DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

APPROVAL

Our STN: BLA STN [103000/5189]

Allergan, Inc.
Attention: Gus Aromin
Director, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612-1599

Dear Mr. Aromin:

Please refer to your supplement to your biologics license application (BLA), dated September 29, 2009, received September 30, 2009 submitted under section 351 of the Public Health Service Act for Botox (onabotulinumtoxinA) Injection.

We also acknowledge receipt of your amendments dated November 13, November 24, December 28, 2009; and your REMS assessment dated January 14, 2010.

Your submission of September 29, 2009 constituted a complete response to our May 22, 2009, action letter.

This supplement to your BLA provides for the use of Botox (onabotulinumtoxinA) Injection for the treatment of upper limb spasticity and proposes modifications to the Medication Guide and the approved Risk Evaluation and Mitigation Strategy (REMS).

Your request to supplement your biologics license application for Botox (onabotulinumtoxinA) has been approved.

CONTENT OF LABELING

Within 14 days of the date of this letter, submit 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. The content of labeling should be submitted by updating your applications by referencing the SPL file submitted to the drug establishment registration and drug listing system. To do this, place a link in your application submissions that directs FDA to your SPL file. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 103000/5189.**" In addition,

within 14 days of the date of this letter, amend any pending supplements for this BLA with content of labeling in SPL format to include the changes approved in this supplement. For additional information on submitting labeling to drug establishment registration and drug listing and to applications, see the FDA guidances at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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

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 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 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.

PMR – 1:.

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:	March 31, 2010
Study Completion:	February 28, 2011
Final Report Submission:	December 31, 2011

PMR-2:

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:	June 30, 2010
Study Completion:	May 31, 2015
Final Report Submission:	January 15, 2016.

PMR-3:

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-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-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 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).

Final Protocol submission:	June 30, 2010
Study Completion:	May 31, 2015
Final Report Submission:	January 15, 2016.

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 Assessment".**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Botox (onabotulinumtoxinA) Injection was originally approved on July 31, 2009. The proposed REMS modification, submitted on December 28, 2009, contains a revised Medication Guide reflecting the addition of upper limb spasticity as an indication.

Your proposed modified REMS, appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. The timetable for submission of assessment 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.

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:

BLA 103000 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 103000
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.

If you have any questions, call Vandna Kishore, R.Ph., Regulatory Project Manager, at (301) 796-4193.

Sincerely,

/ Russell Katz/

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

Enclosures: Appendix A: REMS
Package Insert/Medguide