CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

REMS

BLA STN 125360 XEOMIN® (incobotulinumtoxinA)

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

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.

II. REMS ELEMENTS

The XEOMIN® REMS includes a Medication Guide for patients and a Communication Plan.

A. 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.

Please see the appended Medication Guide.

B. Communication Plan

Merz will implement a communication plan consisting of a Dear Healthcare Professional (DHCP) Letter disseminated once within 60 days after 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 and will also be presented to physicians within 60 days after product approval when called upon by Merz sales representatives to convey the risks outlined in the REMS.

Please see the appended Dear Healthcare Professional Letter (See Appendix B).

C. Elements to Assure Safe Use

The REMS for XEOMIN® does not require Elements to Assure Safe Use.

D. Implementation System

The REMS for XEOMIN® does not require an Implementation System.

E. Timetable for Submission of Assessments

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.

APPENDIX B: SUPPORTING DOCUMENT

APPENDIX 1: DEAR HEALTHCARE PROFESSIONAL LETTER

IMPORTANT SAFETY INFORMATION

Dear Healthcare Provider:

Merz Pharmaceuticals, the manufacturer of XEOMIN® would like to notify you that XEOMIN® has been approved for the treatment of adults with cervical dystonia and blepharospasm. With regard to cervical dystonia, XEOMIN® is indicated to reduce the severity of abnormal head position and neck pain in patients. With regard to blepharospasm, XEOMIN® is indicated in adults previously treated with onabotulinumtoxinA (Botox®).

XEOMIN® (incobotulinumtoxinA) inhibits the release of acetylcholine and acts as a peripheral neuromuscular blocking agent.

In order to ensure that the benefits of XEOMIN® treatment outweigh the potential risks of XEOMIN® treatment, a Risk Evaluation and Mitigation Strategy (REMS) has been implemented. 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 other licensed botulinum toxins and
- inform prescribers and patients about the potential for the distant spread of toxin effect beyond the injection site.

Non-Interchangeability of botulinum toxin units:

It is important to note that the potency units of XEOMIN® are specific to the preparation and assay method utilized. They are not interchangeable with licensed botulinum toxins of other manufacturers. Units of biological activity of XEOMIN® cannot be compared to or converted into units of licensed botulinum toxins of other manufacturers.

The recommended total XEOMIN® dose for the treatment of **cervical dystonia** is 120 Units. Doses above 120 Units are not associated with additional relief from the symptoms of cervical dystonia. The dose per muscle should be tailored to the individual patient's need. Previous patient response, duration of effect, and adverse event history should be taken into consideration when determining dose.

In the treatment of **blepharospasm**, only patients previously treated with onabotulinumtoxinA (Botox®) were included in the Xeomin pivotal clinical trials.

The recommended initial dose is 1.25-2.5 Units at each site. The total initial dose should not exceed 70 Units (35 Units/eye). In clinical trials, the average total XEOMIN® dose was up to 35 U per eye The decision regarding the dose, number and location of injections should be influenced by the patient's previous experience with onabotulinumtoxinA (Botox®) injections. Subsequent dosing per muscle should be tailored to the individual patient's need.

XEOMIN® is injected into the medial and lateral orbicularis oculi muscle of the upper lid and the lateral orbicularis oculi muscle of the lower lid. Additional sites in the brow area, the lateral orbicularis muscle and the upper facial area may also be injected if spasms in these areas interfere with vision.

When prescribing XEOMIN® to your patients please take care to appropriately document the unique established drug name of XEOMIN®, "incobotulinumtoxinA" to reduce the potential for medication errors that may arise from confusion between licensed botulinum toxins from different manufacturers.

Spread of Toxin Effect:

All botulinum toxins including XEOMIN® have the potential to cause side effects related to the spread of Botulinum toxin type A to sites distant from the site of administration. These effects are consistent with the pharmacological action of botulinum toxin. The risk of adverse events may be reduced by using the lowest effective dose and not exceeding the recommended dose for each indication.

Closely monitor and use with caution in immobile or sedentary patients, and in patients with weak or atrophied target muscles, peripheral neuromuscular dysfunction, bleeding disorders, in patients receiving anticoagulant therapy, patients with severe muscle weakness (especially with underlying neurological disorders) and in patients with a history of dysphagia or aspiration (see section 5.4 of enclosed PI).

Patients and/or their care partner should be informed of the potential risk of distant spread of botulinum toxin effect associated with the use of XEOMIN®. They should be instructed to recognize the early symptoms of toxicity (difficulty swallowing, breathing, or speaking) and urged to seek immediate medical advice if they experience any of them. Patients and/or their care partner should also be instructed to inform other healthcare providers about their use of botulinum toxin when being treated for other medical conditions.

Distant, Untoward, or Pronounced Effects

Post-marketing reports indicate that the effects of XEOMIN® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat spasticity and cervical dystonia, and at lower doses.

Further information can be found in the XEOMIN® Full Prescribing Information, Section 5.2: Spread of Toxin Effect.

You are advised to discuss the risks associated with XEOMIN® therapy outlined in the enclosed Medication Guide with patients and caregivers. In addition, please share the Medication Guide and Dear Healthcare Provider Letter materials with anyone in your practice who is involved in the preparation, prescribing, and/or injection of XEOMIN®.

The Patient Medication Guide and Full Prescribing Information are also available from your local Merz Pharmaceuticals sales representative, on our website at www.XEOMIN.com or by calling 1-888-493-6646.

Please remember to report suspected adverse reactions associated with XEOMIN® treatment at 1-888-493-6646 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

We look forward to serving you and your patients.

Best regards,
Merz Pharmaceuticals, LLC
Greensboro, NC

APPENDIX 3

Information Needed for REMS Assessments

A. A survey of patients' understanding of the serious risks of XEOMIN®.

B. 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.

C. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

D. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.

E. An assessment of use data including:

   i. extent of use (denominator estimates)

   ii. number of patients by age

F. A summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection with XEOMIN®.

G. A summary of reports of all medication errors involving interchangeability of XEOMIN® units with those of other licensed botulinum toxin products.

H. The extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed.

This information will be submitted at least 90 days before the evaluation is to be conducted.