DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BLA 103000/5215

APPROVAL
October 15, 2010

Allergan, Inc.
Attention: Mary O'Sullivan, MPH
Senior Director, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612-1599

Dear Ms. O'Sullivan:

Please refer to your supplemental Biologics License Application (sBLA), dated September 28, 2009, received September 29, 2009, submitted under section 351 of the Public Health Service Act for Botox® (onabotulinumtoxinA) Injection.

We also acknowledge receipt of the following amendments dated:

January 6, 2010	May 3, 2010	July 14, 2010	October 14, 2010
January 26, 2010 (2)	May 4, 2010	September 7, 2010	
March 22, 2010	July 1, 2010	October 6, 2010	
April 9, 2010	July 7, 2010	October 11, 2010	

This "Prior Approval" efficacy supplement to your BLA provides for a new indication for the prophylaxis of headaches in adults with chronic migraine.

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 in content to the enclosed labeling text (text for the package insert, 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/U

CM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 103000/5215.**"

Also within 14 days, amend all pending supplemental applications for this BLA, including pending 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.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

The SPL will be accessible via publicly available labeling repositories.

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

We are waiving the pediatric study requirement for ages 0 to 11 years because necessary studies are impossible or highly impracticable. This is because chronic migraine is rare in children under 12 years of age (as chronic migraine typically develops after several years of episodic migraine, which is relatively infrequent below age 12).

We are deferring submission of your pediatric studies for ages 12 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 are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1. Deferred pediatric Placebo-Controlled Efficacy and Safety Study under PREA for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include a prospective baseline observation period of at least 4 weeks followed by a double-blind treatment phase of at least 12 weeks. The study must include an adequate evaluation of dose-response. The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities and allow the use of appropriate rescue treatment. The protocol for this study must be submitted as a Special Protocol Assessment (SPA) and receive Division concurrence prior to the initiation of the study.

Final Protocol Submission: March 31, 2011
Study Completion: September 30, 2016
Final Report Submission: September 30, 2017

2. Deferred pediatric 12-month Open-Label Safety Study under PREA for prophylaxis of headaches in adolescents ages 12 to 17 with chronic migraine. The study must include at least 300 patients who received two BOTOX treatments at clinically relevant doses over a 6-month period (with at least 100 patients treated at the maximum recommended dose), and at least 100 patients who received four BOTOX treatments at clinically relevant doses over a 12-month period (with at least 60 patients treated at the maximum recommended dose). The study must assess local reactions, distant spread of toxin effects, BOTOX effects on blood glucose, and BOTOX effects on alkaline phosphatase (as a marker of bone metabolism). The safety study must include an adequate evaluation of immunogenicity.

Final Protocol Submission: March 31, 2011
Study Completion: September 30, 2017
Final Report Submission: September 30, 2018

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessments**".

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Botox® (onabotulinumtoxinA) was originally approved on July 31, 2009 and a REMS modification was approved on March 9, 2010. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of a revised Medication Guide which includes the addition of the indication for which you are seeking approval.

Your proposed modified REMS, submitted on October 6, 2010 and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on July 31, 2009.

There are no changes to the REMS assessment plan described in our July 31, 2009 letter.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must

include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify submissions containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 103000
REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 103000-PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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
Division of Drug Marketing, Advertising, and Communications
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. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this BLA, to CDERMedWathSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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, please contact Ms. Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:
Package Insert
REMS