

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
125338

OTHER REVIEW(S)



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: December 22, 2009
To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology
Products (DAARP)
Through: Claudia Karwoski, PharmD, Division Director
Division of Risk Management (DRISK)
Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management
From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management
Subject: Corrected DRISK Review of Patient Labeling
(Medication Guide). This replaces the DRISK review
dated December 18, 2009
Drug Name(s): XIAFLEX (collagenase clostridium histolyticum)
Application Type/Number: BLA 125338/0
Submission number: 0039
Applicant/sponsor: Auxilium Pharmaceuticals
OSE RCM #: 2009-1022

*Mary Wiley
for Claudia
Karwoski*

Sharon R. Mills

*Sharon R. Mills
for Latonia Ford*

1 INTRODUCTION

Auxilium Pharmaceuticals submitted an original Biologics License Application (BLA 125338/0/0) on February 27, 2009, for XIAFLEX (collagenase clostridium histolyticum). The proposed indication for XIAFLEX (collagenase clostridium histolyticum) is for the treatment of **adult patients with Dupuytren's contracture with a palpable cord.**

This review is written in response to a request by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) for the **Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for XIAFLEX (collagenase clostridium histolyticum).** Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

The proposed REMS is being reviewed by DRISK and will be provided to DAARP under separate cover.

2 MATERIAL REVIEWED

- Draft XIAFLEX (collagenase clostridium histolyticum) Prescribing Information (PI) submitted February 27, 2009, and revised by the Review Division throughout the current review cycle, and provided by the Review Division on December 4, 2009
- Draft XIAFLEX (collagenase clostridium histolyticum) Medication Guide submitted on December 2, 2009 and revised by the Review Division throughout the current review cycle, and provided by the Review Division on December 4, 2009

Results of review

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- **ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)**

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

CC List

DAARP:

Christopher Hilfiger
Eric Brodsky
Bob A. Rappaport

OSE:

Claudia Karwoski
Mary Dempsey
Elizabeth A Donohoe
Suzanne Berkman Robottom
Sharon Mills
LaShawn Griffiths
Latonia M. Ford
Cherye Milburn
Abolade Adeolu

DDMAC:

Wayne Amchin
Twyla Thompson



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: December 18, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology
Products (DAARP)

Through: Claudia Karwoski, Division Director *Claudia Karwoski*
Division of Risk Management (DRISK)
Sharon R. Mills, BSN, RN, CCRP *Sharon R. Mills 12/18/2009*
Senior Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA *Sharon R. Mills on behalf*
Patient Labeling Reviewer *of Latonia M. Ford*
Division of Risk Management *12/18/2009*

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): XIAFLEX (collagenase clostridium histolyticum)

Application Type/Number: BLA 125338/0

Submission number: 0039

Applicant/sponsor: Auxilium Pharmaceuticals

OSE RCM #: 2009-1022

1 INTRODUCTION

Auxilium Pharmaceuticals submitted an original Biologics License Application (BLA 125338/0/0) on February 27, 2009, for XIAFLEX (collagenase clostridium histolyticum). The proposed indication for XIAFLEX (collagenase clostridium histolyticum) is for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

This review is written in response to a request by the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for XIAFLEX (collagenase clostridium histolyticum). Please let us know if DAARP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

The proposed REMS is being reviewed by DRISK and will be provided to DAARP under separate cover.

2 MATERIAL REVIEWED

- Draft XIAFLEX (collagenase clostridium histolyticum) Prescribing Information (PI) submitted February 27, 2009, and revised by the Review Division throughout the current review cycle, and provided by the Review Division on December 4, 2009
- Draft XIAFLEX (collagenase clostridium histolyticum) Medication Guide submitted on December 2, 2009 and revised by the Review Division throughout the current review cycle, and provided by the Review Division on December 4, 2009

Results of review

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

CC List

DAARP:

Christopher Hilfiger

Eric Brodsky

Bob A. Rappaport

OSE:

Claudia Karwoski

Mary Dempsey

Elizabeth A Donohoe

Suzanne Berkman Robottom

Sharon Mills

LaShawn Griffiths

Latonia M. Ford

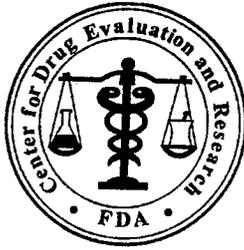
Cherye Milburn

Abolade Adeolu

DDMAC:

Wayne Amchin

Twyla Thompson



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 17, 2009

To: Bob Rappaport, Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Thru: Carlos M. Mena-Grillasca, R.Ph., Team Leader *C. Mena 11/17/09*
Denise Toyer, Pharm D., Deputy Director *Dr. Toyer 11/18/09*
Carol Holquist, R.Ph., Director *C. Holquist 11/18/09*
Division of Medication Error Prevention and Analysis (DMEPA)

From: Walter Fava, R.Ph., Safety Evaluator *Walter Fava 11-17-09*
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Xiaflex (Collagenase Clostridium Histolyticum) for Injection
0.9 mg/vial

Application Type/Number: BLA: 125338

Applicant: Auxilium Pharmaceuticals, Inc.

OSE RCM #: 2009-425

CONTENTS

1	INTRODUCTION	3
2	METHODS AND MATERIALS.....	3
3	RECOMMENDATIONS.....	3
3.1	Comments to the Sponsor.....	3
	Appendices.....	5

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products to evaluate the container labels, carton and package insert labeling for the product Xiaflex (BLA# 125338), to identify areas that could lead to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and carton labeling submitted on August 27, 2009 and insert labeling submitted on August 22, 2009 (see Appendices A and B for images).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling can be improved upon to provide more optimal presentation for increased understanding and readability. We have provided recommendation to address these areas in section 3.1 below. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Sponsor with regard to this review. If you have further questions or need clarifications, please contact, Cheryle Milburn, OSE Project Manager, at 301-796-2084.

3.1 COMMENTS TO THE SPONSOR

A. CONTAINER LABEL OF ACTIVE

1. Increase the prominence of the established name to improve readability. As currently presented, the condensed font used is difficult to read.
2. Include the dosage form statement following the established and proprietary name statements to read 'for injection'.
3. Delete statement, 'Refer to product carton for additional information' to allow for relocation of the product strength.
4. Relocate the strength statement to appear immediately below the proprietary and established names.
5. Increase the prominence and readability of the strength statement, '0.9 mg per vial'. As currently presented, the font size in combination with the orange font color on the white background makes it difficult to read.
6. Revise the font style used to present the proprietary name to make it easier to read. As currently presented, the fanciful cross stroke transversing the adjacent letters 'A' and 'F' makes these letters difficult to read.

B. CONTAINER LABEL OF DILUENT VIAL

1. Revise the presentation of the amount of calcium chloride dihydrate to be expressed in milligrams instead of a percentage. As currently presented, 0.03% calcium chloride dihydrate does not convey the amount of calcium chloride dihydrate in the diluent. This presentation should also be consistent with the presentation of this information on the carton labeling. For example: 'X mg calcium chloride dihydrate in 0.9% sodium chloride'.
2. Relocate and increase the prominence of the statement, 'For reconstitution of Xiaflex only' to appear immediately below, 'Sterile Diluent'.

3. Ensure that the diluent label is differentiated from the active drug label. Consider increasing the prominence of the word “Diluent” to an extent that is not confused with the name Xiaflex in the statement “For reconstitution of Xiaflex only”.

C. CARTON LABELING

1. See comments A 1, A 2, A 4, A 5, and A 6.
2. Revise statement, ‘One single-dose vial containing collagenase clostridium histolyticum 0.9 mg’ to read, ‘One single use vial containing collagenase clostridium histolyticum.’
3. Revise statement, ‘One single-dose vial containing sterile diluent 3 mL’ to read, ‘One single use vial containing sterile diluent 3 mL’.
4. Include the statement, ‘Single Use Vials. Discard Unused Portion’, to the upper right hand corner of the principal display panel.
5. Relocate the ‘Rx only’ statement to the principal display panel.
6. As currently presented the light grey font makes it difficult to read important information. Use a darker font to improve readability.

APPENDICES

Appendix A: Container Labels for Xialfex and required Sterile Diluent

(b) (4)

A large rectangular area of the page is completely redacted with a solid grey fill, covering the majority of the content under Appendix A.

Appendix B: Carton labeling

(b) (4)

A very large rectangular area of the page is completely redacted with a solid grey fill, covering the majority of the content under Appendix B.

MEMORANDUM

To: Christopher Hilfiger
Division of Anesthesia, Analgesia, and Rheumatology Products

From: Iris Masucci, PharmD, BCPS *IM*
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: October 1, 2009

Re:

BLA	125338
Drug Name	Xiaflex (collagenase clostridium histolyticum)
Indication	Treatment of Dupuytren's contracture
Applicant	Auxilium Pharmaceuticals
Date(s)	Stamp Date: 2/27/2009 PDUFA Date: 8/29/2009
Review Priority	Priority

We have reviewed the proposed label for Xiaflex (FDA version received by SEALD 9/29/09) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the Division after a full review of the submitted data.

Please see attached label for recommended changes.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: September 18, 2009

To: Chris Hilfiger – Regulatory Project Manager
Margarita Tossa – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer *MF for Mathilda Fienkeng*
Twyla Thompson – Regulatory Review Officer *TF*
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Through: Mike Sauer – Group Leader
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
BLA 125338 XI AFLEX™ (collagenase clostridium histolyticum)

DDMAC has reviewed the proposed product labeling (PI), and patient labeling (PPI) for XI AFLEX™ (collagenase clostridium histolyticum) (XI AFLEX), submitted for consult on March 10, 2009.

The following comments are provided using the updated proposed PI and PPI sent via email on September 18, 2009 by Chris Hilfiger. If you have any questions about DDMAC's comments, please do not hesitate to contact us

19 Pages Withheld as b(4) Draft Labeling

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: August 27, 2009

TO: Margarita Tossa, Regulatory Project Manager
Eric Brodsky, M.D., Medical Officer
Division of Reproductive and Urologic Drugs Products

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

THROUGH: Tejashri Purohit Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: BLA 125338

APPLICANT: Auxilium Pharmaceuticals, Inc.

DRUG: Clostridial collagenase (Xiaflex™)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of Dupuytren's Disease

CONSULTATION REQUEST DATE: February 23, 2009

DSI Due Date: August 27, 2009

PDUFA DATE: August 28, 2009
(Application goal date has been delayed to October 15, 2009 by the review division due to pending Advisory Committee Meeting)

I. BACKGROUND:

The conduct of two protocols were inspected:

Protocol #DUPY 303A, entitled “A Double-Blind, Randomized, Placebo-Controlled Study of the Relative Safety and Efficacy of Collagenase Therapy in the Treatment of Residula-Type Dupuytren’s Disease”, and

Protocol #AUX-CC-857, entitled “A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of the Safety and Efficacy of AA4500 in the Treatment of Subjects With Dupuytren's Contracture”

The sites for Drs. Hurst, Hentz, and Kaplan were selected for inspection because of they were among the highest enrolling sites demonstrating a greater treatment effect of the investigational drug compared to overall study results.

The primary efficacy endpoint was the proportion of patients that achieved a reduction of the primary contracture to 0 to 5 degrees, 30 days after the last injection.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Lawrence Hurst, M.D. SUNY at Stony Brook Health Sciences Center, T-18 Stony Brook, NY 11794-0001	DUPY 303A / 35 and AUX-CC-857/ 28	17 Jun-6 Jul 2009	Pending. Interim classification is VAI.
Vincent Hentz, M.D. 770 Welch Road, Suite 400 MC 5715 Stanford University Hand and Upper Extremity Surgery Palo Alto, CA 94304	AUX-CC-857/ 37	28 May-16 Jun 2009	Pending. Interim classification is VAI.
F. Thomas Kaplan, M.D. Indiana Hand Center 8501 Harcourt Road Indianapolis, IN 46280	AUX-CC-857/ 25	17-19 Jun 2009	Pending. Interim classification is NAI.
Auxilium Pharmaceuticals, Inc. 40 Valley Stream Parkway, Malvern, PA 19355 Benjamin Del Tito, Jr., Ph.D. Ph: (484) 321-5989	DUPY 303A and AUX-CC-857	4-7 Aug 09	Pending. Interim 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. Lawrence Hurst, M.D.
SUNY at Stony Brook
Health Sciences Center, T-18
Stony Brook, NY 11794-0001

Note that Dr. Badalemente and Dr. Hurst collaborated in the conduct of both studies, and as such, only one inspection report was submitted. The findings below are pertinent to the findings at this one inspectional site.

a. What was inspected:

For Protocol #DUPY303A

At this site, 42 subjects were screened and 35 enrolled. All Informed Consent Forms (ICFs) were reviewed. The records of 18 subjects were audited, including, but not limited to, laboratory reports, sponsor correspondence, source documentation, IRB communications, monitoring reports, protocol deviations, adverse events, concomitant medications, test article accountability, and the primary efficacy endpoints

For Protocol #AUX-CC-857

At this site, 37 subjects were screened and 28 enrolled. All Informed Consent Forms (ICFs) were reviewed. The records of 14 subjects were audited, including, but not limited to, source documents, IRB communications, monitoring reports, laboratory reports, adverse events, concomitant medications, test article accountability, and the primary efficacy endpoints.

- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. The most significant observations on the Form FDA 483 follow:

For Protocol #DUPY303A

- Complete physical exams were not conducted as required by protocol. Examinations were limited to hands and disease status.
- Subject 1-140 was treated with Lidocaine 1% prior to obtaining approval from the IRB.

For Protocol #AUX-CC-857

- Complete physical examinations were not conducted as required by protocol. Examinations were limited to hands and disease status.

- c. Assessment of data integrity:** Although complete physical examinations, as required by protocol, were not done for any of the subjects of either study, the relevant components of the physical examination were conducted as pertinent to the primary endpoint for all subjects. DSI considers the data collected in support of efficacy and safety as reliable. However, the review division may wish to consider the impact, if any, of this lack of information on overall data quality.
 2. Vincent Hentz, M.D.
770 Welch Road, Suite 400 MC 5715
Stanford University Hand and Upper Extremity Surgery
Palo Alto, CA 94304

 - a. What was inspected:** At this site, 37 subjects were screened and enrolled in the study. The records of 19 subjects were reviewed. Study records reviewed included, but were not limited to, consent forms, inclusion/exclusion criteria, test article accountability, concomitant medications, and IRB and monitoring correspondence.
 - b. General observations/commentary:** At the end of the inspection, a Form FDA 483 was issued. Finger goniometry was not performed per protocol requirements at specified visits for Subjects 4203, 4204, 4206, 4207, 4233, 4235, 4239, and 4240. There were several examples of inadequate documentation of revisions to goniometric measurements, IRB approval/expiration dates, dates of evaluations, and revisions to values for joint range of motion. All subjects were consented with an outdated consent form. 36 were re-consented with one subject again being re-consented with an outdated consent form
 - c. Assessment of data integrity:** In general, the data is considered acceptable in support of this NDA. However, the review division may wish to consider the impact, if any, of the lack of complete goniometric data for the subjects noted above in their assessment of efficacy.
 3. F. Thomas Kaplan, M.D.
Indiana Hand Center
8501 Harcourt Road
Indianapolis, IN 46280

 - a. What was inspected:** At this site, 32 subjects were screened and 25 were enrolled. The records for all study subjects were reviewed, including, but not limited to, informed consent forms (ICFs), case report forms, (CRFs), IRB communications, source documents, and drug accountability records
 - b. General observations/commentary:** At the end of the inspection, a Form FDA 483 was not issued. Review of the records noted above revealed no significant discrepancies/regulatory violations.
 - c. Assessment of data integrity:** Data appear acceptable in support of the respective application.

4. Auxilium Pharmaceuticals, Inc.
40 Valley Stream Parkway,
Malvern, PA 19355

- a. **What was inspected:** The CRFs for 15 subjects from Dr. Hentz's site, 11 CRFs from Dr. Hurst's site, and 10 CRFs from Dr. Kaplan's site were reviewed and compared with data listings for studies DUPY 303A and AUX-CC-857. The firm's standard operating procedures (SOPs) were reviewed along with monitoring SOPs. Other records reviewed included, but were not limited to, IRB approvals, drug accountability, clinical site correspondence, and monitoring reports.
- b. **General observations/commentary:** At the end of the inspection, a Form FDA 483 was not issued. Review of the records noted above revealed no significant discrepancies/regulatory violations.
- c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical sites were inspected in support of this application. Regarding data from Dr. Hurst's site, complete physical examinations as required by protocol were not performed for any of the enrolled subjects, and the review division may wish to consider the impact, if any, of this lack of data. However, DSI considers the data acceptable in support of efficacy and safety as key components of the physical examination as pertinent to efficacy were conducted. At Dr. Hentz's site, the review division may wish to consider the impact, if any, of the lack of complete goniometric data for Subjects 4203, 4204, 4206, 4207, 4233, 4235, 4239, and 4240. Otherwise, the data generated by the clinical sites of Drs. Hurst, Hentz, and Kaplan appear acceptable in support of the respective application.



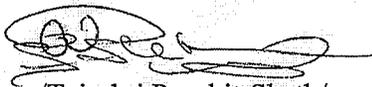
/Roy Blay/

Roy Blay, Ph.D.

Good Clinical Practice Branch II

Division of Scientific Investigations

CONCURRENCE:



/Tejashri Purohit-Sheth/

Tejashri Purohit-Sheth, M.D.

Branch Chief

Good Clinical Practice Branch II

Division of Scientific Investigations



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

Office of Biotechnology Products
Federal Research Center
Silver Spring, MD
Tel. 301-796-4242

Memorandum

PROJECT MANAGER'S REVIEW

Application Number: STN 125338/0
Name of Drug: Xiaflex™
Sponsor: Auxilium Pharmaceuticals, Inc.
Material Reviewed: Xiaflex™ (collagenase clostridium histolyticum) Carton and Container Labels
OBP Receipt Date: March 11, 2009

Background:

STN 125338/0 for collagenase clostridium histolyticum is an original Biologic License Application (BLA) indicated for the treatment of advanced Dupuytren's disease. The product is a sterile, lyophilized powder for intralesional injection. The product is supplied in single use glass vial containing 0.9 mg to deliver a 0.58 mg dose after reconstitution with 0.03% calcium chloride in 0.9% sodium chloride, USP.

Labels Reviewed:

Xiaflex™ (collagenase clostridium histolyticum) Container Label
Vial label
Diluent Vial label
Xiaflex™ (collagenase clostridium histolyticum) Carton Label
Carton label
Xiaflex™ Prescribing Information

Review

The carton and container labels for Xiaflex™ (collagenase clostridium histolyticum) were reviewed and found to be adequate under most of the following regulations: 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. The U.S. Pharmacopeia, USP 32/NF 27 (5/1/09-8/1/09). Please see the comments in the conclusions section.

Conclusions

1. The following comments were noted on the initial review of the carton and container labels submitted for clostridial collagenase:

- Please revise the term “single-use vial” to “single dose vial” on all labeling to comply with The U.S. Pharmacopeia, USP 32/NF 27 (5/1/09-8/1/09) -General Notices-Preservation, Packing, Storage, and Labeling.
- Please provide font size configurations of all Proper name and Trade name presentations on the Carton and Container labels to comply with 21 CFR 610.62.
- Please add the statement “No U.S. standard of potency” to the carton label to comply with regulation 21CFR 610.61(r).

- If light sensitive, please add the statement “Protect from Light. Store in carton until use” on the carton label per 21 CFR 610.61.
- Please add license number to manufacturer information on both carton and container labeling per 21 CFR 610.60 and 21 CFR 610.61.
- Revise the statement “Clostridial collagenase for injection” to read “clostridial collagenase” as the established name on all labeling per 21 CFR 201.10.
- Please provide the preservative used and its concentration, or if no preservative is used, add the statement “No preservative” per 21 CFR 610.61.
- Display the inactive ingredients listed on the carton in alphabetical order to comply with The U.S. Pharmacopeia, USP 32/NF 27 (5/1/09-8/1/09)-General Chapter <1091> Labeling of Inactive ingredients on the carton.
- Please include a reference on the carton to the identity of each microorganism used in manufacture per 21 CFR 610.61(q).

2. Revised labels submitted by the sponsor included replacement of clostridial collagenase for injection with collagenase clostridium histolyticum and the following changes:

Revised Container



Revised Carton

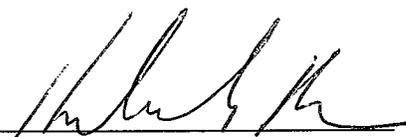
(b) (4)

- Please revise the term “single-use vial” to “single dose vial” on all labeling to comply with The U.S. Pharmacopeia, USP 32/NF 27 (5/1/09-8/1/09) -General Notices-Preservation, Packing, Storage, and Labeling. Revised as requested. Acceptable.
- Please provide font size configurations of all Proper name and Trade name presentations on the Carton and Container labels to comply with 21 CFR 610.62. Information provided. Not acceptable. Please see comments to the sponsor.
- Revise the statement “Clostridial collagenase for injection” to read “clostridial collagenase” as the established name on all labeling per 21 CFR 201.10. Revised USAN approved name is collagenase clostridium hystolyticum.
- Please add the statement “No U.S. standard of potency” to the carton label to comply with regulation 21CFR 610.61(r). Revised as requested. Acceptable.
- If light sensitive, please add the statement “Protect from Light. Store in carton until use” on the carton label per 21 CFR 610.61. Product is not light sensitive.
- Please add license number to manufacturer information on both carton and container labeling per 21 CFR 610.60 and 21 CFR 610.61. Revised as requested. Acceptable.

- Please provide the preservative used and its concentration, or if no preservative is used, add the statement "No preservative" per 21 CFR 610.61. Revised as requested. The statement, "No preservative" was added to the carton.
- Display the inactive ingredients listed on the carton in alphabetical order to comply with The U.S. Pharmacopeia, USP 32/NF 27 (5/1/09-8/1/09)-General Chapter <1091> Labeling of Inactive ingredients on the carton. Revised as requested. Acceptable.
- Please include a reference on the carton to the identity of each microorganism used in manufacture per 21 CFR 610.61(q). Information provided. Acceptable.

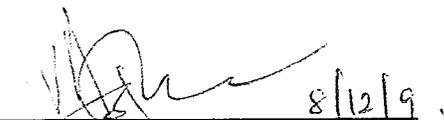
3. Comments to the sponsor:

- Revise the prominence and placement of the proper name and trade name to comply with 21 CFR 610.62.
- Please indicate how the label is affixed to the vial and where the visual area of inspection is located to comply with 21 CFR 610.60(e).
- Please provide the amount of product in the container per vial prominently on the primary panel to comply with 21 CFR 610.61(g).



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

Comment/Concurrence:



Ashutosh Rao, Ph.D.
Product Reviewer
Division of Therapeutic Proteins
CDER/OPS/OBP



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



Memorandum

Date: October 5, 2009

From: Rafael Arroyo
Compliance Officer
New and Generic Drug Manufacturing Team
DMPQ (HFD-322), Office of Compliance
Center for Drug Evaluation and Research

Subject: Concurrence with CDER/OC/DMQP/BMT Approval Recommendation
BLA STN 125338 Xiaflex (Drug Substance AA4500, Collagenase Clostridium Histolyticum)

Thru: Concepcion Cruz, Team Leader, Manufacturing Assessment & Pre-Approval Compliance Branch
(HFD-322) *CC 10/5/09*

To: Anastasia G. Lolas (HFD-328)

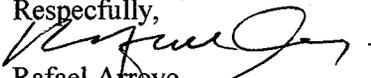
Applicant: Auxilium Pharmaceutical, Inc.
102 Witmer Rd
Horsham, PA 19044

The Division of Manufacturing and Product Quality (DMPQ) has completed its review of an establishment inspection report (EIR) for a preapproval inspection (PAI) of BLA STN 125338 Xiaflex (Drug Substance AA4500, Collagenase Clostridium Histolyticum) conducted from August 17-21, 2009 at Auxilium Pharmaceutical, Inc. located in Horsham, PA.

DMPQ **concurs** with CDER/OC/DMPQ/BMT recommendation for approval of the subject application. The firm's responses to the inspectional observations were reviewed by CDER/OC/DMPQ. The responses have been found adequate and justify the approval of Biological License Application (BLA) STN 125338. The corrections described in the firm's response should be further evaluated during the next surveillance inspection of this facility.

The EIR states that the warehouse is located at 201 Witmer Rd. This is a different location than where Xiaflex (Drug Substance AA4500, Collagenase Clostridium Histolyticum) is manufactured. It is recommended to include the warehouse address in the manufacturing section of the Biological License Application (BLA).

Respectfully,


Rafael Arroyo

cc:

HFD-328 BMT Team Leader, Patricia Hughes, Ph.D.
HFD-323 MAPCB (Acting) Branch Chief, Barry Rothman
HFD-323 NGDMT (Acting) Team Leader, Tara Gooen
HFD-323 Shared Drive \\cdsnas\OCS1\OC_320\HFD-323\Domestic PAI Case Management
HFD-323 NGDMT CSO, Colleen Hoyt