DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125360/S-067

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENT
RELEASE FROM POSTMARKETING COMMITMENT

Merz Pharmaceuticals
Attention: Patricia Murphy, PhD
Regulatory Affairs Manager
6501 Six Forks Road
Raleigh, NC 27615

Dear Dr. Murphy:

Please refer to your Supplemental Biologics License Application (sBLA), dated February 23, 2015, received February 23, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Xeomin (incobotulinumtoxinA) injection.

This Prior Approval supplemental biologics application provides for the addition of the following indication: treatment of upper limb spasticity in adult patients.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is

identical to the enclosed labeling (text for the package insert and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on December 18, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125360/067**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for children less than 2 years of age because necessary studies are impossible or highly impracticable. This is because the diagnosis of cerebral palsy, the most frequent cause of spasticity in children, is not reliable until children are two years of age and older.

We are deferring submission of your pediatric studies for ages 2 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

3012-1 A juvenile rat toxicology study is required to identify the unexpected, serious risk of adverse effects of Xeomin (incobotulinumtoxinA) on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of Xeomin (incobotulinumtoxinA) on growth, reproductive development, and neurological and neurobehavioral development.

Final Report Submission: 11/10 (submitted)

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).

Final Report Submission: 03/17

Submit the protocol(s) to your IND 110686, with a cross-reference letter to this BLA.

Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

We note that PMR 3012-1 may be addressed by submission of the final report intended to address PMR 2565-1 (identified as postmarketing requirement #1) in the July 30, 2010, approval letter for BLA 125360 and sBLA 125360/001). When submitting the final report, please reference both PMRs 3012-1 and 2565-1 in the cover letter.

RELEASE OF POSTMARKETING COMMITMENT

We remind you of the following postmarketing commitment (PMC) listed in the July 30, 2010, approval letter for BLA 125360 and sBLA 125360/001.

2565-6 (identified as PMC #6 in the letter dated July 30, 2010):

Randomized, double-blind, adequate and well-controlled, multiple fixed-dose, 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 determined that you are released from the above commitment because it is being replaced by PMR 3012-2 above.

FULFILLMENT OF POSTMARKETING COMMITMENT

We have received your submission dated February 23, 2015, received February 23, 2015, containing the final report for the following postmarketing commitment (PMC) listed in the July 30, 2010, approval letter for BLA 125360 and sBLA 125360/001.

2565-8 (identified as PMC #8 in the letter dated July 30, 2010):
Randomized, double-blind, adequate and well-controlled, multiple fixed-dose, parallel group clinical trial of Xeomin (incobotulinumtoxinA) in botulinum toxin-naïve adults 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 commitment was fulfilled.

We remind you that there are postmarketing requirements and commitments listed in the July 30, 2010, approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, RPh, Regulatory Project Manager, via email or telephone at Taura.Holmes@fda.hhs.gov or (301) 796-1932.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Division of Neurology Products

ENCLOSURE: Content of Labeling

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

/s/

ERIC P BASTINGS
12/22/2015