BLA 103000/S-5309

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENTS
FULFILLMENT OF POSTMARKETING COMMITMENT

Allergan, Inc.
Attention: Bonnie Safyurtlu, MS, RAC
Director, Global Regulatory Affairs
2525 Dupont Drive, AND200
Irvine, CA 92623-9534

Dear Ms. Safyurtlu:

Please refer to your supplemental biologics license application (sBLA), dated December 20, 2018, received December 20, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Botox (onabotulinumtoxinA).

This Prior Approval sBLA provides for the addition of the following indication for Botox (onabotulinumtoxinA): Treatment of upper limb spasticity in pediatric patients 2 to 17 years of age.

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 HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we 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, 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 FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 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 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENTS (PMRs) UNDER 505(o) and PREA

Your December 20, 2018, submission contains the final report for the following PMR listed in the April 29, 2009, Supplement Request letter for BLA 103000, March 9, 2010, approval letter for BLA 103000/S-5189, June 1, 2010, Information Request and Fulfillment of Postmarketing Requirements/Commitments letter for BLA 103000, and April 17, 2015, approval letter for BLA 103000/S-5282.

1. PREA PMR 2342-1

   (Identified as PREA PMR #2607-1 for BLA 103000, PMR #1 in the letter of April 29, 2009, PREA PMR #1 in the letter of March 9, 2010, PMR #1 in the letter of June 1, 2010, and PREA PMR #2342-1 in the letter of April 17, 2015.)

[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.

A juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of Botox 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 must evaluate effects of Botox on growth, reproductive development, and neurological and neurobehavioral development.

Your December 20, 2018, submission contains the final report for the following PREA PMR listed in our March 9, 2010, approval letter for BLA 103000/S-5189, and April 17, 2015, approval letter for BLA 103000/S-5282.

2. PREA PMR 2342-2

(Identified as PREA PMR #2 in the letter of March 9, 2010, and PREA PMR #2342-2 in the letter of April 17, 2015.)

Deferred pediatric efficacy study under PREA for the treatment of upper limb spasticity, to decrease the severity of increased muscle tone in the elbow flexors, wrist flexors, and finger flexors in pediatric patients ages 2 years through 16 years 11 months.

Your June 10, 2019, submission contains the final report for the following PREA PMR listed in our March 9, 2010, approval letter for BLA 103000/S-5189, and April 17, 2015, approval letter for BLA 103000/S-5282.

3. PREA PMR 2342-3

(Identified as PREA PMR #3 in the letter of March 9, 2010, and PREA PMR #2342-3 in the letter of April 17, 2015.)

Deferred pediatric long-term safety study (minimum 12 months) under PREA for the treatment of upper limb spasticity in pediatric patients ages 2 years through 16 years 11 months. The doses evaluated must be at least as high as those shown effective in the pediatric efficacy study (PMR #2342-2), or those commonly used to treat upper limb spasticity in pediatric patients, if an effective dose is not identified in the pediatric efficacy study (PMR #2342-2). The study must assess distant spread of toxin effects, and the effects of Botox on blood glucose and alkaline phosphatase. The study report must include safety information on at least 300 patients who received 2 injections over a 6-month period, with at least 100 patients who received 4 injections over a 12-month period, with at least 60 patients who received the highest recommended dose (if any).

We have reviewed your submissions and conclude that the above requirements were fulfilled.

FULFILLMENT OF POSTMARKETING COMMITMENT (PMC) SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

Your December 20, 2018, submission contains the final report for the following FDAAA PMC listed as a PMC subject to the reporting requirements of 21 CFR 601.70 in our June 1, 2010, Information Request and Fulfillment of Postmarketing Requirements/Commitments letter for BLA 103000.

1. FDAAA PMC 2607-4

   (Identified as PMC #4 in the letter of June 1, 2010.)

   Randomized, double-blind, adequately controlled, multiple fixed-dose, parallel-group clinical trial of Botox (onabotulinumtoxinA) in botulinum toxin-naïve children age 2-17 years with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. 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.

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 Prescribing Information 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 *Providing Regulatory Submissions in Electronic and*

Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

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, GWCPM, Senior Regulatory Project Manager, at Taura.Holmes@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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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.

/s/

NICHOLAS A KOZAUER on behalf of ERIC P BASTINGS
06/20/2019 05:37:57 PM