CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761085Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th><strong>Application Type</strong></th>
<th>BLA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application Number</strong></td>
<td>761085</td>
</tr>
<tr>
<td><strong>PDUFA Goal Date</strong></td>
<td>05/15/2018</td>
</tr>
<tr>
<td><strong>OSE RCM #</strong></td>
<td>2017-93</td>
</tr>
<tr>
<td><strong>Reviewer Name(s)</strong></td>
<td>Charlotte Jones, MD, PhD, MSPH</td>
</tr>
<tr>
<td><strong>Team Leader</strong></td>
<td>Donella Fitzgerald, Pharm.D.</td>
</tr>
<tr>
<td><strong>Deputy Division Director</strong></td>
<td>Jamie Wilkins Parker, Pharm.D.</td>
</tr>
<tr>
<td><strong>Review Completion Date</strong></td>
<td>December 21, 2017</td>
</tr>
<tr>
<td><strong>Subject</strong></td>
<td>Evaluation of Need for a REMS</td>
</tr>
<tr>
<td><strong>Established Name</strong></td>
<td>DWP-450 Botulinum Toxin, Type A</td>
</tr>
<tr>
<td><strong>Trade Name</strong></td>
<td>Jeuveau</td>
</tr>
<tr>
<td><strong>Name of Applicant</strong></td>
<td>Evolus, Inc</td>
</tr>
<tr>
<td><strong>Therapeutic Class</strong></td>
<td>Botulinum Toxin</td>
</tr>
<tr>
<td><strong>Formulation(s)</strong></td>
<td>Single Use 100 Unit vial</td>
</tr>
<tr>
<td></td>
<td>Reconstituted to 4 units/0.1ml</td>
</tr>
<tr>
<td><strong>Dosing Regimen</strong></td>
<td>4 units intramuscularly into each of 5 sites</td>
</tr>
</tbody>
</table>
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. In 2012, after an evaluation of post marketing data and the lack of new safety signals, the REMS was eliminated. 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.

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. 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.

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

Reference ID: 4199354
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.³ 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.⁴

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.

---

³ 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.
⁴ 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

<table>
<thead>
<tr>
<th>Product Trade Name (Generic)</th>
<th>Indication</th>
<th>Dosing/Administration</th>
<th>Important Safety and Tolerability Issues</th>
<th>Risk Management Approaches/Boxed Warning, Medication Guide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox Cosmetic* (OnabotulinumtoxinA)</td>
<td>Moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity</td>
<td>Botox Cosmetic is administered by intramuscular injection.</td>
<td>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.</td>
<td>Boxed Warning for Distal Spread of Toxin Medication Guide</td>
</tr>
<tr>
<td>Approval 1991</td>
<td>Moderate to severe lateral canthal lines associated with orbicularis oculi activity</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate to severe forehead lines associated with frontalis muscle activity</td>
<td>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).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4199354
| 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 |

Reference ID: 4199354
In addition to the botulinum toxins there are a number of facial fillers approved by the FDA. 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 vision, 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.\textsuperscript{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.\textsuperscript{e} The subjects in the long term open label studies could receive up to 4 doses of botulinum toxin.\textsuperscript{e}

<table>
<thead>
<tr>
<th>% of Subjects who experienced a &gt;2-point improvement in glabellar lines assessed by investigator and subject at maximal frown</th>
<th>Trial EV-001</th>
<th>Trial EV-002</th>
</tr>
</thead>
<tbody>
<tr>
<td>DWP-450</td>
<td>Placebo</td>
<td>P-Value</td>
</tr>
<tr>
<td>N= 246</td>
<td>N=84</td>
<td></td>
</tr>
<tr>
<td>66%</td>
<td>1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

5 Risk Assessment & Safe-Use Conditions\textsuperscript{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

\textsuperscript{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.

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

\textsuperscript{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.

Reference ID: 4199354
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLOTTE T JONES
12/21/2017

JAMIE C WILKINS PARKER
12/21/2017