

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125274

OFFICE DIRECTOR MEMO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: April 29, 2009
FROM: Julie Beitz, MD
SUBJECT: Office Director Memo
TO: BLA 125274/1 (formerly BLA 125286)
Dysport (abobotulinumtoxinA)
Ipsen Biopharm Ltd.

Summary

Botulinum toxin Type A is the active ingredient in Dysport (abobotulinumtoxinA). It is a purified neurotoxin Type A complex produced by the fermentation of *Clostridium botulinum* Type A, Hall Strain. It inhibits release of the neurotransmitter, acetylcholine, from peripheral cholinergic nerve endings; this accounts for its utility in diseases characterized by excessive efferent activity in motor nerves. This memo documents my concurrence with the Division of Dermatology and Dental Product's (DDDP's) recommendation for the approval of the BLA for Dysport (abobotulinumtoxinA) for the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients < 65 years of age.

Description and Dosing

Dysport (abobotulinumtoxinA) is supplied in single use, sterile 500 Unit or 300 U vials for reconstitution intended for intramuscular injection. For dermatologic use, a total dose of 50 U, divided in five equal aliquots should be administered to affected muscles. Retreatment should not occur more frequently than every 3 months.

Regulatory History

Dysport (abobotulinumtoxinA) is under review in two review divisions under different BLAs. BLA 125274 for the treatment of cervical dystonia was originally submitted to the Division of Neurology Products (DNP) on November 29, 2007. On November 6, 2008, FDA notified the applicant (under BLA 125274) that a risk evaluation and mitigation strategy or REMS will be required for DYSPORT (abobotulinumtoxinA) and that the elements of the REMS will be a Medication Guide, Communication Plan, and a timetable for the submission of assessments of the REMS. The applicant submitted a proposed REMS on December 3, 2008. The BLA received a complete response action on December 23, 2008 as the established name had not been determined, and therefore, the product label and proposed REMS could not be finalized. The applicant submitted a complete response on February 27, 2009; that submission has a PDUFA goal date of April 29, 2009.

BLA 125286 was originally submitted to DDDP on March 12, 2008 for the temporary improvement in the appearance of moderate to severe glabellar lines. Submission of a major amendment extended the review clock to April 13, 2009. Action on this application was delayed so that a coordinated action could be taken on the two applications on April 29, 2009. The action letter will state that both indications are approved. BLA 125286 will be converted into efficacy supplement 125274/1 under the parent BLA 125274. BLA 125286 will be voided as of the date of the approval letter.

Neither application was taken before an FDA Advisory Committee because Dysport (abobotulinumtoxinA) is not the first in its class, the clinical study designs were acceptable, no significant safety or efficacy issues

were raised, no significant public health questions were raised regarding the role of the product in the diagnosis, cure, mitigation, treatment or prevention of a disease, and outside expertise was not necessary.

Efficacy

The efficacy of Dysport (abobotulinumtoxinA) was evaluated in three placebo-controlled randomized trials in healthy adults, aged 19-75, with glabellar lines of at least moderate severity at maximum frown. Subjects received either Dysport (abobotulinumtoxinA) 50 Units in five divided doses or placebo. Investigators and subjects assessed efficacy at maximum frown by using a 4-point scale (none, mild, moderate, severe). Treatment success was defined as glabellar line severity of none or mild with at least a two grade reduction from baseline by assessment of both the investigators and subjects on day 30. At day 30, treatment success in Dysport (abobotulinumtoxinA)-treated subjects was 55%, 52% and 60%, respectively, in the three trials; treatment success in placebo-treated subjects was 0% in these trials. The median time to onset of treatment response to Dysport (abobotulinumtoxinA) was three days. Treatment with Dysport (abobotulinumtoxinA) reduced the severity of glabellar lines for up to four months.

Safety

In placebo-controlled trials of Dysport (abobotulinumtoxinA) for treatment of glabellar lines, the most frequently reported adverse events (in at least 2% of subjects) were nasopharyngitis, upper respiratory tract infection, headache, injection site pain or reaction, eyelid edema, ptosis, sinusitis, and nausea.

Some subjects received up to twelve treatments with Dysport (abobotulinumtoxinA). Adverse events were reported in 57% of these subjects and were similar to those reported with less frequent use. Events that emerged in 2-3% of subjects after repeated injections included bronchitis, influenza, pharyngolaryngeal pain, cough, contact dermatitis, injection site swelling and discomfort. The incidence of eyelid ptosis did not increase with repeated injections at intervals of three months or more.

Distant Spread of Toxin Effect. Postmarketing reports indicate that Dysport (abobotulinumtoxinA) and all botulinum toxin products (botulinum toxins Type A and Type B) may spread from the area of injection to produce symptoms consistent with botulinum toxin effect. These symptoms include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported within hours to weeks after injection, and in some cases, swallowing and breathing difficulties have been life-threatening. The risk appears greatest in children treated for spasticity, but symptoms have been reported in adults treated for spasticity and in patients with underlying conditions that would predispose them to these symptoms. Most cases received doses comparable to those used to treat neurologic conditions such as cervical dystonia, or lower doses.

Lack of Interchangeability between Botulinum Toxin Products. One unit of Dysport (abobotulinumtoxinA) corresponds to the calculated median lethal intraperitoneal dose (LD₅₀) in mice. Due to differences in the use of vehicles, dilution schemes, and laboratory protocols for various mouse LD₅₀ assays, Units of biological activity of Dysport (abobotulinumtoxinA) are not interchangeable with, and cannot be compared to or converted to, Units of any other botulinum toxin product assessed with any other specific assay method.

Considerations Regarding Facial Anatomy. Caution should be exercised when administering Dysport (abobotulinumtoxinA) to patients with surgical alterations to the facial anatomy, excessive weakness or atrophy in the target muscle(s), marked facial asymmetry, inflammation at the injection site, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin or the inability to substantially lessen glabellar lines by physically spreading them apart.

Chemistry, Manufacturing, and Controls

Data submitted support the conclusion that the manufacture is well-controlled and leads to a product that is potent and safe when used according to the product label. The product is free from endogenous or

adventitious infectious agents. The product will be placed on lot release. The applicant has agreed to several postmarketing commitments regarding drug substance release specifications, additional characterization tests, potency testing, drug product identity testing, reference standards, and the drug product lot release protocol. The applicant also agrees to develop a 125 Unit single use dosage form appropriate for the dermatologic indication.

Established and Proprietary Names

Because of the potential for medication errors related to the lack of interchangeability of Dysport with other licensed botulinum toxin products, DNP informed the applicant on December 11, 2008 via teleconference that the established name for this product must include a prefix plus the suffix "botulinumtoxinA". After review of several proposed names, FDA found "abobotulinumtoxinA" acceptable.

The proprietary name "Dysport", submitted under BLA 125274, was found acceptable by the Division of Medication Error and Analysis (DMEPA) and DNP. The proprietary name "Reloxin", submitted under BLA 125286, however, was considered to be promotional by the Division of Drug Marketing, Advertising and Communications (DDMAC). Furthermore, the Division of Therapeutic Proteins (DTP), DMEPA, and DDDP concurred that a single name would be preferable from a safety standpoint, since the risks of the product could be expected to affect any patient population administered the product, including the potential for distant spread of botulinum toxin after local injection, and the potential for medication errors related to the lack of interchangeability with other licensed botulinum toxin products.

On April 2, 2009, the applicant was informed via teleconference that "Reloxin" was not acceptable and that the product should be marketed for both indications under the name "Dysport".

Required Pediatric Assessments

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for the temporary improvement in the appearance of moderate to severe glabellar lines because necessary studies are impossible or highly impracticable. This condition does not exist in children.

Postmarketing Requirements under 505(o)

No postmarketing studies or clinical trials will be required under Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 for the dermatologic indication.

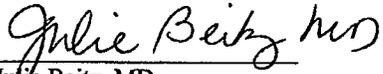
Risk Evaluation and Mitigation Strategy (REMS)

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Dysport (abobotulinumtoxinA) outweigh its risks for dermatology patients. The risks that are addressed in the REMS could be expected to affect any patient population taking Dysport (abobotulinumtoxinA), namely the potential for distant spread of botulinum toxin after local injection, and the potential for medication errors related to the lack of interchangeability of Dysport (abobotulinumtoxinA) with other licensed botulinum toxin products.

In accordance with section 505-1 of the Federal Drug, and Cosmetic Act, FDA has determined that a Medication Guide is required for Dysport (abobotulinumtoxinA). Pursuant to 21 CFR Part 208, FDA has determined that Dysport (abobotulinumtoxinA) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Dysport (abobotulinumtoxinA). FDA has determined that Dysport (abobotulinumtoxinA) is a product that has serious risks of which patients should be made aware because information concerning

the risks could affect patients' decisions to use, or continue to use Dysport (abobotulinumtoxinA) and for which patient labeling could help prevent serious adverse effects related to the use of the product.

The elements of the REMS will be a Medication Guide, Communication Plan, and a timetable for submission of the REMS.



Julie Beitz, MD
Director,
Office of Drug Evaluation III
CDER, FDA