

BLA 103000/S-5310

**SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENTS**

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 supplemental biologics application provides for the addition of the following indication for Botox (onabotulinumtoxinA): Treatment of lower 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 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 Effectuated” (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 REQUIREMENT (PMR) UNDER 505(o)

We have reviewed your submissions dated December 20, 2018, and January 30, 2019, reporting on the following postmarketing requirement listed in the April 29, 2009, Supplement Request letter and June 1, 2010, Information Request and Fulfillment of Postmarketing Requirements/Commitments letter for BLA 103000.

1. FDAAA PMR 2607-2

(Identified as FDAAA PMR #2607-2 for BLA 103000, PMR #2 in the letter of April 29, 2009, and PMR #2 in the letter of June 1, 2010.)

Submit safety data assessing distant spread of toxin effects after multiple administrations of Botox (onabotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years) and 100 adult patients (approximately half upper and half lower limb extremity spasticity).

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>.

In addition, submit data assessing the effects of Botox (onabotulinumtoxinA) on blood glucose and alkaline phosphatase as a marker of bone metabolism. These safety data could come from open-label extensions of the clinical studies, from separate longer-term open-label safety studies, or from a long-term controlled safety and efficacy study. The doses evaluated must be at least as high as those shown effective in these studies, or those commonly used to treat spasticity.

Your supplemental applications for the treatment of upper and lower limb spasticity in pediatric patients 2 to 17 years of age (BLA 103000/S-5309 and BLA 103000/S-5310) adequately address the PMR requirements pertaining to the assessment of safety in pediatric patients with upper and lower limb spasticity.

The January 21, 2016, approval letter for BLA 103000/S-5252 acknowledged that the data contained in your supplemental applications for the treatment of upper and lower limb spasticity in adults (BLA 103000/S-5189 and BLA 103000/S-5252) adequately address the PMR requirements pertaining to the assessment of safety in adult patients with upper and lower limb spasticity.

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

FULFILLMENT OF POSTMARKETING REQUIREMENT UNDER PREA

Your December 20, 2018, submission contains the final report for the following PREA PMR listed in our January 21, 2016, approval letter for BLA 103000/S-5252.

1. PREA PMR 3018-1

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

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

FULFILLMENT OF POSTMARKETING REQUIREMENT UNDER 505(o) and PREA

Your January 30, 2019, submission contains the final report for the following PMR listed in our April 29, 2009, Supplement Request letter for BLA 103000, June 1, 2010, Information Request and Fulfillment of Postmarketing Requirements/Commitments letter for BLA 103000, and January 21, 2016, approval letter for BLA 103000/S-5252.

1. PREA PMR 3018-2

(Identified as FDAAA PMR #2607-2 for BLA 103000, FDAAA PMR #2 in the letter of April 29, 2009, FDAAA PMR #2 in the letter of June 1, 2010, and PREA PMR #3018-2 in the letter of January 21, 2016.)

Pediatric long-term safety study (minimum 12 months) for the treatment of lower limb spasticity in pediatric patients ages 2 to 17 years. The doses evaluated must be at least as high as those shown effective in the pediatric efficacy study (PMR #3018-1), or those commonly used to treat lower limb spasticity in pediatric patients, if an effective dose is not identified in the pediatric efficacy study (PMR #3018-1). 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 the highest recommended dose (if any), and safety information on 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 submission and conclude that the above requirement 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

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>.

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
Director (Acting)
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Medication Guide

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>

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/

ERIC P BASTINGS
10/18/2019 04:27:02 PM