DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

CBER-03-012

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

VIA FACSIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Mr. Peter A. Kresel
Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92713-9534

June 23, 2003

Dear Mr. Kresel:

This Warning Letter objects to Allergan, Inc.'s dissemination of promotional materials for the marketing of BOTOX® COSMETIC Botulinum Toxin Type A. Specifically, we refer to three journal advertisements for BOTOX® COSMETIC titled, "People Like You" (BTXC142) and (BTXC140) and "We promised to grow old together, not look old together " (BTXC141) that have been disseminated in May and June 2003. The Advertising and Promotional Labeling Branch (APLB) in the Food and Drug Administration's (FDA's) Office of Compliance and Biologics Quality has reviewed these advertisements and has concluded that they are in violation of Section 502(n) of the Federal Food, Drug and Cosmetic Act (the "Act") and its implementing regulations.

The agency has concluded that your journal advertisements are false and/or misleading because they falsely identify your product as a cosmetic treatment, fail to reveal material facts about the product's use, and minimize the risk information presented.

Moreover, we remind you that APLB previously objected, in an untitled letter dated September 5, 2002, to your dissemination of promotional materials for BOTOX® COSMETIC that failed to appropriately communicate the approved indication for use. We are very concerned that by continuing to promote BOTOX® COSMETIC in a false and misleading manner these materials are raising significant public health concerns.

Background

Botulinum Toxin Type A is a drug under section 201(g) of the Food, Drug, and Cosmetic Act (the Act) [21 U.S.C.§ 321(g)] and a biologic, as defined in section 351(i) of the Public Health Service Act, (PHS Act) [42 U.S.C.§ 262]. On December 9, 1991, BOTOX® was approved for the treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia and the treatment of strabismus and blepharospasm associated with dystonia. On April 12, 2002, a supplement to the Botulinum Toxin Type A license application was approved for treatment of glabellular lines. Under this approval, Botulinum Toxin Type A is marketed and labeled for this new indication as BOTOX® COSMETIC.

Misbranding Your Product

Your advertisements misbrand your product by claiming that it is a cosmetic treatment, e.g., "More than half a million people have already been wowed by BOTOX® COSMETIC, **America's most popular cosmetic treatment** [emphasis added]". Your product is a drug as defined in section 201(g) of The Act and a biologic, as defined in section 351(i) of the PHS Act. Your advertisement and promotion of BOTOX® COSMETIC as a cosmetic treatment minimizes the risks associated with the use of this biological drug.

Overbroadening of Indication

Your advertisements misleadingly suggest that this drug is effective, for conditions beyond those that have been approved by the Food and Drug Administration.

The advertisements include the claims, "FDA-approved for the temporary treatment of frown line in people aged 18 to 65" and the phrases: "cause frown lines to form," and, "…the appearance of frown lines."

BOTOX® COSMETIC is not approved for the treatment of "frown lines." The approved indication for use is:

> "BOTOX® COSMETIC is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age."

In our previous untitled letter of September 5, 2002, FDA advised Allergan about the use of the correct indication statement. We stated:

> "In addition, the term "toughest wrinkle" does not adequately specify the approved indication for use and misleadingly suggests that BOTOX® Cosmetic is for use in all tough wrinkles. Please immediately cease distribution of these and similarly worded, materials and revise these statements…to appropriately identify the approved indication for use…"

Allergan's response on October 18, 2002,

> "As requested by the Agency, this revision will be made in subsequently-distributed versions of this guide. It has already been revised on the BOTOX Cosmetic.net website."

Allergan continues to promote BOTOX® COSMETIC in a way that misrepresents the approved indications.

Minimization of risk information

The addition of the statement, "...if any occur...," to your fair balance statement minimizes important risks associated with the use of BOTOX® COSMETIC. In the absence of the presentation of more detailed data associated with the side effects that occur with this biological drug, the inclusion of this terminology minimizes the fact that adverse events do occur. In fact, the clinical trials supporting approval of the glabellar lines indication demonstrated that almost 44% of patients experienced some adverse event. The package insert states:

> "In clinical trials of BOTOX® COSMETIC the most frequently reported adverse events following injection of BOTOX® COSMETIC were headache, respiratory infection, flu syndrome, blepharoptosis and nausea." "Adverse events of any cause [randomized, multi-center, placebo controlled studies] were reported for 177 subjects treated (43.7%) N=405 and 54 placebo treated subjects (41.5%) N= 130." In addition, the package insert includes the following: "In the open-label, repeat injection study, ...adverse events of any type were reported for 49.1% (183/373) of subjects overall."

The statement, "...if any occur...," minimizes the data from the clinical trials which documented that almost one-half of all BOTOX® COSMETIC subjects exhibited adverse events.

Conclusions and Requested Actions

You have disseminated promotional journal advertisements that

fail to disclose that BOTOX® COSMETIC is a biological drug,
2. omit important limitations on the indicated use of the product, and
3. minimize important risk information.

We request that you immediately cease dissemination of these, and all promotional materials that contain the same or similar violations outlined in this letter. You should provide a detailed response to the issues raised in this Warning Letter that includes:

1) Your agreement to immediately cease the dissemination of these advertisements in the magazines and on the your website, and all promotional materials now, and in the future, that contain the same or similar violations outlined in this letter.

2) Providing a plan of action to disseminate accurate and complete corrective information to the audience(s) to which you have disseminated the misleading messages. Any plan must include a specific timeline for implementation.

3) A written statement of your intent to immediately comply with the above requests.

Please respond in writing to APLB within 10 days of the date of this letter, of your intent to comply with APLB's request. If you have any questions or comments, please contact Glenn N. Byrd, MBA, RAC, Chief, APLB, or Maryann Gallagher, by facsimile at 301-827-3528, or at the address listed below.

We remind you that only written communications are considered official.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality, Division of Case Management
Advertising and Promotional Labeling Branch, HFM-602
1401 Rockville Pike, 200S
Rockville, MD 20852-1448

Sincerely,

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

Enclosure
cc: Mr. David Garbe