

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125274Orig1s001

OTHER REVIEW(S)

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications. You cannot have multiple indications under supplement submissions. If the sponsor submits multiple indications under a supplement, you must unbundle the submission.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125286 Product: Botulinum Toxin Type A Applicant: Ipsen

Final Review Designation (circle one) Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 4/28/08 Committee Recommendation (circle one) File RTF

RPM: Tamara 4/21/09
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):

Part A – RPM

Part B – Product/CMC/Facility Reviewer(s): Ennan Guan / Michelle Clark-Stuart

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): Jill Merrill

Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical)

Reviewers Tapash Ghosh Jang Ik-Lee Kathleen Fritsch

- Memo of Filing Meeting Denise Cook

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?		If not, justification, action & status
Cover Letter	<input checked="" type="radio"/>	N	
Form 356h completed	<input checked="" type="radio"/>	N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	<input checked="" type="radio"/>	N	
<input type="checkbox"/> If foreign applicant, US Agent signature.	<input checked="" type="radio"/>	N	
Comprehensive Table of Contents	Y	<input checked="" type="radio"/>	
Debarment Certification with correct wording (see * below)	<input checked="" type="radio"/>	N	
User Fee Cover Sheet	<input checked="" type="radio"/>	N	
User Fee payment received	<input checked="" type="radio"/>	N	
Financial certification &/or disclosure information	<input checked="" type="radio"/>	N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	<input checked="" type="radio"/>	N	
Pediatric rule: study, waiver, or deferral	<input checked="" type="radio"/>	N	
Labeling:	<input checked="" type="radio"/>	N	
<input type="checkbox"/> PI –non-annotated	<input checked="" type="radio"/>	N	
<input type="checkbox"/> PI –annotated	<input checked="" type="radio"/>	N	
<input type="checkbox"/> PI (electronic)	<input checked="" type="radio"/>	N	
<input type="checkbox"/> Medication Guide	Y	<input checked="" type="radio"/>	
<input type="checkbox"/> Patient Insert	<input checked="" type="radio"/>	N	
<input type="checkbox"/> package and container	<input checked="" type="radio"/>	N	
<input type="checkbox"/> diluent	Y	N	N/A
<input type="checkbox"/> other components	Y	N	N/A
<input type="checkbox"/> established name (e.g. USAN)	Y	<input checked="" type="radio"/>	
<input type="checkbox"/> proprietary name (for review)	<input checked="" type="radio"/>	N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

Examples of Filing Issues	Yes?		If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?:	<input checked="" type="radio"/>	N	
Examples include:			
<input type="checkbox"/> legible	<input checked="" type="radio"/>	N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/>	N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/>	N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/>	N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/>	N	
<input type="checkbox"/> summary reports reference the location of individual data and	<input checked="" type="radio"/>	N	

Examples of Filing Issues	Yes?	If not, justification, action & status
records <input type="checkbox"/> protocols for clinical trials present <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y <input checked="" type="radio"/> N <input checked="" type="radio"/> N	
companion application received if a shared or divided manufacturing arrangement	Y N	N/A
if CMC supplement: <input type="checkbox"/> description and results of studies performed to evaluate the change <input type="checkbox"/> relevant validation protocols <input type="checkbox"/> list of relevant SOPs	Y N Y N Y N	N/A
if clinical supplement: <input type="checkbox"/> changes in labeling clearly highlighted <input type="checkbox"/> data to support all label changes <input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)	Y N Y N Y N	N/A
if electronic submission: <input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted	Y <input checked="" type="radio"/> N	Electronically signed documents in the eCTD

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
 If yes, review committee informed? NO

Does this submission relate to an outstanding PMC? NO

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: N/A
- Dates: N/A

Recommendation (circle one): File RTF

RPM Signature: [Signature]

Branch Chief concurrence: [Signature]

DDMAC Review of Medication Guide

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: April 20, 2009

To: Tamika White, Regulatory Project Manager, DDDP
Denise Cook, M.D., Medical Officer, DDDP
Tamy Kim, Regulatory Project Manager, DNP

From: Shefali Doshi, Regulatory Review Officer, DDMAC ^{SSD}
Sharon Watson, Regulatory Review Officer, DDMAC ^{SSD signing for Sharon Watson}

CC: Robert Dean, DTC Group Leader, DDMAC
Marci Kiester, DTC Group Leader, DDMAC
Andrew Haffer, Regulatory Review Officer, DDMAC
Amy Toscano, Regulatory Review Officer, DDMAC

Subject: BLA 125274 & 124286
DDMAC labeling comments for Dysport (abobotulinumtoxin A)
Injection Medication Guide

DDMAC has reviewed the draft Medication Guide for Dysport (abobotulinumtoxin A). These comments are based on the draft PI from April 2009/revision 6. DDMAC's comments on the draft Medication Guide for Dysport begin on the following page.

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



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Biotechnology Products
Rockville, MD 20852
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125286/0/14

Name of Drug: Reloxin® (botulinum Toxin A)

Sponsor: Ipsen Biopharm Limited

Material Reviewed: Reloxin® (botulinum Toxin Type A) Carton and Container Labels

OBP Receipt Date: February 10, 2009

Amendment Reviewed:

Background:

STN 125286/0 for Botulinum Type A Toxin is an original Biologic License Application (BLA) intended to achieve and maintain improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adult patients. The neurotoxin is supplied as a 300 unit pellet for reconstitution with sterile saline and is injected intramuscularly. The single use vial label contains a unique hologram.

Labels Reviewed:

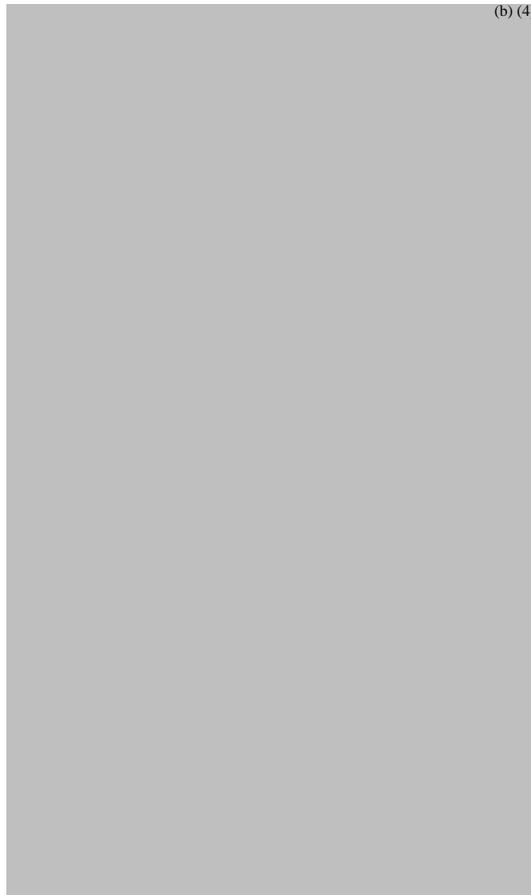
Reloxin® (botulinum Toxin Type A) Container Label
Professional Sample Vial Label
Vial Label

Reloxin® (botulinum Toxin Type A) Carton Label
Professional Sample Carton Label
Carton Label

Review

The carton and container labels for Reloxin® (botulinum Toxin Type A) were reviewed and conformed to a majority of the regulations under 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57 and 21 CFR 200.100; and The U.S. Pharmacopeia, USP31/NF36 (12/1/08-4/30/09) except where noted in the conclusions section of this review memo. Please see the comments in the conclusions section.

Professional Sample Vial Label



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

I. Conclusions

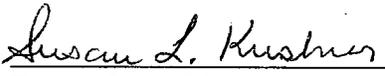
- A. The proposed carton and vial labeling are acceptable only upon the following changes:
1. Please provide the vial size and indicate how the label is affixed to the vial to permit inspection of the contents per 21CFR 610.60 (e).
 2. The route of administration is not provided on the vial labels or on the primary panels of the cartons. Per 21 CFR 201.5 (f) and 21 CFR 610.61 (k), please add the route of administration to the vial labels and to the primary panels of the cartons.
 3. The license number does not appear on any labeling with the manufacturer information. Please add the license number with the manufacturing information per 21 CFR 610.60(2) and 21 CFR 610.61(b).
 4.  (b) (4)
 5. Manufacturer information per the 356h form identifies one manufacturer, Ipsen Biopharm Ltd. Wrexhem, UK; however the carton labels display two manufacturers. Please clarify if Medicis Pharmaceutical Corporation is a second manufacturer or a distributor and use the appropriate regulation to display the information. If it is a second manufacturer, please comply with 21 CFR 610.63 and if is a second distributor, please comply with 21 CFR 610.64.
 6. If the product is light sensitive, please add "Protect from Light" and "Do not Freeze" statements to the carton labels and the "How supplied section" of the package insert per 21 CFR 610.61(i).
 7. Per USPC Official 12/1/08-4/30/09, USP 31/NF26, <1091> Labeling of Inactive Ingredients, please list the names of all inactive ingredients from the current edition of one of the following reference works (in the following order of precedence): (1) the United States Pharmacopeia or the National Formulary; (2) USAN and the USP Dictionary of Drug Names; (3) CTFA Cosmetic Ingredient Dictionary; (4) Food chemicals codex. The ingredients must also be listed in alphabetical order.

8. Please consider adding the trade name on the side panel above the lot and expiration information and the back panel.

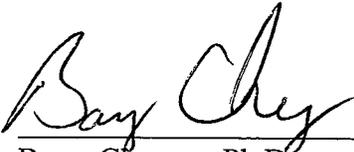
 4/14/09

Kimberly Rains, Pharm.D
Regulatory Project Manager
CDER/OPS/OBS

Comment/Concurrence:

 for Ennan Guan 4/14/09

Ennan Guan, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP

 4-14-09

Barry Cherney, Ph.D.
Deputy Director
Division of Therapeutic Proteins
CDER/OPS/OBP/DTP

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: December 1, 2008

TO: Tamika White, Regulatory Project Manager
Denise Cook, M.D., Medical Officer
Division of Dermatologic and Dental Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA#: 125286

APPLICANT: Ipsen Biopharm Limited

DRUG: Reloxin[®] (botulinum type A toxin-hemagglutinin complex)

NME: Yes

THERAPEUTIC
CLASSIFICATION: Standard Review

INDICATIONS: Treatment of glabellar lines

CONSULTATION
REQUEST DATE: July 9, 2008

DIVISION ACTION
GOAL DATE: January 8, 2009

PDUFA DATE: January 12, 2009

I. BACKGROUND:

The protocols inspected include:

Protocol #Y-97-52120-719 entitled "A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Reloxin[®] in the Treatment of Glabellar Lines", and

Protocol #A-2006-01 entitled "A Phase III, Randomized, Placebo-Controlled, Multi-Center, Double-Blind Study of the Safety and Duration of Efficacy of Reloxin[®] (Botulinum Type A Toxin) in Correction of Moderate to Severe Glabellar Lines (and Including a Sub-Study to Detect Any Treatment Related QT Interval Changes), and

Protocol #Y-97-52120-085 entitled "A Phase III, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Reloxin[®] in the Re-Treatment of Glabellar Lines Following Open-Label Treatment".

The conduct of protocol #s A-2006-01 and Y-97-52120-085 was inspected at the site of Joel Schlessinger, M.D., and the conduct of protocol #s A-2006-01 and Y-97-52120-719 was inspected at the site of Fredric Brandt, MD. (b) (6)

[REDACTED]. Both sites also demonstrated pronounced efficacy.

The primary objectives of these studies were: (1) for protocol # Y-97-52120-719, to demonstrate the efficacy of a single treatment of Reloxin[®] (50 units) compared with placebo in the treatment of glabellar lines; (2) for protocol # Y-97-52120-085, to demonstrate the efficacy of repeat treatment with Reloxin[®] (50 units) in the treatment of glabellar lines; and (3) for protocol # A-2006-01, to establish the safety and efficacy of Reloxin[®] when used to produce a sustained reduction in glabellar line severity. The efficacy of treatment for these protocols was, in general, determined by both subject and investigator assessments of glabellar line severity at different time points during and after treatment with the study article.

II. RESULTS (by Site):

Name of CI, or Sponsor/ Location	Protocol #: and # of Subjects:	Inspection Dates	Final Classification
Joel Schlessinger, M.D. Skin Specialists P.C. 2802 Oak View Mall Drive Omaha, NE 68144	Y-97-52120-085/ 6/ 65/ and A-2006-01/ 88/ 36/	21-23 Oct 08	NAI
Fredric Brandt, MD Dermatology Research Institute LLC 4425 Ponce de Leon Blvd., Suite 200 Coral Gables, FL 33146	A-2006-01/ 73/ 25/ and Y-97-52120-719/ 1/ 54/	20-24 Oct 08	VAI
Medicis Pharmaceutical Corporation 7720 North Dobson Road Scottsdale, AZ 85256 Diane Stroehmann, RAC Manager, Regulatory Affairs Medicis Pharmaceutical Corporation Phone: 480-291-5611 Fax: 480-291-8611 E-mail: dstroehmann@medicis.com	#Y-97-52120-719, and #A-2006-01, and #Y-97-52120-085	Oct-Nov 08	Pending (Preliminary classification is NAI.)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. Joel Schlessinger, M.D.

Skin Specialists P.C.

2802 Oak View Mall Drive

Omaha, NE 68144

- a. **What was inspected:** 42 subjects were consented for protocol #A-2006-01, 6 were screen failures, and 35 completed the study. 70 subjects were consented for the initial portion and 35 subjects were consented for the extension of protocol Y-97-52120-085. There were five screen failures in the initial study

protocols be reviewed and that sponsor/monitor responsibilities be reviewed and documented.

- b. **General observations/commentary:** Personal communications with the field investigator indicate that no regulatory violations were observed.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data generated by the clinical sites of Drs. Schlessinger and Brandt appear acceptable in support of the respective application.

A final classification of the inspection of Medicis is pending receipt and review of the inspection report. An addendum to this clinical inspection summary will be forwarded to the review division should there be any observations of clinical and regulatory significance discovered after reviewing the establishment inspection report (EIR).

Roy Blay Ph.D. 1 DEC 08

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, MD, MPH 12/1/08

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations