CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125274

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

BLA No.:	STN 125286
SUBMISSION DATE:	03/14/08
SPONSOR:	Ipsen Biopharm Limited
PRODUCT (Generic Name):	Clostridium botulinum toxin type A hemagglutinin complex
PRODUCT (Proposed Brand Name):	Reloxin*
DOSAGE FORM:	Single Use Freeze Dried product for IM injection
DOSAGE STRENGTHS:	50 U
INDICATION:	Treatment of glabellar lines
PROPOSED DOSE:	50U – 80U @ no more frequently than every three months.
OCP DIVISION:	DCP 3
OND DIVISION:	DDDP (HFD 540)
REVIEWER:	Tapash Ghosh, Ph.D.
SECONDARY REVIEWER:	Jang-Ik Lee, Pharm.D., Ph. D.

* The proposed brand name, Reloxin, has not been approved at the completion of this review although the name was used throughout this review.

BACKGROUND

Reloxin is a botulinum Type A toxin-hemagglutinin complex for intramuscular injection only. In this BLA submission, the sponsor seeks an approval of Reloxin for the proposed indication "to achieve and maintain improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients." Currently, the preceding BLA submission (BLA125274 submitted on 12/29/2007) is under review by the Division of Neurology Products under the trade name Dysport, for the treatment of cervical dystonia.

The sponsor proposes a vial for marketing that contains 300 units of Reloxin in a freeze-dried pellet formulation that, when reconstituted with 2.5 mL of normal saline, will yield a solution with a concentration of 12 units of Reloxin per 0.1 mL.

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. Pre-clinical 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.

Pharmacokinetic section of Botox® (botulinum toxin type A) labeling also states that botulinum toxin type A is not expected to be present in peripheral blood at measurable levels following intramuscular or intradermal injection at recommended doses.

It is proposed that patients should receive a dose dependent on gender and muscle mass such that female patients can receive between 50 units and 70 units of Reloxin and male patients can receive between 60 units and 80 units of Reloxin. The dose selection was based on clinical safety and effectiveness of the product, as no possible comparison in blood concentrations is feasible.

There were a total of 2368 patients exposed to Reloxin; 1626 patients in the Enrolled Population and 1554 patients in the Safety Population. At the dose and treatment interval used in the Reloxin glabellar lines program, there were very few Reloxin treated patients that were seropositive on anti-product antibodies by competitive antibody radioimmunoprecipitation assay (RIPA-C) (5/1554; 0.32%) and none of these were Positive in the mouse protection assay (MPA). Patients that were classified as Positive by RIPA-C had no evidence of reduced efficacy or an altered safety profile.

RECOMMENDATION

There was no clinical pharmacokinetic or drug interaction information to review in this submission. Other information submitted in this BLA is acceptable from a clinical pharmacology standpoint.

Tapash Ghosh, Ph.D.
Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Date: 11/3/2008

Jang-Ik Lee, Pharm.D., Ph.D.
Secondary Clinical Pharmacology Reviewer
Division of Clinical Pharmacology 3
Office of Clinical Pharmacology

Date: 11/3/2008

Clin. Pharm. and Biopharm. Information

Reloxin, is not approved in the United States for any indication. Currently, a BLA is under review in the Division of Neurology under the trade name Dysport, for cervical dystonia. Reloxin, marketed as Dsyport, 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 treatment of the cosmetic indication of facial lines in 23 countries.

Several trials make up the basis for efficacy in phase 3 of Reloxin: trial 719, trial A-2006-01, Part C of trial 085, trial 718 and trial 096. Together these trials, excluding trial 096, comprised an evaluation of 1607 subjects, 1047 subjects on Reloxin and 560 subjects on placebo. Of these subjects, 633 took part in the short term trials with Reloxin 50 units, 398 treated with Reloxin and 235 treated with placebo.

Two hundred subjects treated with Reloxin 50 units were treated with CAMR instead of the to-be-marketed IBL Reloxin. The sponsor was asked to perform a clinical bridging study to establish equivalence of clinical efficacy and safety between the two manufacturing sites. Trial 096 is that trial. They were manufactured at different locations but using the same manufacturing methodology from one of two BAS batches. There were 2 active arms, CAMR and IBL, each a 50 unit dose. The co-primary efficacy endpoints of the trial were an Investigator's live assessment and a patient self-assessment of 1+ grade improvement of glabellar lines at maximum frown on Day 30. There were 50 botulinum naïve subjects in each arm. The results of the trial demonstrated that IBL BAS and CAMR BAS were not clinically different as assessed by Investigator and patient assessments, adverse events, clinical laboratory tests, and vital signs.

Botulinum toxin therapy is administered directly into the clinically affected muscles and it is considered to be a localized treatment. At therapeutic doses, BTX-A is not expected to be present in the peripheral blood at measurable levels following I.M. injection. Therefore no formal comparative BA or BE studies were conducted. According to the sponsor, dosing recommendations for Reloxin are not based on blood-level response because the product is injected locally in nanogram amounts into the target muscles. The sponsor claims that it is not systemically detectable. Pre-clinical studies conducted in rats by 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. Thus, a decision was made to not conduct any pharmacokinetic studies in humans Dose selection was based on clinical safety and effectiveness of the product, as no possible comparison in blood levels is available.

No drug interaction studies have been conducted.

Data on development of antitoxin antibodies across the six studies comprising the Safety Population were assessed. The serum samples used in this study were taken from 1626 patients exposed to Reloxin, most of whom were initially naïve to any botulinum toxin complex exposure (including Botox). In Studies 085, 096, 718, and 719, enrollment criteria required that each enrolled patient be evaluated for naïveté to any form of botulinum toxin. The two multiple dose safety studies (Study 720 and Study 732) permitted patients to be enrolled with prior exposure, but participation in Study 732 was limited to those previously enrolled in a prior single dose study for which naïveté was required, and Study 720 enrolled some patients from Study 718 which also required naïveté. Thus, for most patients enrolled in this study, a Baseline serum sample was obtained for evaluation of the presence of serum antibodies to Reloxin before any botulinum toxin complex treatment.

In the single dose studies (Study 096, Study 718, and Study 719), serum samples for antibody assessment were also obtained at Day 30 (Study 096), Day 150 (Study 718), or Day 180 (Study 719) or at study termination whichever was later. In the multiple dose studies (Study 085, Study 720, Study 732), serum samples for antibody assessment were also obtained immediately before any retreatment (when patients were required to have relapsed to a Grade 2 or 3 GLSS) and at study close.

Samples were also obtained from placebo-treated patients across the studies. However, patients who have only received placebo throughout the program were not included in the analyses of efficacy and safety.

The first and last blood sample from each patient were tested by a radioimmuno-precipitation assay (RIPA) developed for the detection of botulinum toxin antibodies. Samples that were Positive in the RIPA were confirmed using a competitive antibody radioimmunoprecipitation assay (RIPA-C).

There were a total of 2368 patients exposed to Reloxin; 1626 patients in the Enrolled Population and 1554 patients in the Safety Population. At the dose and treatment interval used in the Reloxin glabellar lines program, there were very few Reloxin treated patients that were seropositive by RIPA-C (5/1554; 0.32%) and none of these were Positive in the MPA. Patients that were classified as Positive by RIPA-C had no evidence of reduced efficacy or an altered safety profile.

For detailed review of the immunogenicity, please check Clinical and CMC reviews.

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	BLA125286	**Brand Name**	Reloxin for Injection
OCP Division (I, II, III)	DCP-3	**Generic Name**	Clostridium botulinum toxin type A hemagglutinin complex
Medical Division	HFD-540	**Drug Class**	Hemagglutinin complex
OCP Reviewer	Tapash Ghosh	**Indication(s)**	Treatment of glabellar lines
OCP Secondary Reviewer	Jang Ik Lee	**Dosage Form**	Reloxin is supplied as a 300 U pellet for reconstitution with sterile saline.
		Dosing Regimen	A minimum dose of 50 U if Reloxin should be administered to achieve clinical effect. Doses up to 70 U for adult females and 80 U for adult males may be administered based on clinical assessment no more frequently than every three months.
Date of Submission	03/14/08	**Route of Administration**	IM Injection
Estimated Due Date of OCP Review	11/07/08	**Sponsor**	Ipsen Biopharm Limited
PDUFA Due Date	01/14/09	**Priority Classification**	Standard
Division Due Date	10/31/08		

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
Renal impairment:				
Hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				

replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	NO PK studies			

Filability and QBR comments

I.	"X" if yes	Comments
II. Application filable?	Yes	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
III. Comments sent to firm? IV.	none	
QBR questions (key issues to be considered)		
Primary reviewer Signature and Date	Tapash Ghosh	
Secondary reviewer Signature and Date	Jang Ik Lee	