CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125274Orig1s000

SUMMARY REVIEW

Office Director Decisional Memo

Date	04/29/09
From	Ellis F. Unger, M.D., Deputy Director (acting), ODE-I
Subject	Office Director Decisional Memo
NDA/BLA #	BLA STN 125274
Applicant Name	Ipsen Biopharm, Limited
Dates of Key Submissions	11/29/07; 12/28/08 (major amendment); 02/27/09 (response to Complete Response Letter)
PDUFA Goal Date	9/28/08, extended (major amendment) to 12/28/08; Based on Response to Complete Response Letter, 04/29/09.
Proprietary Name / Established (USAN) Name	Dysport abobotulinumtoxinA
Dosage Forms / Strength	For injection: lyophilized, 500 Units/single-use 3 mL glass vial (for cervical dystonia indication)
Proposed Indication(s)	…for the treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients.
Action:	***Approval***

Material Reviewed/Consulted	
Medical Officer	Carole L. Davis
Safety Team	Marc Stone, Sally Yasuda
Statistical Review	Ohidul Siddiqui, Kun Jin
Pharmacology Toxicology	Barbara Wilcox, Lois Freed, Paul Brown
CMC Review/OBP	Ennan Guan, Susan Kirshner, Amy Rosenberg
Microbiology	not applicable.
Clinical Pharmacology	Veneeta Tandon, Ramana Uppoor
DDMAC	Amy Tuscano, Michelle Safarik
DSI	Jose Tavarez
CDTL	Devanand Jillapalli
OSE/DMEPA	Walter Fava, Linda Kim-Jung, Denise Toyer, Carol Holquist
OSE/DRISK	Sharon Mills, Jodi Duckhorn
DMPQ	Brenda Uratani, Donald Obenhuber, Patricia Hughes
Director, Division of Neurology Products	Russell Katz

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error and Prevention
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
DMPQ=Division of Manufacturing & Product Quality
OBP=Office of Biotechnology Products
CDTL=Cross-Discipline Team Leader

Introduction

Dysport is a therapeutic biologic product that is a new molecular entity to the US, although it has been marketed in the United Kingdom since 1990 for the treatment of blepharospasm and hemifacial spasm. Subsequently, the product has been licensed in over 70 countries for a number of indications including glabellar lines, blepharospasm, adult post-stroke arm spasticity, hemifacial spasm, cervical dystonia, pediatric cerebral palsy spasticity, and hyperhidrosis. The product is purified Botulinum Toxin Type A, which causes neuromuscular blockade by preventing release of neurotransmitters through fusion of neurosecretory vesicles with the synaptic membrane.

The applicant seeks an indication for the treatment of cervical dystonia, as well as a dermatologic indication, reviewed as a supplement to this NDA by ODE-III. Aside from allergic reactions (which are rare), the main safety concerns are directly related to the Dysport's mechanism of action. The product has the potential to spread to contiguous muscles and cause weakness or paralysis, i.e., "local spread." Of greater concern, however, is the potential for systemic neuromuscular blockade at distant sites. The latter can cause respiratory compromise and death, but is very rare and appears to be largely dose related. These concerns are common to all botulinum products.

Established Name – Interchangeability Issues and Potential Medication Errors

The application was given a Complete Response on December 23, 2008, primarily because the planned established name for Dysport (Botulinum Toxin Type A) was the same as that of Botox, a marketed product that is widely-used. The existence of a single established name for both products would have strongly implied that the two were interchangeable. The units of use and potencies differ between the two products, however, and they are neither interchangeable nor inter-convertible. Lacking distinguishable established names for Dysport and Botox, there would have been substantial potential for medication errors, which could have led to overdoses with fatal consequences.

The Division asked the applicant to propose candidate established names for consideration. They provided four; however, none were deemed acceptable, largely because each conveyed an undesirable meaning (b) (4) . Subsequent to receiving the Complete Response letter, the sponsor proposed "abobotulinumtoxinA" as the established name for Dysport. This has been approved by USAN, and deemed acceptable by the Division.

Spread of Product Effects beyond Injection Site

During review of the BLA, the Division of Neurology Products and Divisions within the Office of Surveillance and Epidemiology evaluated adverse events resembling botulism, associated with marketed botulinum products. The Agency also asked companies with relevant marketed products (Allergan, Inc., marketer of Botox, and Solstice

Neurosciences, Inc., marketer of Myobloc [Botulinum Toxin Type B]) to provide their own analyses of cases suggestive of systemic spread of botulinum toxin. In addition, a Citizen's Petition was submitted by Public Citizen during the initial review cycle (January 23, 2008), requesting various Agency actions related to safety of botulinum products.

As summarized by Dr. Katz, there appeared to be a few cases of "distant spread of the toxin's effect" associated with on-label use; however, nearly all cases were reported in pediatric patients treated for unapproved indications, primarily lower limb spasticity.

Risk Evaluation and Mitigation Strategy (REMS)

Pursuant to its reviews of adverse events with marketed botulinum products, as noted above, the Agency has determined that all botulinum products must include Risk Evaluation and Mitigation Strategies (REMS) because of the risk of systemic spread of toxin after intramuscular injection. For Dysport, the REMS also serves to decrease the potential for medication errors related to the lack of interchangeability of Dysport with Botox and Myobloc, primarily through disparate established names, education of prescribers, a survey to assess the success of educational efforts, and solicitation of reports of medication errors involving interchangeability of Dysport units with those of related products.

Specifically, the REMS (reviewed and agreed to by the applicant) includes:

- A Medication Guide
- A communication plan (a Dear Health Care Provider letter)
- An assessment plan, including:
  - A survey of patients' understanding of the serious risks of Dysport
  - A survey of prescribers' understanding of the serious risks and the lack of interchangeability of Dysport units with those of other botulinum toxin products
  - Periodic assessments of the distribution and dispensing of the Medication Guide
  - A report on failures to adhere to distribution and dispensing requirements; corrective actions to address non-compliance
  - Assessment of use data including extent of use and numbers of patients by age
  - Summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after Dysport treatment
  - A summary of reports of all medication errors involving interchangeability of Dysport units with those of other licensed botulinum toxin products.

There are also 4 postmarketing requirements, 3 non-clinical and 1 clinical:

1. A juvenile rat toxicology study, to identify potential adverse effects on postnatal growth and development

2. A rabbit embryo-fetal development study, to assess Dysport's risk on embryo-fetal development.

3. A study to establish tighter potency acceptance criteria for the qualification of new reference standards, to ensure consistent potency assessment when different reference standards are used.

4. Submission of safety data assessing distant spread of toxin effects after multiple administrations of Dysport for spasticity. The data are be collected in ≥100 pediatric patients and ≥100 adult patients, approximately half of whom have upper, and half lower extremity spasticity, and are to include ≥12 months of use. In addition, the applicant will collect safety data assessing the effects of Dysport on blood glucose and alkaline phosphatase as a marker of bone metabolism. These safety data could be obtained from open-label extension studies of the postmarketing commitments noted below, from separate long-term open-label safety studies, or from a long-term controlled safety and efficacy study.

Postmarketing Commitments:

There are postmarketing commitments for 4 studies to assess the efficacy and safety of Dysport in limb spasticity: each is a ≥12 week, randomized, double-blind, controlled, multiple fixed dose, parallel group study of Dysport in botulinum toxin-naïve patients. The 4 studies are designed to assess upper and lower limb spasticity in pediatric and adult patients (2 sites) X (2 populations) = 4 studies.

Advisory Committee

As noted in the Complete Response letter of 12/23/08, the Division did not refer this application to an FDA advisory committee. Although Dysport is a therapeutic biologic and technically a new molecular entity, its active ingredient (Botulinum toxin Type A) is the same as that of Botox, which was approved under section 351 of the Public Health Service Act in 1991. The pharmacological properties of Botulinum toxin Type A are well-recognized and established, and Dysport's safety and efficacy data are consistent with expectations. The clinical study designs were acceptable, no significant safety or efficacy issues were raised by the application, and no significant public health questions were raised regarding the role of the product in the diagnosis, cure, mitigation, treatment or prevention of a disease. For these reasons, the Division determined, early in the review cycle, that outside expertise was not necessary for consideration of this application, and the Office concurred with that view.

Conclusions

Given that the concerns raised in the Complete Response letter of 12/23/08 have been appropriately addressed: the applicant has obtained an appropriate USAN-approved established name to differentiate the product from other botulinum toxin products, appropriate REMS are being implemented, and there are no ongoing disagreements or controversies among members of the review team, or within OND or OSE, I concur with the Division of Neurology Products' decision to approve Dysport (abobotulinumtoxinA) for the treatment of cervical dystonia.