc. (hereafter referred to as the Applicant) submitted Biologics Licensing Application (BLA) 761127 on November 24, 2019 for daxibotulinumtoxinA-lanm with the proposed indication for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients.[1] The risks associated with daxibotulinumtoxinA-lanm (hereafter referred to as daxibotulinumtoxinA) include the serious risk of distant toxin spread that can cause life threatening swallowing and breathing difficulties. A Complete Response (CR) Letter was issued to the Applicant on October 14, 2021 due to a product quality deficiency.[2] DRM completed a REMS Determination Review on July 15, 2020 and concluded that a REMS is not necessary to ensure the benefits daxibotulinumtoxinA outweigh its risk for the proposed indication for treatment of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients.[3]

On March 8, 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 and is the subject of this memo.[5] 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 daxibotulinumtoxinA on the basis of the efficacy and safety information available.[6,7] The benefit-risk profile is unchanged from our previous REMS Determination review. DRM concludes a REMS is not necessary to ensure the benefits daxibotulinumtoxinA outweigh its risk for the proposed indication for treatment of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients.

References:

1. Revance Therapeutics Inc. Orig-1 for daxibotulinumtoxinA, BLA 761127 submitted on November 24, 2019 and received by Agency on November 25, 2019.
2. Beitz J. Complete Response Letter for daxibotulinumtoxinA, BLA 761127. October 14, 2021.
3. Gentles C. Division of Risk Management. NME REMS Determination Review for daxibotulinumtoxinA, BLA 761127. July 15, 2020.
4. Revance Therapeutics Inc. Resubmission for daxibotulinumtoxinA, BLA 761127 March 8, 2022.
5. Searcy K. Acknowledge - Class 2 Resubmission Letter for daxibotulinumtoxinA, BLA 761127. April 21, 2022.

6. Food and Drug Administration. Center for Drug Evaluation and Research. Division of Dermatology and Dentistry. NDA/BLA Multi-Disciplinary Review and Evaluation, DaxibotulinumtoxinA, BLA 761127. November 20, 2020.
7. Li-Masters T. Personal Email Communication regarding daxibotulinumtoxinA, BLA 761127 clinical analysis. Received July 13, 2022.

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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	761127
PDUFA Goal Date	November 25, 2020
OSE RCM #	2019-2406
Reviewer Name(s)	Carlisha Gentles, PharmD
Acting Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	July 15, 2020
Subject	Evaluation of Need for a REMS
Established Name	Daxibotulinumtoxin A
Trade Name	(b) (4)
Name of Applicant	Revance Therapeutics, Inc.
Therapeutic Class	Acetylcholine release inhibitor and neuromuscular blocking agent
Formulation(s)	Single Use 50 unit vial and 100 unit vial (reconstituted to 8 units/0.1 mL)
Dosing Regimen	0.1 mL (8 units) by intramuscular injection into each of the 5 sites, for a total dose of 40 units

Table of Contents

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 (b) (4) (daxibotulinumtoxin A) is necessary to ensure the benefits outweigh its risks. Revance Therapeutics, Inc. submitted a Biologic Licensing Application (BLA) 761127 on November 24, 2019 for daxibotulinumtoxin A with the proposed indication for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients. The clinical reviewer concluded that daxibotulinumtoxin A was effective in helping patients temporarily minimize the appearance of moderate to severe glabellar lines. There were no treatment related deaths in the clinical trials; however similar to other products in this class of drugs, Daxibotulinumtoxin A carries the serious risk of distal toxin spread that can cause life threatening swallowing and breathing difficulties which could lead to death. The applicant did not submit a proposed REMS with this application but proposed a medication guide (MG) as part of labeling to align with the other botulinum toxin products and inclusion of the class wide boxed warning for distal spread of the effects of botulinum toxin.

The safety profile of daxibotulinumtoxin A is consistent with other botulinum toxins approved for the same indications. The Division of Risk Management (DRM) and the Division of Dermatology and Dental Products (DDP) agree that a REMS is not necessary to ensure that the benefits of daxibotulinumtoxin A outweigh its risk for the proposed indication for treatment of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients.

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) (b) (4) (daxibotulinumtoxin A) is necessary to ensure the benefits outweigh its risks. Revance Therapeutics, Inc. submitted a Biologic Licensing Application (BLA) 761127 on November 24, 2019 for daxibotulinumtoxin A with the proposed indication for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients. This application is under review in the Division of Dermatology and Dental Products. The applicant did not submit a proposed REMS but proposed a medication guide as part of labeling and inclusion of the class wide boxed warning for distal spread of the effects of botulinum toxin.

2 Background

2.1 PRODUCT INFORMATION

Daxibotulinumtoxin A, a new molecular entity, is a botulinum toxin proposed for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients.[a] Botulinum toxin works by blocking the release of acetylcholine in the neuromuscular junction, thereby decreasing muscle contractions. Daxibotulinumtoxin A is reconstituted to an 8 units/0.1 mL solution from a 50 unit or 100 unit

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

lyophilized powder. The product will be manufactured in a single-use vial and is to be reconstituted and administered intramuscularly. Daxibotulinumtoxin A is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761127 relevant to this review:

- 11/25/2019: BLA 761127 submission for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients received
- 06/03/2020: A Mid-cycle communication was sent to the Applicant. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for daxibotulinumtoxin A

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Daxibotulinumtoxin A is being developed to treat the progressive development of facial lines that are associated with aging, which is an anesthetic condition.[b] The presence of these facial lines leads some patients to consider cosmetic procedures. In 2013, 11 million cosmetic procedures were performed in the United States and 83% of these were nonsurgical.[1] Botulinum toxin use is the most common of the nonsurgical aesthetic procedures.[2,c] The treatment of glabellar lines with botulinum toxin type A (BoNTA) products is one of the most popular facial rejuvenation procedures in the United States (US).[3]

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. Current botulinum toxins approved for the indication of the temporary improvement in the appearance of moderate to severe glabellar lines are listed below:

- Botox Cosmetic (Onabotulinumtoxin A) Approval 1991
- Dysport (Abobotulinumtoxin A) Approval 2009
- Xeomin (Incobotulinumtoxin A) Approval 2010
- Jeuveau (DWP-450 Botulinumtoxin A) Approval 2018

[b] 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.*

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

The current botulinum toxin agents have a class wide boxed warning for the risk of distal toxin spreading and require repeat treatments every 3 to 4 months to maintain effacement of glabellar lines.[4] These products were previously approved with REMS that included a Medication Guide, communication plan and a timetable for submission of assessments. The goal of the REMS was intended to educate prescribers and patients of lack of interchangeability of the licensed botulinum toxins and the risk of distant spread of toxin beyond the injection site. The communication activities were completed, and it was determined in 2012, that the REMS for these products were no longer necessary to ensure the benefits outweigh the risks. The MG is retained as part of labeling.

In addition to the botulinum toxins, there are a number of facial fillers approved by the FDA.[5] 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 pivotal trials supporting efficacy and safety for daxibotulinumtoxin A were SAKURA-1 and SAKURA-2 with additional safety data gathered from an open label safety study, SAKURA-OLS. The two studies were identical in design: randomized, double-blind, multi-center, and placebo-controlled. The studies enrolled a combined total of 609 patients with moderate to severe glabellar lines. Adult participants were randomized (2:1) to receive daxibotulinumtoxin A (N= 406) 0.1 mL (8 units) via intramuscular injection into 5 sites for a total of 40 units or placebo (N=203). The primary endpoint in both pivotal trials was defined as achieving a 2-point improvement or greater from baseline on both the Investigator Global Assessment – Frown Wrinkle Severity (IGA-FWS)[d] scale and Patient Frown Wrinkle Severity (PFWS)[e] at Week 4.[6] Participants were treated for up to 36 weeks with a 24 to 36-week post-treatment follow up period. In both studies, the percentage of participants with treatment success at Week 4 was 74% in the daxibotulinumtoxin A group and 0% in the placebo group. The endpoints in both studies were deemed statistically significant ($p<0.0001$).[7] The clinical reviewer concluded that daxibotulinumtoxin A is approvable for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adult patients at a dose of 0.1 mL (8 Units) by intramuscular injection into each of five sites, for a total dose of 40 Units.

[d] The IGA-FWS is a 4-point rating scale used by study investigators to rate frown wrinkle severity. The scale consists of the rating scores 0, 1, 2, and 3 which correspond to rating labels of None, Mild, Moderate, and Severe, respectively.

[e] The PFWS is a 4-point rating scale used by study subjects to rate their frown wrinkle severity. The scale consists of the rating scores 0, 1, 2, and 3; corresponding to None, Mild, Moderate, and Severe glabellar lines, respectively.

5 Risk Assessment & Safe-Use Conditions

The safety database for daxibotulinumtoxin A is comprised of the two pivotal studies, Sakura-1 and Sakura-2, and an open label repeat-dose safety study (Sakura-OLS) in 2691 participants that received 40 units of daxibotulinumtoxin A. The most commonly reported adverse events (AEs) > 1% in participants were headache at 7% (placebo 2%), followed by injection site reactions (including injection site pain, injection site erythema, injection site edema, injection site bruising, injection site hematoma, injection site papule, injection site pruritus) at 6% (placebo 6%), eyelid ptosis at 2% (placebo 0%), and facial paresis at 1% (placebo 0%). As noted by the clinical reviewer, most of these events were mild or moderate in severity and were self-limited, resolved spontaneously, without treatment. There were no serious adverse events related to the drug treatment. The clinical reviewer concluded that daxibotulinumtoxin A has an acceptable risk-benefit profile for the treatment of glabellar lines in adults.[8]

Death

One death was reported during the development of daxibotulinumtoxin A. The reported death was due to homicide. The death was not considered treatment related per the clinical reviewer and this reviewer.

5.1 Adverse Event of Special Interest - Distant Spread of Toxin

The primary concern for use of botulinum toxin products is the potential spread of botulinum toxin into tissues adjacent to the target muscle or more remotely via tissues planes or into the blood stream. Symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties of which swallowing and breathing difficulties can be life threatening.[9] Post-marketing safety data from other botulinum toxin products suggest that botulinum toxic effects may be observed beyond the site of local infection. Per the clinical reviewer, in the Sakura-1, Sakura-2, and Sakura-OLS studies, participants had AEs considered related to the local spread of the toxin, however, there were no reports of distal spread of toxin. Per class labeling for botulinum toxin products, there will be a medication guide for daxibotulinumtoxin A that will inform patients of the risk of distal spread of toxins as is with the other products in this class.

6 Expected Postmarket Use

Daxibotulinumtoxin A 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.[10]

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for daxibotulinumtoxin A but proposed a Medication Guide as part of labeling to align with the other botulinum toxin products and inclusion of the class wide boxed warning for distal spread of the effects of botulinum toxin.[11]

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of daxibotulinumtoxin A on the basis of the efficacy and safety information currently available.

Daxibotulinumtoxin A is a botulinum toxin that is indicated for the treatment of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. Use of daxibotulinumtoxin A as a temporary cosmetic procedure to improve wrinkle appearance is a very common procedure.

The development for daxibotulinumtoxin A, which included 2 pivotal trials- Sakura-1 and Sakura-2, supports the efficacy of daxibotulinumtoxin A as evidenced by a 74% treatment success rate ($p < 0.0001$) in achieving the desired cosmetic effect with an acceptable safety profile.

There were no treatment related deaths in the clinical trials; however similar to other products in this class of drugs, daxibotulinumtoxin A carries the serious risk of distal toxin spread that can cause life threatening swallowing and breathing difficulties which could lead to death. The class of products continues to carry a boxed warning and Medication Guide in their labeling addressing this risk. Since the risks associated with daxibotulinumtoxin A are risks for the entire class of botulinum toxins, and do not appear to exceed those of other approved products, nor are there any serious safety risks that are unique to daxibotulinumtoxin A, this reviewer has concluded that a REMS is not necessary to ensure the benefits outweigh the risks. Similar to other products in this class, the risk of distal spread toxins will be included in a boxed warning and a Medication Guide, to inform prescribers and patients of the risk.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for daxibotulinumtoxin A to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Pao KY, Mancini R. Nonsurgical periocular rejuvenation: advanced cosmetic uses of neuromodulators and fillers. Current opinion in ophthalmology. 2014;25(5):461-469.

[2] Solish N. Commentary on Aesthetic Treatment With Botulinum Toxin. Dermatologic surgery : official publication for American Society for Dermatologic Surgery [et al]. 2017;43 Suppl 2:S157.

[3] S.H. Dayan, J.P. Arkins, A.B. Patel, T.J. Gal. A double-blind, randomized, placebo-controlled health-outcomes survey of the effect of botulinum toxin type A injections on quality of life and self-esteem. Dermatol Surg, 36 (Suppl 4) (2010), pp. 2088-2097

[4] A. Carruthers, N. Sadick, F. Brandt, et al. Evolution of facial aesthetic treatment over five or more years: a retrospective cross-sectional analysis of continuous onabotulinumtoxinA treatment. Dermatol Surg, 41 (2015), pp. 693-701

[5] Dermal Fillers Approved by the Center for Devices and Radiological Health. https://www.fda.gov/medical-devices/cosmetic-devices/dermal-fillers-approved-center-devices-and-radiological-health-0#approved Accessed June 24, 2020.

[6] Revance Therapeutics, Inc. Clinical Overview for Daxibotulinumtoxin A, November 24, 2019.

[7] Revance Therapeutics, Inc. Clinical Safety Overview for Daxibotulinumtoxin A, November 24, 2019.

[8] Li-Masters, Tong. Clinical Review for Daxibotulinumtoxin A, July 1, 2010.

[9] Revance Therapeutics, Inc. Prescribing Information for Daxibotulinumtoxin A, November 24, 2019.

[10] Ahn CS, Davis SA, Dabade TS, Williford PM, Feldman SR. Cosmetic procedures performed in the United States: a 16-year analysis. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al]. 2013;39(9):1351-1359.

[11] Guidance for Industry Upper Facial Lines: Developing Botulinum Toxin Drug Products. August 2014; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/upper-facial-lines-developing-botulinum-toxin-drug-products. Accessed July 7, 2020.

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