CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: June 18, 2010

To: Russell Katz, MD, Director
Division of Neurology Products (DNP)

Thru: Mary Willy, Ph.D., Deputy Director
Division of Risk Management (DRISK)

Mary Willy 6/18/10

From: XEOMIN Review Team

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Subject: REMS Review

Drug Name(s): XEOMIN® (incobotulinumtoxinA)

Submission Number:

Application Type/Number: BLA 125360

Applicant/sponsor: Merz Pharmaceuticals

OSE RCM #: 2009-1464

1 INTRODUCTION

This review follows a request from the Division of Neurology Products (DNP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Xeomin® (incobotulinumtoxinA).

Merz Pharmaceuticals submitted BLA 125360 for Xeomin® (incobotulinumtoxinA) July 6, 2009, with the proposed indications for the treatment of cervical dystonia (spasmodic torticollis), benign essential blepharospasm, (b) (4) Xeomin® is approved in Argentina, Canada, Mexico, Uruguay, and several European countries for the treatment of blepharospasm and cervical dystonia (spasmodic torticollis) in adults. In Canada, Xeomin® is also approved for the indication of post-stroke spasticity of the upper limb. In Argentina, Xeomin® is also approved for a variety of other indications, including focal spasticities, strabismus, and the temporary improvement of glabellar frown lines.

1.1 BACKGROUND

(b) (4)

the current application is being reviewed for the proposed indications of blepharospasm and cervical dystonia.

The initial BLA submission included a proposed REMS in the European Union Risk Management Plan (EU RMP) format. Merz resubmitted the proposed REMS in the appropriate REMS format on August 13, 2009; however this did not include the Supporting Document. Merz resubmitted the REMS with a Supporting Document on September 1, 2009.

The proposed REMS for Xeomin® addresses the risks of medication errors related to the lack of interchangeability of units of other licensed botulinum toxin products and the spread of toxin effect beyond the injection site. The proposed REMS consists of a Medication Guide (MG), Communication Plan (Dear Healthcare Provider Letter disseminated at the time of product approval), and Timetable for Assessment (18 months, 3 years, and 7 years). Similar REMS are approved for all currently licensed and marketed botulinum toxin products to address these risks, as they affect the entire class.

Merz received interim REMS comments February 19, 2010, and resubmitted the proposed REMS with edits March 1, 2010.

2 MATERIAL REVIEWED

The following document(s) were reviewed:

- Merz Pharmaceuticals revised proposed REMS submission submitted August 13, 2009, September 1, 2009, and March 1, 2010
- DRISK Xeomin REMS Interim Review, dated February 17, 2010 (sent February 19, 2010)
- Merz Pharmaceuticals proposed Prescribing Information (PI) for Xeomin® (incobotulinumtoxinA) injection, submitted September 1, 2009
- FDA email to Merz Pharmaceuticals re: REMS request, August 6, 2009, and August 28, 2009
- Merz original REMS submission received July 6, 2009
- Approved REMS and REMS supporting Documents for Botox, Myobloc, and Dysport

3 PROPOSED REMS

3.1 GOALS

The goals of the REMS are to:

- Minimize the risks of medication errors related to the lack of interchangeability of Xeomin® units with those of licensed botulinum toxins of other manufacturers; and
- Inform prescribers and patients about the potential occurrence of spread of toxin effect beyond the injection site.

3.2 REMS ELEMENTS

The REMS includes a MG, communication plan, (b) (4) . Each element of the REMS is described below. The REMS document is appended in Appendix A.

3.2.1 Medication Guide

A Medication Guide will be dispensed with each vial of Xeomin® in accordance with 21 CFR 208.24. The Medication Guide will be provided with each single vial of Xeomin®.

The label of each container or package of Xeomin® will include a prominent instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and state how the Medication Guide is provided.

The DRISK review of the proposed Medication Guide will be completed under separate cover.

3.2.2 Communication Plan

Merz will implement a communication plan consisting of a Dear Healthcare Professional (DHCP) Letter disseminated (b) (4) product approval. The DHCP Letter will be distributed to neurologists, physiatrists, and other specialties and healthcare professional staff who prescribe or inject Xeomin® or other licensed botulinum toxin products (i.e., physical medical and rehabilitation specialists, dermatologists, ophthalmologists and other specialists who have previously dispensed botulinum toxins).

The DHCP Letter will be distributed by mail (b) (4) and will also be presented to physicians when called upon by Merz sales representatives to convey the risks outlined in the REMS.

Please see the appended Dear Healthcare Professional Letter in Appendix B.

3.2.3 Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use.

3.2.4 Implementation System

An implementation system is not a required component of the proposed REMS if there are no elements to assure safe use.

3.3 Assessment of the REMS

Merz will submit REMS Assessments to FDA at 18 months, 3 years, and 7 years from the date of the initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Merz will submit each assessment so that it will be received by the FDA on or before the due date.

3.4 INFORMATION NEEDED FOR ASSESSMENT (REMS ASSESSMENT PLAN)

Information needed for assessment is not a required element of the REMS Proposal. However, this information should be addressed in the REMS approval letter and discussed in the REMS supporting documents. The REMS and supporting document submitted on September 1, 2009 did not contain a REMS assessment plan; therefore, it was requested in the interim comments dated February 17, 2010 and resubmitted March 1, 2010.

Information needed for assessment will include but is not limited to:

1. A survey of patients' understanding of the serious risks of Xeomin®.
2. A survey of prescribers' understanding of the serious risks of Xeomin® and the lack of interchangeability of Xeomin® units with those of other licensed botulinum toxin products.
3. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
4. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.
5. An assessment of use data including:
    a. extent of use (denominator estimates)
    b. number of patients by age
6. A summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection with Xeomin®.
7. A summary of reports of all medication errors involving interchangeability of Xeomin® units with those of other licensed botulinum toxin products.
8. Verification of sources of recipient lists for the Dear Healthcare Provider Letter
9. Number of recipients on each mailing list
10. Date(s) of mailing
11. Copy of document(s) included in the mailing

3.4.1 Knowledge, Attitude and Behavior Surveys

Knowledge, Attitude, and Behavior (KAB) surveys will be conducted with healthcare providers and patients in order to assess their comprehension of the risks of Xeomin® as described in the Communication Plan and Medication Guide. The surveys will also measure compliance with distribution of the Xeomin® Medication Guide by querying patients about whether they received a copy of the Medication Guide when their prescription for Xeomin® was dispensed and by querying HCPs about whether they received a copy of the DHCP letter.

Surveys will be conducted and submitted with the 18 month, 3 year, and 7 year assessments. Merz submitted proposed physician and patient surveys as part of their August 13, 2009, submission. Comments on the surveys were provided to Merz as part of the interim comments sent February 19, 2010. Merz was advised that they will need to develop and submit the methodology in conjunction with the surveys after the product labeling and Medication Guide are finalized. FDA advised Merz to submit these documents at least 90 days before the surveys are administered.

4 DISCUSSION AND CONCLUSION

The proposed Xeomin® REMS mirrors the REMS requirements of other botulinum toxin products. No additional risks have been identified. Therefore, the Division of Risk Management and the Xeomin® REMS Review Team find the REMS for Xeomin® acceptable once the sponsor accepts the recommended changes in the REMS document and Dear Healthcare Professional Letter (see Appendices A-B attached).

OSE recommends approval of the appended Xeomin® REMS.

We have the following comments for DNP:

We recommend incorporating the information needed for assessment of the REMS into the approval letter.

Information needed for assessment will include but is not limited to:

1. A survey of patients' understanding of the serious risks of Xeomin®.
2. A survey of prescribers' understanding of the serious risks of Xeomin® and the lack of interchangeability of Xeomin® units with those of other licensed botulinum toxin products.
3. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
4. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.
5. An assessment of use data including:
    a. extent of use (denominator estimates)
    b. number of patients by age
6. A summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection with Xeomin®

7. A summary of reports of all medication errors involving interchangeability of Xeomin® units with those of other licensed botulinum toxin products
8. Verification of sources of recipient lists for the Dear Healthcare Provider Letter
9. Number of recipients on each mailing list
10. Date(s) of mailing
11. Copy of document(s) included in the mailing

We have the following comments for the sponsor:

1. Please see attached REMS document and DHCP Letter for track changes (Appendices A-B). Revise the Supporting Document to be consistent with these changes in the REMS.
2. The timetable for submission for REMS assessment communicated in our interim comments was in error; the correct timetable is 18 months, 3 years, and 7 years. This has been corrected in the REMS document.

5 pages withheld immediately following this page as B4 (draft labeling)

MEMORANDUM	Department of Health and Human Services Public Health Service Food and Drug Administration Center for Drug Evaluation and Research

DATE: June 1, 2010

TO: BLA 125-360

THROUGH: Suzanne Barone, Ph. D. Team Leader
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

FROM: Kendra Biddick, CSO
Compliance Risk Management and Strategic Problem Solving Team
Division of Compliance Risk Management and Surveillance
Office of Compliance

SUBJECT: Xeomin (incobotulinumtoxinA) BLA 125360 proposed REMS submission of August 13, 2009

This memo provides comments and recommendations from the CDER Office of Compliance (OC) on the proposed REMs for Xeomin (incobotulinumtoxinA) submitted by Merz Pharmaceuticals GmbH on August 13, 2009. It consists of a Medication Guide, a Communication Plan, and a Timetable for Assessments. OC recommendations are listed at the end of the document.

BACKGROUND

In 2007, the Food and Drug Administration Amendments Act (FDAAA) granted the FDA authority to require risk evaluation and mitigation strategies (REMS) to help ensure that the benefits of a drug outweigh the risks. FDAAA also gave the FDA additional enforcement tools including misbranding charges and civil penalties for sponsors that do not follow requirements of an approved REMS.

Mertz has applied for approval of Xeomin (incobotulinumtoxinA) (BLA 125360) for the treatment of adults with cervical dystonia, benign essential blepharospasm (b) (4). (b) (4) Xeomin is a botulinum neurotoxin product that acts as an acetylcholine release inhibitor and peripherally-acting muscle relaxant.

(b) (4)

RECOMMENDATIONS

Comment to OND/OSE

This is another drug of a class with a REMS. The current REMS for the other Botulinum neurotoxins do not have information in the assessments to verify that the communication plan was conducted according to the REMS. We request that this be added in the future to these REMS since it appears that the communication plan is continual and not a one time mailing.

Comments to the Sponsor:

Communication Plan

The communication plan consists of a Dear Healthcare Provider Letter (DHCPL) to healthcare professionals involved in the prescribing, dispensing, or administration of Xeomin, to be distributed at launch. The timetable for submission of assessments section states that Merz will continually review the success of the Communication Plan and make any changes necessary. This suggests that the DHCPL will be distributed more than once.

The communication plan section of the REMS should include:

1. the distribution date of the DHCPL stated relative to the approval date of the REMS (for instance, within 60 days after approval of the REMS).
2. The distribution frequency
3. The duration of the distribution – unless this is going to be ongoing for the duration of the REMS.

The sponsor should be reminded that changes to the DHCPL must be cleared by FDA before use.

Timetable for Assessments

According to FDAAA the timetable for assessments is linked to the date of the approval of the REMS and not the launch of the drug. The OC requests that the following language be substituted for the timetable for assessments proposed by the sponsor, in accordance with the language in the draft REMS guidance:

Mertz will submit REMS Assessments to FDA at 18 months, 3 years and 7 years from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Mertz will submit each assessment so that it will be received by the FDA on or before the due date.