DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 103000/S-5282

SUPPLEMENT APPROVAL

Allergan, Inc.
Attention: Melina Dass, MS
Senior Manager, Regulatory Affairs
2525 Dupont Drive, P.O. Box 19534
Irvine, California 92632-9534

Dear Ms. Dass:

Please refer to your Supplemental Biologics License Application (sBLA), dated June 17, 2014, received June 17, 2014, submitted under section 351(a) of the Public Health Service Act for Botox (onabotulinumtoxinA).

We acknowledge receipt of your amendments dated August 1 and 26, 2014, January 30, 2015, and April 1, 2015.

The July 17, 2014, submission constituted a complete response to our December 23, 2013, action letter.

This Prior Approval supplemental biologics application provides for the following:

1. Expansion of the existing clinical indication for the treatment of upper limb spasticity in adult patients to include the treatment of the thumb flexors (adductor pollicis and flexor pollicis longus)

2. Increase in the maximum dose to 400 U for upper limb spasticity

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.

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 April 1, 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 103000/5282**." 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 note that pediatric studies for upper limb spasticity were established with the March 9, 2010, approval of sBLA 103000/5189; therefore, no additional pediatric studies are needed at this time.

We are waiving the pediatric study requirement from birth through 23 months of age because the necessary studies are impossible or highly impracticable. Spastic cerebral palsy, the main cause

of spasticity in that age group, 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 through 16 years 11 months for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your March 9, 2010, 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. Per our March 9, 2010, approval letter for sBLA 103000/5189, these required studies are listed below.

#2342-1 (identified as PMR #1 in the letter of March 9, 2010)

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.

Final Protocol Submission:	03/10
Study/Trial Completion:	02/11
Final Report Submission:	12/11

#2342-2 (identified as PMR #2 in the letter of March 9, 2010)

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.

Final Protocol Submission:	06/10
Study/Trial Completion:	05/15
Final Report Submission:	12/16

#2342-3 (identified as PMR #3 in the letter of March 9, 2010)

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).

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

Submit the protocol(s) to your IND 6432, 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.

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:

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

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, PharmD, 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
04/17/2015