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RESEARCH**

APPLICATION NUMBER:

125274

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 24, 2009
From	Tatiana Oussova, M.D., M.P.H.
Subject	Deputy Director Summary Review
NDA/BLA #	BLA 125286; IND 10,673
Applicant Name	Ipsen Biopharm Ltd.
Date of Submission	March 12, 2008
PDUFA Goal Date	April 13, 2009
Proprietary Name / Established (USAN) Name	TRADENAME (botulinum toxin Type A)
Dosage Forms / Strength	Lyophilized powder/solution
Proposed Indication(s)	Moderate to severe glabellar lines
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Denise Cook, M.D.
Statistical Review	Kathleen Fritsch, Ph.D.
Pharmacology Toxicology Review	Jill Merrill, Ph.D.
CMC Review/OBP Review	Ennan Guan, Ph.D.
Microbiology Review	N/A
Clinical Pharmacology Review	Jang-Ik Lee, Pharm. D., Ph.D.
DDMAC	Andrew Haffer, Pharm.D.
DSI	Roy Blay, Ph.D.
CDTL Review	N/A
OSE/DMEPA	Walter Fava, R.Ph.
OSE/DPV	None
OSE/DRISK	TBD
Other	-

OND=Office of New Drugs
 DDMAC=Division of Drug Marketing, Advertising and Communication
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DPV= Division of Pharmacovigilance
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Reloxin is a new molecular entity indicated to achieve and maintain improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients. Reloxin is a purified botulinum type A toxin product. In the current indication, botulinum toxin type A is administered by multiple small injections directly into the affected muscle.

Reloxin, under the name of Dysport, has been marketed in other countries since 1990 and is currently approved in 73 countries for clinical indications including blepharospasm, hemifacial spasm, spasmodic torticollis, equinus foot deformity due to spasticity in pediatric patients with cerebral palsy, hyperhidrosis, and/or spasticity of the arm and leg in patients following a stroke. It is approved for the cosmetic indication (treatment of facial lines) in 23 countries.

The drug product has not been withdrawn from any market for safety reasons. There has been one Direct Healthcare Professional Communication that was distributed in Europe at the request of the EMEA. This was to revise labeling for all therapeutic botulinum toxins to include information on the potential for adverse events due to the spread of the locally injected neurotoxin.

The only product approved for the treatment of glabellar lines in the United States is Botox Cosmetic. The units of Botox Cosmetic are not interchangeable with the Reloxin drug product.

BLA 125274 was submitted on 12/29/07 to the Division of Neurology under the trade name Dysport, for the treatment of cervical dystonia and is under review.

There are a few outstanding issues with this application.

- The major unresolved issue for this application is the postmarketing safety surveillance. The applicant would be required to submit a REMS.
- The applicant proposed tradename Reloxin was found unacceptable by DMEPA. DMEPA recommendation is to use a single name of Dysport for both indications but the final decision is still pending.
- Due to a safety concern (mainly about contamination of unused portion of a 300U vial), the sponsor would be required to develop a 125U single use dosage form. A supplement for approval of this dosage form will be submitted to the Agency.

2. Background

Reloxin blocks neuromuscular transmission by binding to receptor sites on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings:

The sponsor submitted multiple studies in support of efficacy and safety of Reloxin. A phase 2 dose-ranging study 717 was conducted to determine that 50 units of Reloxin is the appropriate dose to treat glabellar lines. Study 096 established a clinical bridge between the CAMR Reloxin and IBL Reloxin. Study 718, one of the pivotal phase 3 studies, used a CAMR Reloxin instead of the to-be-marketed IBL Reloxin, and study 096 data allowed to use study 718 database in the determination of Reloxin efficacy and safety. Studies 718, 719 and 085 databases were used to establish the efficacy and short-term safety of a single dose of Reloxin 50 units for the treatment of moderate to severe glabellar lines. In addition, study 085 database was used to establish the efficacy of repeated doses of Reloxin 50 units. All those studies were found to be sufficient to support the efficacy of Reloxin at a dose of 50 units in subjects ≤ 64 years of age using composite score 2+ as an endpoint. This composite score denotes that both investigator and subject agreed on a 2+ grade improvement.

Additionally, the sponsor conducted a study 2006-01 using higher doses (50 units – 80 units) of Reloxin based on a muscle mass however the data provided were not adequate to establish efficacy and safety of higher doses.

Studies 720 and 732 provided support for the long-term safety of the product. No significant safety issues were raised by a primary reviewer.

However, there are several concerns related to botulinum toxin products that are already on the market. There were post-marketing reports detailing spread of the toxin to both contiguous and distant sites which led to significant morbidity and in some cases has resulted in death. Other potential risk of medication errors related to the lack of interchangeability between different botulinum toxin products by different manufactures. Those concerns prompted multiple reviews of post-marketing data with the resulting boxed warning and request for a REMS for all botulinum toxin products.

3. CMC/Device

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125286 for Reloxin manufactured by IPSEN, Biopharm Limited.

The total recommended dose is 50 units in single session. Each vial of Reloxin contains 300 units of lyophilized *C. botulinum* toxin type A complex, 125 ug human albumin and 2.5 mg

lactose, free of preservatives. Reloxin is prepared for intramuscular injection by reconstituting each vial with 1 ml of 0.9% sodium chloride for injection USP.

The data submitted in this application support the conclusion that the manufacture of purified *C. botulinum* neurotoxin type A complex (BoNT/A complex), naturally secreted by *C. botulinum*, is well controlled, and leads to a product that is potent and safe, when used according to the label. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs.

The CMC reviewer referred to BLA STN 125274 for Post-Marketing Requirement and Commitment.

I concur with the recommendations. Post-marketing commitments and requirement described in the PMCs/PMRs sections below will provide additional information to assure the continued safety and efficacy of the product.

For more details, please see the original review by the Division of Therapeutic Proteins.

4. Nonclinical Pharmacology/Toxicology

The sponsor has submitted studies to satisfy the Division's request for evaluation of both the local and systemic effects of chronic dosing. No systemic toxicity was observed after single (up to 6 U/rat) or repeat (up to 10 U/rat, up to 20 U/rabbit) intramuscular dosing. There were no compound-related lesions of the muscle groups distant to the injection sites or of the peripheral or central nervous systems. Given the structure and mechanism of action of Reloxin, neither genetic toxicology nor carcinogenicity studies were required.

The sponsor has submitted all required reproductive and developmental toxicology studies (fertility in rats, embryotoxicity in rats and rabbits, peri/postnatal in rats). From the Pharmacology/Toxicology standpoint, Botulinum toxin type A hemagglutinin complex has an acceptable safety profile when administered at the appropriate dose by intramuscular injection. However, accidental systemic exposure (inadvertent intravenous injection) could cause systemic toxicity.

At present (11-19-08) the sponsor is seeking a — flagellin specification for the drug product. The maximum level of flagellin contamination qualified by the reproductive toxicology studies is — %. The maximum level of flagellin qualified by the repeat-dose study to examine the effects at the neuromuscular junction is no more than —. This may be an overestimation of the relative flagellin contamination because flagellin is measured by SDS-PAGE and co-elutes with other small peptides, including nontoxic nonhemagglutinin. Therefore the sponsor will be asked to perform the repeat embryofetal study with drug product containing at least — 'flagellin' contamination. The pharmacology/toxicology recommendation for the final drug product specification should be no higher than the maximum amount qualified nonclinically (i.e., — flagellin), but definitely less than —.

b(4)

The pharmacology/toxicology review team has determined that Reloxin/Dysport should receive a pregnancy category C designation as does BOTOX® (Botulinum toxin type A, marketed by Allergan). The sponsor will be required as a post-marketing commitment to repeat the pivotal rabbit embryofetal study, which is considered inadequate. It is appropriate to require this as a post-marketing commitment rather than pre-approval because although the data is needed for inclusion in the label, it does not effect how women of child bearing potential would be informed (i.e., Pregnancy Category).

I concur with the conclusion made by pharmacology/toxicology review team. Above mentioned PMC would be issued by the Division of Neurology Product. There will be no separate PMC requirement by DDDP.

5. Clinical Pharmacology/Biopharmaceutics

The sponsor claims that Reloxin is not systemically available when administered using the proposed dose and route since the product would not produce measurable blood concentrations when injected locally in nanogram amounts into the target muscles. Preclinical studies conducted in rats by intramuscular (IM) injection of iodinated toxin complex indicate that toxin was not systemically detectable, whether administered in free or complexed form. After periocular injection into the eyelids of rabbits, both the neurotoxin complex and the free neurotoxin remained localized at the injection site and no labeled toxin spread to the eye. The administration of quantities that would result in systemic measurement would produce serious safety concerns due to the resulting untoward pharmacological activity. Thus, the sponsor decided not to conduct pharmacokinetic studies in humans. No drug interaction studies have been conducted.

From Clinical Pharmacology standpoint, there are no outstanding issues with this application that would preclude its approvability.

I concur with the conclusion of pharmacology/toxicology review team. The issue of potential toxicity associated with higher than labeled doses would be reflected in the label.

6. Clinical Microbiology

No clinical microbiology review was provided.

7. Clinical/Statistical-Efficacy

I concur with the conclusion made by primary clinical reviewer Dr. Denise Cook that the applicant has provided sufficient evidence of efficacy of Reloxin 50 units compared to placebo in achieving and maintaining improvement in the appearance of moderate to severe glabellar lines in adult patients younger than 64 years of age. The subpopulation of patient older than 64 years of age was too small to provide a meaningful conclusion about efficacy and safety of the product in that subpopulation.

The efficacy data were derived from three pivotal phase 3 trials: identical placebo-controlled RCT 718 and 719, and Cycle C of study 085 that provided an adequate database to support the efficacy of a single dose and repeated doses of Reloxin. In study 718, two hundred subjects were treated with CAMR Reloxin 50 units instead of to-be-marketed formulation of IBL Reloxin. CAMR and IBL Reloxin were manufactured at different locations but using the same manufacturing methodology from one of two BAS batches. Study 096 was conducted to establish a clinical bridge between those two formulations. There were 2 co-primary efficacy endpoints used in these phase 3 trials, the investigator's and the patient's assessment of glabellar severity score (GLSS) at maximum frown on day 30 after treatment. The efficacy was observed in 52%-60% of subjects across trials.

8. Safety

The clinical reviewer did not raise any major safety concerns that would preclude the approval of Reloxin 50 units for the treatment of glabellar lines. The safety database consisted of several placebo-controlled trials: 718, 719, 085 and A2006-01, and two long-term safety trials 720 and 732. All trials employed 50 units of Reloxin except for the trial A2006-01 which used various doses of Reloxin between 50 and 80 units. Trials 718, 719 and A2006-01 evaluated a single dose of Reloxin. Trial 085 was a multi-dose open-label trial followed by a placebo-controlled randomized phase. The other trials 720 and 732 were multi-dose trials. Trial 720 was 13 months in duration, and trial 732 was 36 months in duration and is ongoing. Subjects from all the trials were to be rolled-over into trial 732, the 36 month trial and would receive 50 units of Reloxin whenever an additional treatment was necessary.

In addition to 50 unit dose, the sponsor was also seeking variable dosing based on muscle mass however the efficacy and safety database provided with this application were not sufficient to make a definite conclusion about the efficacy or safety of higher doses of Reloxin. The 50 unit dose safety database consisted of 2491 subjects treated with Reloxin and 580 subjects treated with placebo. The long-term trials were designed such that some subjects could receive up to 8 cycles of treatment with Reloxin. An additional 522 subjects received a single dose of 60- 80 units of Reloxin.

Most adverse events in the short-term trials were expected for local injection of botulinum toxin type A products for this indication, e.g., eyelid ptosis, headache, injection site pain, reaction, bruising, and swelling. Most of the cases were mild to moderate and resolved spontaneously. There were no discontinuations because of adverse events in the short-term trials. Long-term data over 21 months with repeated injections demonstrated a slight increase in the percentage of subjects with injection site reactions, 4.0% vs. 3.0%, and subjects who developed contact dermatitis, pharyngolaryngeal pain, and cough (2% each). However, there were no subjects who discontinued the trials secondary to these adverse events. Importantly, there was no increase in the incidence of eyelid ptosis after repeated injections of Reloxin 50 units.

There were no cases of dysphagia or aspiration pneumonia reported in the safety database. These types of adverse events are mostly seen with the use of higher doses of Reloxin for neurologic indications. That population may also be more susceptible to the effects of

botulinum toxin type A. A REMS would be required of all botulinum toxin type A drug product to mitigate this risk.

Since the International Birth Date of Dysport®, 09 December 1990, there have been 1780 adverse events associated with Dysport® use reported, up to and including 30 June 2007, on an estimated — patient years of exposure. They are provided by category (glabellar lines, other aesthetic indications, medical indications using doses up to and more than 200 units, unspecified dose, unspecified indications, and literature). The global database includes events reported spontaneously and those drawn from European studies.

b(4)

There were five patients with ptosis captured in the global database when the drug was being used in the glabellar region, 39 when used for other aesthetic indications.

From July 1, 2007 until December 31, 2007, an update to the post-marketing report revealed 278 AEs. Of these 278 AEs, 26 described eyelid ptosis. The indication for Dysport® use was treatment of glabellar lines in 2 cases. In 8 cases, the product was used for other aesthetic purposes. Of note, 2 of these 8 cases were considered serious (required intervention in 1 case; required hospitalization and intervention in the second case). The remaining 16 AEs were identified in the scientific literature.

There were 2 reports of death secondary to the use of Dysport in the global safety database. Neither of these was secondary to dermatologic indications.

Cross-divisional discussion between DDDP, DNP and OSE of potential safety issues associated with botulinum toxin products resulted in a conclusion that a boxed warning, a REMS consisting of a Medication Guide and a communication plan would be necessary to emphasize the potential risk of local and distant spread of a toxin and the potential adverse events associated with the lack of interchangeability between different botulinum toxin type A products.

I concur with this conclusion and recommend that a REMS is necessary for Reloxin to ensure that the benefits of this drug outweigh its potential risks.

The REMS should contain a Medication Guide, a communication plan, timetable for assessments of the REMS and supporting documents, including Dear Healthcare Provider Letter, Dosing Card, Physician Survey and Patient Survey of understanding of the serious risks of Reloxin.

The Medication Guide should be developed as provided for under 21CFR Part 208. The communication plan must provide for the dissemination of information about the serious product risks including potential systemic spread of botulinum toxin after local injection and lack of interchangeability of Reloxin units with those of other licensed botulinum toxin products.

POSTMARKETING REQUIREMENTS UNDER 505(0)

CMC Post-Marketing Requirement

- To establish tighter potency acceptance criteria for the qualification of new reference standards. The acceptance criteria should ensure consistent potency assessment when different reference standards are used. This is critical as potency is reported relative to the potency of the reference standard. Amended criteria will be submitted to the Agency by [SPONSOR PROPOSE DATE].

Justification for the post-marketing requirement: The potency units for dosing are relative potency units established by normalizing the results of test lots of drug substance or product to the results obtained using the reference standard. This helps ensure consistent dosing from batch to batch. The potency specifications for drug product and drug substance are wide, but are supported by clinical and manufacturing data. Nevertheless, it is unacceptable to allow such wide limits to be applied to the qualification of new reference standards as this could allow the product to drift in potency over time. New reference standards are only infrequently created so this issue can be safely addressed post-approval.

CMC Post-Marketing Commitments

I concur with the recommendations for CMC post marketing commitments including:

1. Regarding specifications
 - a. To establish a drug substance release specification for Clp protease. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].
 - b. To establish a drug substance release specification for aggregates using a validated, sensitive method for quantification. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].
 - c. To develop and validate a sensitive immunologically based method to replace the FPLC and SDS-PAGE identity tests. The proposed specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].
 - d. To provide information on control of destaining the GelCode Blue gel to prevent over-destaining the minor bands on the gel. The information will be provided to the Agency by [SPONSOR PROPOSE DATE].
2. Regarding stability
 - a. To perform a comprehensive analysis of the degradation products and pathways, including the contribution of the Clp protease system to degradation. A summary report together with any proposed modifications to the process and/or stability protocol that

will improve drug product stability will be submitted to the Agency by [SPONSOR PROPOSE DATE].

3. Regarding additional characterization tests
 - a. To develop a Western blot assay for further characterization of the drug substance. Results of this analysis together with the implementation plan for this assay (i.e. specifications or characterization) should be provided to the Agency by [SPONSOR PROPOSE DATE].
4. Regarding potency test
 - a. To investigate reducing the observation time period for animal death in the mouse LD50 assay from 96 to 72 hours. A summary report together with any proposed modifications to the method will be submitted to the Agency by [SPONSOR PROPOSE DATE].
 - b. To investigate the development and implementation of a non-animal based potency assay(s) for drug substance and drug product release testing. A summary report together with any proposed modifications to the process and/or stability protocol will be submitted to the Agency by [SPONSOR PROPOSE DATE].
5. Regarding drug product identity test
 - a. To develop and implement a non-animal based identity test for drug product. The animal based identity test for the first lot of drug product manufactured from every new lot of drug substance should be maintained. A summary report together with any proposed modifications to the process and/or stability protocol will be submitted to the Agency by [SPONSOR PROPOSE DATE].
6. Regarding reference standards:
 - a. To develop drug substance and drug product reference standards from material made at the IBL facility. Routine use of new reference standards will be implemented by [SPONSOR PROPOSE DATE].
 - b. To provide a protocol that describes extension of the dating period for reference standards. The protocol will be submitted to the Agency by [SPONSOR PROPOSE DATE].
7. Regarding the drug product lot release protocol:
 - a. To add SE-HPLC results for bulk drug substance to the lot release protocol upon validation of the SE-HPLC assay(s). A supplement for approval of this drug substance release specification will be submitted to the Agency by [SPONSOR PROPOSE DATE].

To develop a 125U single use dosage form. A supplement for approval of this dosage form will be submitted to the Agency by [SPONSOR PROPOSE DATE].

9. Advisory Committee Meeting

None.

10. Pediatrics

All pediatric age groups are to be waived, as this indication does not occur in the pediatric age group.

11. Other Relevant Regulatory Issues

During the initial steps in the proprietary name review process (Expert Panel Discussion), the DDMAC did not recommend the use of the proposed proprietary name, Reloxin, from a promotional perspective because the name overstates the efficacy of the drug product. Therefore, DMEPA did not proceed with the safety review of the proposed proprietary name, Reloxin, and recommended the sponsor be notified of the decision to object to the name based on promotional concerns and that an alternate proprietary name be submitted for review. In addition, since the product is currently under review with DNP for a different indication by the same manufacturer under the proposed proprietary name Dysport, DMEPA evaluated safety issues which may potentially result from two different proprietary names for this product. In their assessment DMEPA concluded that managing this product under one proprietary name for all indications would be the safest option. DMEPA final review is pending.

12. Labeling

The package insert was reviewed this cycle, however, we will not provide our proposed labeling to the sponsor at this time. We will defer labeling discussion until the next review cycle.

A REMS will be requested that will include a Medication Guide, communication plan and timetable for assessments.

13. Decision/Action/Risk Benefit Assessment

- Recommendation for Regulatory Action: Complete Response
- Risk benefit Assessment will be completed following submission and review of the REMS
- Recommendation for Postmarketing Risk Management Activities: The applicant should provide a REMS consisting of a medication Guide and Communication plan as described above

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- Recommendations for other Postmarketing Study Commitments: These will be conveyed with the approval action



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