BLA 125360/S-078

**SUPPLEMENT APPROVAL**
**FULFILLMENT OF POSTMARKETING REQUIREMENTS**

Merz Pharmaceuticals GmbH
Attention: Hadley Iliff, MA, MBA
Director, US Regulatory Affairs
6501 Six Forks Road
Raleigh, NC 27615

Dear Ms. Iliff:

Please refer to your supplemental biologics license application (sBLA) dated October 18, 2019, received October 18, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for Xeomin (incobotulinumtoxinA).

We also acknowledge receipt of your amendment dated August 4, 2020.

This Prior Approval supplemental new drug application provides for the addition of the following indication: Treatment of upper limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

## WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

## CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

## REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirement for all relevant pediatric age groups for this application.

## FULFILLMENT OF POSTMARKETING REQUIREMENT (PMR) UNDER 505(o)

We have reviewed your submission dated October 18, 2019, reporting on the following postmarketing requirement listed in the July 30, 2010, approval letter for BLA 125360 and 125360/S-001.

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[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

2565-3

(Identified as FDAAA PMR #2565-3 for BLA 125360 and BLA 125360/S-001, and PMR #3 in the letter of July 30, 2010.)

Submit safety data assessing distant spread of toxin effects after multiple administrations of Xeomin (incobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years). Approximately one half of the patients must be treated for upper and the other half treated for lower limb extremity spasticity. Patients can be enrolled in either an upper or lower limb safety trial, but not both, and should not receive concomitant botulinum toxin injections for another reason. These safety data could come from open-label extensions of the clinical trials you have committed to perform (see below), from separate longer-term open-label safety trials, or from a long-term controlled safety and efficacy trial. The doses evaluated must be at least as high as those shown effective in these trials, or those commonly used to treat spasticity.

Your supplemental application for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age (BLA 125360/S-078) adequately addresses the PMR pertaining to the assessment of safety in pediatric patients with upper limb spasticity.

The assessment of safety in pediatric patients with lower limb spasticity was considered to be adequately addressed in your April 14, 2017, final report submission for postmarketing commitment (PMC) 2565-5 that was considered fulfilled in the April 13, 2018, Fulfillment of Postmarketing Commitment letter for BLA 125360 and BLA 125360/S-001.

We have reviewed your submissions and conclude that the above requirement was fulfilled.

**FULFILLMENT OF POSTMARKETING REQUIREMENT UNDER PREA**

Your October 18, 2019, submission contains the final report for the following PREA PMR listed in our December 22, 2015, approval letter for BLA 125360/S-067:

3012-2

Randomized, double-blind, adequate and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naïve children age 2-17 years with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. You should propose a method to actively monitor for adverse events related to spread of toxin. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements that are still open.

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

**REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Taura Holmes, PharmD, MS, Senior Regulatory Project Manager, at Taura.Holmes@fda.hhs.gov.

Sincerely,

*{See appended electronic signature page}*

Eric Bastings, MD
Director (Acting)
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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