DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103000/S-5252

SUPPLEMENT APPROVAL
RELEASE FROM POSTMARKETING COMMITMENT

Allergan Inc.
Attention: Melina Dass, MS
Senior Manager, Regulatory Affairs
2525 Dupont Drive, P.O. Box 19534
Irvine, California 92623-9534

Dear Ms. Dass:

Please refer to your Supplemental Biologics License Application (sBLA), dated March 30, 2012, received March 30, 2012, and your amendments, submitted under section 351(a) of the Public Health Service Act for Botox (onabotulinumtoxinA).

We acknowledge receipt of your amendment dated July 21, 2015, which constituted a complete response to our January 28, 2013, action letter.

This Prior Approval supplemental biologics application proposes the addition of the following indication: treatment of lower 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

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, 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.

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 spasticity is not reliably diagnosed until after two years of age; therefore, there is a limited population of patients, and the patients are geographically dispersed.

We are deferring submission of 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.

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.

Trial Completion:	05/2017
Final Report Submission:	01/2019

3018-2 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).

Study Completion: 05/2018
Final Report Submission: 01/2019

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.

RELEASE OF POSTMARKETING COMMITMENT

We refer to the following postmarketing commitment (PMC) that was listed as a PMC subject to the reporting requirements of 21 CFR 601.70 in our April 29, 2009, Supplement Request letter and as PMC #3 in our June 1, 2010, Advice and Postmarketing letter for BLA 103000:

2607-3 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 lower 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).

Final Protocol Submission: 05/10
Trial Completion: 05/15
Final Report Submission: 01/16

We have determined that you are released from the above commitment because it is being replaced by PMR 3018-1 described above.

ADDITIONAL POSTMARKETING REQUIREMENT AND COMMITMENT COMMENTS

We acknowledge that the data contained in your supplemental applications for the treatment of upper and lower limb spasticity in adults (sBLA 103000/S-5189 and sBLA 103000/S-5252) adequately address the adult upper and lower limb spasticity requirements for the safety data portion of PMR 2607-2 (identified as PMR #2 in the letters of April 29, 2009, and June 1, 2010):

2607-2 Submit safety data assessing distant spread of toxin effects after multiple administrations of Botox (onabotulinum toxin A), 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). In addition, submit data assessing the effects of Botox (onabotulinum toxin type A) 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.

Final Protocol Submission:	06/10
Trial Completion:	05/15
Final Report Submission:	01/16

However, as noted in our June 1, 2010, letter, in order to completely fulfill PMR 2607-2, you will also need to provide data assessing the distant spread of toxin effects after multiple administrations of Botox, during a minimum period of 12 months, collected in at least 100 pediatric patients, ages 2 to 17 years (approximately half of the patients treated for upper limb and half for lower limb extremity spasticity).

We further acknowledge that PMC 2607-5 (identified as PMCs subject to reporting requirements of 21 CFR 601.70 in the letter of April 29, 2009, and identified as PMC #5 in the letter of June 1, 2010) was determined to be fulfilled in our letter dated May 8, 2014.

We remind you that there are additional postmarketing requirements and commitments listed in the following letters that are still open: December 9, 1991, May 13, 1996, July 9, 1997, November 24, 1997, April 12, 2002, August 23, 2007, April 29, 2009, March 9, 2010, June 1, 2010, October 15, 2010, August 24, 2011, and January 18, 2013.

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
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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
01/21/2016