CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761085Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	761085
PDUFA Goal Date	05/15/2018
OSE RCM #	2017-93
Reviewer Name(s)	Charlotte Jones, MD, PhD, MSPH
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	December 21, 2017
Subject	Evaluation of Need for a REMS
Established Name	DWP-450 Botulinum Toxin, Type A
Trade Name	Jeuveau
Name of Applicant	Evolus, Inc
Therapeutic Class	Botulinum Toxin
Formulation(s)	Single Use 100 Unit vial
	Reconstituted to 4 units/0.1ml
Dosing Regimen	4 units intramuscularly into each of 5 sites

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Jeuveau (Botulinum Toxin A DWP-450) is necessary to ensure the benefits outweigh its risks. Evolus, Inc. (Evolus) submitted a Biologic Licensing Application BLA 761058 for DWP-450 with the proposed indication of 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 DWP-450 include distal spread of botulinum toxin and eyelid ptosis. The applicant did not submit a 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.

In 2009 the first REMS was approved for a Botulinum Toxin Dysport, to address the safety concern of distal spread of toxin effect and lack of interchangeability of licensed botulinum toxin. The REMS included a medication guide, and communication plan.[1] In 2012, after an evaluation of post marketing data and the lack of new safety signals, the REMS was eliminated.[1] The safety profile of DWP-450 is consistent with other botulinum toxins with the same indication. DRISK has determined that a REMS is not needed to ensure the benefits of DWP-450 Botulinum Toxin A (Jeuveau) outweigh its risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Jeuveau ((DWP-450 Botulinum toxin, Type A (DWP-450)) is necessary to ensure the benefits outweigh its risks. Evolus Inc (Evolus) submitted a Biologics Licensing Application (BLA) 761058 for DWP-450 with the proposed indication of temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or 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 REMS with this application but proposed a medication guide (MG) as part of labeling and inclusion of the class wide boxed warning for distal spread of the effects of botulinum toxin.

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2 Background

2.1 PRODUCT INFORMATION

DWP-450, a new molecular entity, is a botulinum toxin proposed for temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and or procerus muscle activity.[a] Botulinum toxin works by blocking the release of acetylcholine in the neuromuscular junction, thereby decreasing muscle contractions. DWP-450 is reconstituted to a 4 units/ 0.1ml solution from a 100 unit vacuum dried powder. The product will be manufactured in a single-use vial and is to be reconstituted and administered intramuscularly. DWP-450 is not currently approved in any jurisdiction.

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

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761085 relevant to this review:

- 05/15/2017: NDA 761085 submission for the temporary improvement in the appearance of glabellar lines was received.
- 09/15/2017: Day 120 Safety Update Report received. Sponsor identified no new safety data during the interval period of 5/15/2017- 9/01/2017.
- 10/25/2017: A Mid-cycle meeting was held where the Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for DWP-450.[2]

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE CONDITION

DWP-450 is being developed to treat the progressive development of facial lines that are associated with aging, which is an aesthetic 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.[3] Botulinum toxin use is the most common of the nonsurgical aesthetic procedures.[c4]

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 in Table 1.

[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.*

Table 1 Botulinum Toxins Indicated for the Treatment of Glabellar Lines

Product Trade Name (Generic) Year of Approval	Indication	Dosing/Administration	Important Safety and Tolerability Issues	Risk Management Approaches/Boxed Warning, Medication Guide
Botox Cosmetic* (OnabotulinumtoxinA) Approval 1991	Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity Moderate to severe lateral canthal lines associated with orbicularis oculi activity Moderate to severe forehead lines associated with frontalis muscle activity	Botox Cosmetic is administered by intramuscular injection Glabellar Lines Administration: 0.1 mL (4 Units) into each of 5 sites, for a total dose of 20 Units (2.3) Lateral Canthal Lines Administration: 0.1 mL (4 Units) into each of 3 sites per side (6 total injection points), for a total of 24 Units Forehead Lines Administration: 0.1 mL (4 Units) into each of 5 forehead line sites (20 Units) with 0.1 mL (4 Units) into each of 5 glabellar line sites (20 Units), for a recommended total of 40 Units (2.3)	Potency Units of BOTOX Cosmetic are not interchangeable with other preparations of botulinum toxin Spread of toxin effects; swallowing and breathing difficulties can lead to death. Potential serious adverse reactions after administration of BOTOX for unapproved uses Adverse event reports have been received involving the cardiovascular system, some with fatal outcomes. Use caution when administering to patients with pre-existing cardiovascular disease. Concomitant neuromuscular disorder may exacerbate clinical effects of treatment Use with caution in	Boxed Warning for Distal Spread of Toxin Medication Guide

			patients with compromised respiratory function or dysphagia	
Dysport abobotulinum toxinA Approval 2009	The temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age	Administer a total dose of 50 Units, divided in five equal aliquots of 10 Units each, intramuscularly to affected muscles to achieve clinical effect	The potency Units of DYSPORT® are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT® cannot be compared to or converted into units of any other botulinum toxin products Recommended dose and frequency of administration should not be exceeded Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties Concomitant neuromuscular disorder may exacerbate clinical effects of treatment DYSPORT® contains human albumin. There is a risk for transmission of Creutzfeldt-Jakob disease (CJD) however, no cases of transmission of viral diseases or CJD have ever been identified for albumin	Boxed Warning for Distal Spread of Toxin Medication Guide

Xeomin incobotulinumtoxinA Approval 2010	temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity	Glabellar Lines: recommended dose is 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; wait a minimum of three months before retreatment	Respiratory, speech, or swallowing difficulties: Increased risk if bilateral neck muscle injections are needed or with pre-existing muscular disorders; immediate medical attention may be required The potency Units of XEOMIN are not interchangeable with other preparations of botulinum toxin products Corneal exposure and ulceration: protective measures may be required Risk of ptosis: follow dosage recommendations	Boxed Warning for Distal Spread of Toxin Medication Guide

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 this application consisted of EV-001 (NCT02334423) and EV-002 (NCT02334436). These were two similar US based, double-blind, placebo controlled, multicenter studies that evaluated the impact of DWP-450 injections. The primary endpoint consisted of "responders" where both the investigator and subject identified a greater than 2-point improvement in the assessment of glabellar lines at maximum frown and rest on day 30. The FDA biostatistics reviewer

documented that the data demonstrated that for the combined pivotal studies demonstrated a statistically significant p<0.001 difference between responders in the treated group and the placebo group for the primary endpoint.[d]

Additionally, there were three other studies which informed the safety population: a European trial for efficacy EV-003 (no NCT number) which included a Botox comparison group, and two long term studies EV-004 (NCT02184988), and EV-006 (NCT02428608). The latter two studies were multi-dose open label studies completed in multiple sites in the US.[6] The subjects in the long term open label studies could receive up to 4 doses of botulinum toxin.[e]

Table 2 Efficacy Results for the Primary and Secondary Endpoints for Trials EV-001 and EV-002 (Reviewer's Analysis)[7]

	Trial EV-001			**Trial EV-002**		
	DWP-450	Placebo	P-Value	DWP-450	Placebo	P-Value
	N= 246	N=84		N=246	N=78	
% of Subjects who experienced a >2-point improvement in glabellar lines assessed by investigator and subject at maximal frown	66%	1%	<0.001	69%	1%	<0.001

5 Risk Assessment & Safe-Use Conditions[f]

The safety population for this product is comprised of 2116 patients who received at least one dose of DWP-450, BOTOX, or placebo in the 5 studies encompassing the DWP-450 development program. Of these, 1659 subjects received treatment with DWP-450. The two common adverse events that were

[d] 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.

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

[f] 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.

reported by more than 5% of subjects and assessed as related to study drug were headache and eyelid ptosis. The clinical and statistical reviewer found there was no statistical difference in the frequency of headache between Placebo and DWP-450 subjects. Eyelid ptosis is described below in adverse events of special interest.

5.1 DEATHS

There was a single death during the development program; a female subject who had been diagnosed with breast cancer prior to study entry had a bilateral mastectomy after her first treatment. This subject subsequently had a second serious adverse event when she died as a result of a drug overdose with Xanax and Restoril 138 days after the initial treatment. This death was considered by the clinical reviewer as unrelated to the study drug.

5.2 SERIOUS ADVERSE EVENTS

Serious adverse events occurred in 32/1659 (1.9%) of subjects who received DWP-450. There were two severe adverse events that occurred in treated subjects: Headache affected 6/1659, 0.4% of DWP-450 treated subjects and breast cancer 3/1659, 0.2%. No serious adverse events were assessed by the clinical reviewer as related to the study drug. Three subjects discontinued the study due to serious adverse events, one BOTOX subject discontinued due to cardia valve fibroelastoma, two DWP-450 subjects withdrew due to serious adverse events: 1 due to a transient ischemic attack, and 1 due to death described in section 5.1

5.3 ADVERSE EVENTS OF SPECIAL INTEREST

Eye disorders were reported by 32/1659 (1.9%) of DWP-450 Subjects, 4/246 (1.6%) of Botox subjects, and no pooled placebo subjects. Eyelid ptosis occurred in 24/1659 (1.4%) subjects receiving DWP-450, and no Botox or placebo patients. Among the 24 subjects, there were no episodes of severe eyelid ptosis; 3 subjects experienced moderate events and twenty-one had episodes categorized as mild.

Potential hypersensitivity reactions were reported by 30/1659 (1.8%) of DWP-450 subjects, 5/246 (2.0%) of Botox subjects and 3/211 (1.4%) of placebo subjects. None of the reactions were serious and none led to study discontinuation. The clinical reviewer found no evidence that this product causes more hypersensitivity in this population than any of the other botulinum toxin products for the treatment of glabellar lines.

6 Expected Postmarket Use

Botulinum toxin for cosmetic use is likely to be prescribed and administered in the outpatient setting by plastic surgeons and dermatologists. These specialties constitute up to 70% of the physician population providing cosmetic procedures.[8]

7 Risk Management Activities Proposed by the Applicant

The applicant has included in the proposed label the boxed warning required for all Botulinum Toxin products advising of the risk of distal spread, as well as a MG.[9]

8 Discussion of Need for a REMS

Based on the ongoing review the Clinical Reviewer recommends approval of DWP-450 on the basis of the efficacy and safety information currently available.

DWP-450 is a botulinum toxin that is indicated for the cosmetic treatment of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. Use of botulinum toxin as a temporary cosmetic procedure to improve wrinkle appearance is a very common procedure.

The development program for DWP-450, which included 3 efficacy trials and 2 long term extension studies, supports that DWP-450 is effective in achieving the desired cosmetic effect with an acceptable safety profile.

DWP-450, as a botulinum toxin, carries the serious risk of distal spread that can cause life threatening swallowing and breathing difficulties which could lead to death. In 2012 after an evaluation of post marketing data and lack of new safety signals, the REMS requirement originally approved in 2009, for botulinum toxins was eliminated by the FDA.[1] The class of products continues to carry a boxed warning and MG in their labeling addressing this risk. Since the risks associated with DWP-450 are risks for the entirety of the class of botulinum toxins, and do not appear to exceed those of the other approved products, nor are there any serious safety risks that are unique to DWP-450, a boxed warning and a medication guide, to inform prescribers and patients of the risk of distal spread of toxins will be included in the labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Jeuveau (DWP-450 Botulinum Toxin A) to ensure the benefits outweigh the risks. At the time of this review, the final evaluation of safety information was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

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