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Food and Drug Administration  
Center for Biologics Evaluation and Research  
1401 Rockville Pike  
Rockville MD 20852-1448

August 22, 2001

**CBER 01-025**

**WARNING LETTER**

BY FACSIMILE AND CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Mr. David Garbe  
Director, Scientific Information and Medical Compliance  
Allergan, Inc.  
2525 Dupont Drive TL-1L  
P.O. Box 19534  
Irvine, CA 92623-9354

Dear Mr. Garbe:

This letter is in regard to Allergan, Inc.'s (Allergan) promotional activities and materials for the marketing of BOTOX (botulinum toxin type A). As part of its routine monitoring and surveillance program, the Advertising and Promotional Labeling Branch (APLB) has reviewed your promotional activities and materials and has concluded that they are misleading and lacking in fair balance within the meaning of 21 U.S.C. § 352(a) of the Federal Food, Drug, and Cosmetic Act (the Act) and its implementing regulations under Title 21, Code of Federal Regulations, Parts 202 and 601.

You have engaged in repeated promotional activities that suggest the amount of protein in BOTOX minimizes the formation of antibodies. No formal clinical studies have been performed to study BOTOX treatment with different amounts of protein with respect to the formation of antibodies. Additionally, you have repeatedly included favorable data or conclusions from nonclinical studies of BOTOX in a way that suggests they have clinical significance when, in fact, no such clinical significance has been demonstrated. We have previously objected to these activities in Review Memoranda dated December 12, 1998 and September 25, 2000, and untitled letters dated November 7, 2000, February 14, 2001, and April 12, 2001.

Specifically, we have identified a clinical update titled, "Immunologic Considerations" (BTX 0065), and the revised BOTOX Internet website at [www.BOTOX.com](http://www.BOTOX.com), that are misleading and lack fair balance.

## **Misleading**

### Nonclinical Data

Your promotional material contains favorable data or conclusions from nonclinical studies, such as in laboratory animals or in vitro, in a way that suggests they have clinical significance when, in fact, no such clinical significance has been demonstrated. For example, your statements, “In the immunology literature, more frequent injections of a protein antigen have been shown to increase the immunological response,” and “One of the fundamental findings in immunology is that higher amounts of a protein are associated with a higher probability of antibody formation,” are misleading as they are based on animal data, but you fail to clearly define it as such and to note that the clinical significance of the animal data is unknown.

### Unsubstantiated Efficacy Claims

Your promotional materials contain favorable information or conclusions from studies that are inadequate in design, scope, or conduct to furnish significant support for such information or conclusions. For example, the following statements are based on retrospective studies that do not provide sufficient details of study design that permit a valid comparison with a control and a quantitative assessment of drug effect:

“The investigators found a relationship between the neurotoxin complex exposure (dose and, thus, protein load) that patients had received in the preceding year and the percentage of patients who tested positive for neutralizing antibodies.”

“The potential link between neurotoxin complex protein load and antibody formation is also suggested by the ophthalmic literature.”

“It can be derived that incidence of sensitization is not only related to dose exposure in LD<sub>50</sub> units per injection cycle but also nanograms of botulinum toxin exposure per injection cycle (protein load).”

“They suggested that the higher risk of antibody formation in cervical dystonia patients was related to the higher doses per treatment and attendant higher protein load.”

There have been no formal clinical studies performed to compare the formation of antibodies during treatment with botulinum toxin type A (BTX-A) formulations containing different amounts of protein.

In the absence of well-controlled clinical studies, which evaluate the predictive qualities of the Mouse Protection Assay (MPA) and the Frontalis Antibody Test (FTAT) for the potential for clinical response with BTX-A, your statements, “Although the sensitivity of the MPA may be somewhat low, its specificity for predicting clinical responses or treatment failure due to resistance is relatively high” and “Thus, the FTAT may provide physicians with a simple means of detecting the potential for clinical response with BTX-A” are misleading.

Statements that imply that antibody formation in clinical experience with the current BOTOX formulation will be lower than in the original formulations are unfounded. You do not have well-controlled clinical studies to support the statement, “However, due to its lower neurotoxin complex protein load, it is theorized to have a lower antigenic potential than the original formulation.”

#### Unsubstantiated Comparison Claim

Your promotional material contains a representation or suggestion that is not approved or permitted for use in the labeling that BTX-A is better, more effective, safer, has fewer or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience [21 CFR 202.1]. Your comparative claim of superiority, “However, patients who lose their ability to respond are faced with treatments that may be less effective or associated with more adverse events” is misleading.

#### **Lack of Fair Balance**

##### Minimizing Side Effects

You fail to present information relating to side effects and contraindications with a prominence and readability reasonably comparable with the presentation of information relating to effectiveness of the drug, taking into account all implementing factors, such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis [21CFR 202.1]. For example, the safety information contained in the clinical update is in a print size that is smaller than that of the efficacy information.

You minimize the side effects of BOTOX by stating, “All medications have some side effects” at the beginning of the website sections titled, “What Side Effects May Be Experienced When Using BOTOX.” This statement minimizes the risks of treatment with BOTOX by suggesting that it has the same risks as any other medication. You go on to state, “With BOTOX, side effects are usually transient and mild to moderate in nature. Some people notice temporary weakness of muscles or discomfort at the injection site.” Your presentation minimizes the side effects and is not consistent with the approved product labeling which presents this general information after the warnings, precautions, and reports of deaths.

##### Omission of Important Risk Information

You fail to present all of the serious and important risks associated with BOTOX therapy. For example, your website pages that discuss the approved uses of BOTOX and your clinical update fail to present the following risk information:

1. There have been rare spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility, after treatment with botulinum toxin.

2. Cervical dystonia patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia.
3. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.
4. Reduced blinking from BOTOX injection of the orbicularis muscle in blepharospasm patients can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders.
5. Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects, including severe dysphagia and respiratory compromise from typical doses of BOTOX.
6. The effects of BOTOX therapy may be increased with the use of aminoglycoside antibiotics or with other drugs that interfere with neuromuscular transmission.
7. During the administration of BOTOX for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred from needle penetration into the orbit.

Furthermore, in the website sections titled, “What Side Effects May Be Experienced When Using BOTOX,” you state, “With BOTOX, side effects are usually transient and mild to moderate in nature” omitting that adverse events may have a duration of several months and may be severe in intensity, and “Some people notice temporary weakness of muscles or discomfort at the injection site” omitting that weakness of adjacent muscles may also occur due to spread of toxin.

#### **Other Violative BOTOX Promotional Materials**

We have identified the following promotional materials that are misleading and lack fair balance for similar reasons as stated above: a Journal ad (BTX 0101); a CD announcement letter for payers (SIMC01-091); a clinical update mailing, doctor follow-up letter and envelope (BTX 9907); a Questions and Answers Brochure (BTX 0124); a physician guide (BTX 9903); and BOTOX Clinical Update Slides from the [www.BOTOX.com](http://www.BOTOX.com) website.

In addition, the statement “Success that Endures” on the journal ad and the Questions and Answers Brochure is misleading in that it suggests better efficacy than has been shown in adequate and well-controlled clinical studies.

Furthermore, the statement, “Maintaining the response to botulinum neurotoxin therapy,” on the clinical update mailing, doctor follow-up letter, and envelope is misleading since the efficacy of repeated treatments over long periods has not been evaluated in clinical trials; therefore, we do not have a complete understanding of the rate at which individuals cease to seek BOTOX therapy and their reasons for doing so.

**Failure To Submit Promotional Material**

You failed to submit specimens of the revised promotional material for BOTOX on your Internet website at [www.BOTOX.com](http://www.BOTOX.com) at the time of initial dissemination of the revised material.

**Conclusions and Requested Actions**

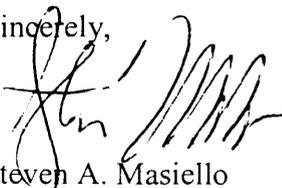
The violations noted in this letter represent continuing examples of violative promotion or advertising materials disseminated by Allergan. You should take prompt action to correct the violations in the noted materials and all promotional materials for BOTOX that contain violations like those outlined in this letter. Failure to promptly correct these violations may result in the initiation of regulatory action by FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

This letter is not intended to be an all-inclusive list of deficiencies that may be associated with Allergan's promotion of BOTOX. It is your responsibility to ensure that materials distributed are in conformance with the requirements of the Act and its implementing regulations.

Your written response with the specific steps that you have taken to correct the violations should be submitted to this office within 10 working days of receipt of this letter. Your response should be directed to the address listed below. If you have any questions involving this matter, please contact Ms. Miller at 301-827-3028. We remind you that only written communications are considered official.

Ms. Catherine A. Miller  
Acting Branch Chief  
Advertising and Promotional Labeling Branch  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
1401 Rockville Pike, Suite 200S  
Rockville, MD 20852-1448

Sincerely,



Steven A. Masiello  
Director  
Office of Compliance and Biologics Quality  
Center for Biologics Evaluation and Research