

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857



Our STNs: BL 103000/5210  
BL 103000/5209

Allergan, Inc.  
Attention: Melina M. Dass, MS, RAC Manager  
Regulatory Operations and Intelligence  
2525 Dupont Drive  
Irvine, CA 92612-1599

Dear Ms. Dass:

Please refer to your supplemental biologics license application submitted under section 351 of the Public Health Service Act for Botox/Botox Cosmetic (onabotulinumtoxinA).

We acknowledge receipt of your submissions dated May 15, 2009; July 1, 2009; July 7, 2009; July 9, 2009; July 9, 2009; and July 27, 2009.

Reference is also made to our letter dated April 29, 2009 notifying you, under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA), of new safety information that we believe should be included in the labeling for Botox/Botox Cosmetic (onabotulinumtoxinA). This information pertains to the increased risk of distant spread of botulinum toxin effects and the lack of interchangeability between botulinum toxin product dosing units. The letter also notified you, under Section 505-1 of the FDCA, that you were required to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) for Botox/Botox Cosmetic (onabotulinumtoxinA).

This supplemental biologics license application provides for revisions to the labeling for Botox/Botox Cosmetic (onabotulinumtoxinA) to include the new safety information, a proposed REMS, and the new USAN-adopted established name, "onabotulinumtoxinA."

We have completed our review of this supplemental application. This application is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### CONTENT OF LABELING

Within 21 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/oc/datacouncil/spl.html>, that is identical in content to the enclosed labeling text (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative

purposes, please designate this submission “Product Correspondence – Final SPL for approved STN BL 103000.”

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

### **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and container labels that are identical to the enclosed draft labels 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 (October 2005)*. 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 STN BL 103000.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Since Botox/Botox Cosmetic (onabotulinumtoxinA) was approved in 1989, we have become aware of information indicating that the use of botulinum toxin products, including Botox/Botox Cosmetic (onabotulinumtoxinA), has been associated with spread of toxin effects from the site of injection to distant sites causing generalized weakness, resulting in hospitalization and, in some cases, death. We have also received postmarketing reports of patients who had received botulinum toxin injections in the head, neck and shoulder areas having symptoms of dysphagia, ptosis, and difficulty holding their heads up. These symptoms are consistent with the local spread of botulinum toxin. Respiratory problems after botulinum toxin injections have also been reported.

We have also become aware of the potential for medication errors related to the lack of interchangeability between botulinum toxin product dosing units. Because there are other marketed botulinum toxin products with different dose to potency ratios, medication errors related to interchanging the products may occur. Some botulinum toxin products will have different units of dosing, even for the same indication such as cervical dystonia. We have determined that medication errors including overdosing and underdosing can occur due to the potential for healthcare providers to substitute one product for another and interchange dose units, and we have received postmarketing reports associated with overdoses.

We consider this information to be “new safety information” as defined in FDAAA.

Your proposed REMS, submitted on July 27, 2009, and 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 REMS assessment plan should include but is not limited to the following:

- A. Results of a survey of patients' understanding of the serious risks of Botox/Botox Cosmetic (onabotulinumtoxinA)
- B. Results of a survey of prescribers' understanding of the serious risks of Botox/Botox Cosmetic (onabotulinumtoxinA)
- C. An assessment of use data including – extent of use (denominator estimates), number of patients by age
- D. A summary of reports of all potential or diagnosed cases of systemic spread of botulinum toxin after local injection with Botox/Botox Cosmetic (onabotulinumtoxinA)
- E. A summary of reports of all medication errors involving interchangeability of Botox/Botox Cosmetic (onabotulinumtoxinA) units with those of other licensed botulinum toxin products
- F. Report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24
- G. Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance
- H. The extent to which the elements of the REMS are meeting the goals of the REMS and whether modifications to the elements or goals are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in 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. 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 505-1(g) could result in enforcement action.

We remind you that 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 the submission containing the REMS assessments or proposed modifications 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**

Since the revised approved product labeling for Botox/Botox Cosmetic contains significant new risk information, the Division of Drug Marketing, Advertising, and Communications requests that all promotional materials for Botox/Botox Cosmetic that include representations about the product be revised to include the new risk information immediately. These revisions should include prominent disclosure of the important new safety information pertaining to the risks related to the BOXED WARNING, WARNINGS, PRECAUTIONS, and OVERDOSE sections in the revised approved product labeling. Please submit a written response to this request on or before August 14, 2009, stating whether you intend to comply with this request, to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications by facsimile at (301) 796-8444 or at 5901-B Ammendale Road, Beltsville, MD 20705.

Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to <http://www.fda.gov/cder/biologics/default.htm> for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

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If you have any questions, please contact Tamy Kim, PharmD, Senior Regulatory Project Manager, at (301) 796-1125.

Sincerely,

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

Susan Walker, MD  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosures: Labeling (Package Insert, Medication Guide, Carton and Container)  
REMS