

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125274Orig1s000

OTHER ACTION LETTERS



Our STN: BL 125274/0

COMPLETE RESPONSE

Ipsen Biopharm Limited
Attention: Steven Scott
Senior Director, Regulatory Affairs
27 Maple Street
Milford, MA 01757

COMPLETED DEC 23 2008

Dear Mr. Scott:

Please refer to your biologics license application, dated November 29, 2007, received November 29, 2007 submitted under section 351 of the Public Health Service Act for Dysport® for injection (Clostridium botulinum toxin type A hemagglutinin complex).

We acknowledge receipt of your amendments dated:

February 14, 2008	March 20, 2008	April 10, 2008	April 18, 2008
April 30, 2008	May 8, 2008	June 11, 2008	June 19, 2008
July 18, 2008	July 21, 2008	August 18, 2008	August 27, 2008
September 10, 2008	September 11, 2008	September 19, 2008	September 19, 2008
September 19, 2008	September 22, 2008	September 23, 2008	September 25, 2008
October 10, 2008	December 5, 2008	December 5, 2008	December 5, 2008
December 8, 2008	December 9, 2008	December 11, 2008	December 11, 2008

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

1. In a December 11, 2008, teleconference, we notified you of a decision that the Agency has made regarding the established names of botulinum toxin products. The Agency concluded that the established name for this product would include a prefix plus the suffix botulinumtoxinA. In response to this teleconference, you submitted four proposed established names; however, these proposed names are unacceptable because the prefixes do not meet our criteria of being devoid of meaning. Since the established name has not been determined, the Risk Evaluation and Mitigation Strategy (REMS) and labeling cannot be finalized. We acknowledge that you have submitted alternative names; these names are under review.

2. In response to our Information Request letter dated November 6, 2008, notifying you that a REMS is required for this application, we note that you submitted your proposed REMS on December 3, 2008. This submission contained the proposed REMS and supporting documents, which included the Dear Healthcare Provider Letter, Dysport Dosing Card, Physician Survey and Patient Survey. After review of these items, we have identified the following deficiencies:

General comments that apply to all REMS documents and materials:

- The new established name should be reflected on the label and all documents related to REMS, including the Medication Guide, educational material, and patient and health care provider surveys. You should also prominently include in all documents related to the REMS, including the Medication Guide, educational material, and patient and health care provider surveys, a statement that “Dysport (established name) is a botulinum toxin product.” In the REMS and in the Dear Healthcare Provider Letter, you should state that, “The potency Units of DYSPORT are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of DYSPORT cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.”
- In the REMS and in the Dear Healthcare provider letter (DHCP), you should provide more detailed information about why a REMS is necessary for your product. As proposed, the general tone of the DHCP Letter suggests that this is a “casual/nice-to-have” program rather than a program required to ensure that the benefits of the drug outweigh the risks of the drug. Since the target audience is the healthcare provider you should provide the labeling language regarding Spread of Toxin Effect (sections 5.2), Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia (section 5.3), and Pre-Existing Neuromuscular Disorders (section 5.4).
- The phrase (b) (4) should be deleted throughout the REMS Documents. In the REMS Goals replace “undesirable effects at sites remote from” with “spread of toxin effect beyond.”
- In the REMS and in the DHCP Letter, state that Dysport is an “acetylcholine release inhibitor and neuromuscular blocking agent” for consistency with the Indications and Usage section of the draft PI. In addition, please remove any reference to a comprehensive series of programs and materials in these documents.
- Delete the second paragraph of the proposed DHCP Letter. Delete the statement, (b) (4) (b) (4) in the fourth paragraph. The statement is promotional in tone and inappropriate in a REMS designed to educate health care providers on the risks of the drug.

- (b) (4)

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated 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>.

Add the following bolded statement or appropriate alternative to the carton and container labels per 21 CFR 208.24(d): "ATTENTION PHARMACIST: Each patient is required to receive the enclosed Medication Guide."

We reserve comment on the draft carton and container labeling until the application is otherwise adequate.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
 - Present tabulations of the new safety data combined with the initial data.
 - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.
6. Provide updated exposure information for the clinical trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

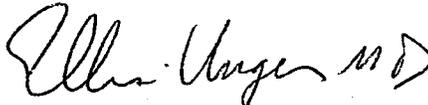
Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application can be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

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

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

Sincerely,



Ellis F. Unger, MD
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosed: Draft Labeling and Medication Guide

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page