DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125338/0

BLA APPROVAL
February 2, 2010

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

Attention: Benjamin J. Del Tito, Jr., Ph.D.
Senior Vice President, Quality and Regulatory Affairs

Dear Dr. Del Tito:

Please refer to your biologics license application (BLA), dated and received February 27, 2009, submitted under section 351 of the Public Health Service Act (PHSA) for Xiaflex (clostridial collagenase histolyticum).

We acknowledge receipt of your submissions dated March 24 and 27, April 9, 10, and 14, May 18, June 16, 23, and 29, July 2, 8, 9, 14, 15, 17, 24, and 28, August 12, 19, 21, 25 (2), 27, and 28, September 2, 4, 11 (2), 15, 22 (2), 23, 24, and 25 (2), November 13 and 18, and December 2, 4, 10, 23, and 28, 2009, January 7, 11, and 15, and February 2, 2010.

We have approved your biologics license application for clostridial collagenase histolyticum effective this date, February 2, 2010. You are hereby authorized to manufacture, introduce, and deliver for introduction into interstate commerce clostridial collagenase histolyticum under Department of Health and Human Services U.S. License No. 1816, under the provisions of section 351(a) of the PHSA. Clostridial collagenase histolyticum is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

Under this license, you are approved to manufacture clostridial collagenase histolyticum at your Auxilium Pharmaceuticals facility in Horsham, Pennsylvania. You may label your product with the proprietary name "Xiaflex" and market it in a single-use glass vial containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution with a single-use glass vial containing a sterile diluent (0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride).

The dating period for Xiaflex (0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder) shall be 24 months from the date of manufacture when stored at 5 ± 3°C. The date of manufacture shall be defined as the date of (b) (4) of the formulated drug product. The dating period for the sterile diluent (0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride) shall be 30 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of (b) (4). The dating period for your drug substance shall be 24 months when stored at ≤ -60°C. The expiration date for the

packaged product, collagenase clostridium histolyticum lyophilized powder for reconstitution with calcium chloride dihydrate sterile diluent, shall be dependent on the shortest expiration date of any component, which is 24 months.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12."

You currently are not required to submit samples of future lots of Xiaflex to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging, or labeling of collagenase clostridium histolyticum or in the manufacturing facilities.

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.

Because collagenase clostridium histolyticum has an orphan drug designation for this indication, you are exempt from this requirement.

POSTMARKETING REQUIREMENT UNDER 505(o)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes if FDA makes certain findings required by the statute (section 505(o)(3)(A)).

Since the protein components in Xiaflex (AUX-I and AUX-II) have some sequence homology with human matrix metalloproteinases (MMPs), anti-product antibodies to the protein components of Xiaflex may have a potential to interfere with these endogenous human proteins. Such cross-reactivity was assessed via limited in vitro data from 5 patients. One of 5 patients had anti-AUX-II antibodies that cross-reacted with selected MMPs and resulted in MMP inhibition in this experiment. Therefore, these data indicate a potential for the cross-reactivity of anti-product antibodies with these endogenous proteins and should be further investigated to identify an unexpected serious risk of inhibiting enzymatic activity of the endogenous proteins, matrix metalloproteinases, with treatment with Xiaflex.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify this unexpected serious risk described above.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify this unexpected serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. Submit an in vitro study of human sera from patients who have received multiple Xiaflex injections to evaluate the potential for cross-reactivity of anti-product antibodies (i.e., anti-AUX-I and anti-AUX-II) with endogenous human MMPs (including MMP-1, MMP-2, MMP-3, MMP-8, and MMP-13) with similar homology and relevance to the protein components of Xiaflex. This study should assess the frequency of inhibition of the enzymatic activity of these human proteins by anti-product antibodies and by neutralizing anti-product antibodies. This study should also be designed to assess whether repeated treatment courses of Xiaflex injection result in anti-product antibodies that are more persistent and cross-reactive to endogenous proteins compared to initial anti-product antibody responses.

   The timetable you submitted on December 22, 2009, states that you will conduct this study according to the following timetable:

Final Protocol Submission:	March 2010
Study Completion Date:	June 2010
Final Report Submission:	December 2010

Submit the protocol to your IND, with a cross-reference letter to this BLA, BLA 125338. Submit all final reports to this BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study required under this section. This section also requires you to periodically report to FDA on the status of any study otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70, requires you to report annually on the status of any postmarketing commitments or required studies.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with

505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

2. To evaluate the minimal fill volume required to permit withdrawal of the appropriate dosage volume and to assess patient risk of overdose. The feasibility study report and proposed path forward will be submitted in a supplement.

   The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

   Supplement Submission Date: March 2010

3. To conduct a study to demonstrate microbial control at the end of hold (10 days) for the individual AUX-1 and AUX-II intermediates. The data will be submitted as a CBE supplement.

   The timetable you submitted on August 21, 2009, states that you will conduct this study according to the following timetable:

   Supplement Submission Date: December 2010

4. To qualify the bioburden test for in-process intermediates. The qualification will be performed using three different lots. The data will be submitted as a CBE supplement.

   The timetable you submitted on August 21, 2009, states that you will conduct this study according to the following timetable:

   Supplement Submission Date: December 2010

5. To qualify the endotoxin test on an additional two lots each of AUX-I intermediate, AUX-II intermediate, and drug substance, and three lots each of HIC eluate and TFF-1 concentrate. The summary data will be submitted as a CBE supplement.

   The timetable you submitted on August 21, 2009, states that you will conduct this study according to the following timetable:

   Supplement Submission Date: December 2010

6. To conduct and submit data from an adequate container-closure integrity study for the diluent product with container-closure components that have been subjected to the same or worse (b) (4) cycle. The proposed (b) (4) test protocol

and method for stability testing can be used to fulfill this requirement. Provide (b) (4) test validation results for container-closure integrity testing of lyophilized product and diluent vials in the stability program. The validation report and data will be submitted in a CBE supplement.

The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

Supplement Submission Date: March 2010

7. To determine the D_{121}-value of the biological indicator *G. stearothermophilus* in the diluent product solution and reassess studies conducted. Provide a comparison to the D-values used in the product validation studies. The data will be submitted in a CBE supplement.

   The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

   Supplement Submission Date: March 2010

8. To demonstrate the feasibility of an in vitro study of human sera from patients who have received multiple Xiaflex injections to evaluate the potential for cross-reactivity of anti-product antibodies with two endogenous human proteins, polycystin 1 and KIAA0319, and propose a path forward.

   The timetable you submitted on December 23, 2009, states that you will conduct this study according to the following timetable:

   Supplement Submission Date: December 2010

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We acknowledge your written commitments to perform the following studies:

9. To demonstrate feasibility of an immune-based host cell protein assay and propose a path forward.

   The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

   Final Report Submission: December 2010

10. To characterize the types and amounts of subvisible particles (b) (4) in the drug product under stress conditions, at release, and throughout the dating period, and to propose an appropriate control strategy, based on the risk to product quality.

The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

Final Report Submission: June 2010

11. To establish individual acceptance criteria for AUX-I and AUX-II profile and their mass ratio for the RP-HPLC for release and stability testing of the drug substance and drug product. The updated assay and acceptance criteria will be submitted in a supplement.

    The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

    Supplement Submission Date: September 2010

12. To calculate the protein recovery for each HPLC method validation (SEC and RP-HPLC) using an orthogonal protein measurement assay that provides added assurance that the method is suitable for its intended purpose.

    The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

    Final Report Submission: December 2010

13. To develop and validate the RP-HPLC method to quantify potential impurities for AUX-I intermediate, drug substance, and drug product. The updated assay and acceptance criteria will be submitted in a supplement.

    The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

    Final Report Submission: December 2010

14. To establish and validate a staining and destaining control (e.g., BSA) for SDS-PAGE Coomassie and Silver Stain to ensure an appropriate level of detection for product- or process-related impurities. The updated assay and acceptance criteria will be submitted in a supplement.

    The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

    Supplement Submission Date: February 2010

15. To confirm the accuracy of the SEC-HPLC method for detecting aggregates using stress samples (e.g., light, heat, oxidation) using orthogonal test methods (e.g., AUC or FFF).

The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

Final Report Submission: June 2010

16. To develop and validate an immune-based identity assay and to add the validated assay to the release specifications for the drug substance and drug product. The validated assay and revised release specifications will be submitted in a supplement.

    The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

    Final Report Submission: December 2010

17. To include an accelerated or stress stability condition as part of the annual stability program for the drug substance and drug product.

    The timetable you submitted on November 20, 2009, states that you will conduct this study according to the following timetable:

    Final Approved Protocol Submission and Implementation: June 2010.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this BLA. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKEING COMMITMENT – FINAL REPORT**
- **POSTMARKETING CORRESPONDENCE**
- **ANNUAL STATUS REPORTING OF POSTMARKETING COMMITMENTS**

For each postmarketing commitment subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report. The status report for each commitment should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment;
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted);
- an explanation of the status including the patient accrual rate (i.e., number enrolled to date and the total planned enrollment); and
- a revised schedule if the scheduled milestones have changed and an explanation of the basis for the revision.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

Your proposed REMS, submitted on February 2, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The REMS assessment plan should include but is not limited to the following:

a. A narrative summary and analysis of all cases of serious adverse events of the injected extremity, with special attention to tendon ruptures, and all cases of hypersensitivity reactions, including anaphylaxis. For serious adverse events of the injected extremity, the analysis should include a breakdown by healthcare provider specialty, whether the healthcare provider received/participated in education on the risks and proper injection technique, and total number of injections performed. For hypersensitivity reactions, the analysis should include the number and temporal relationship of previous and most recent Xiaflex injections each patient received, the reported signs and symptoms of systemic allergic reactions, including cutaneous, cardiopulmonary, and gastrointestinal manifestations, changes in vital signs, and any pertinent laboratory parameters such as serum tryptase.

b. A report on the status of healthcare provider education, including the specialty type and number of providers requesting education, the number and percentage of likely providers who received educational materials stratified by educational method (e.g., in person, booklet, DVD, internet), the specialty type and number of providers educated.

c. An assessment of the extent of Xiaflex use stratified by
   - indication
   - healthcare provider specialty
   - receipt of education on the risks and proper injection technique (i.e., the extent to which healthcare providers who have not received education are treating patients with Xiaflex)

d. An evaluation of the healthcare providers' understanding of proper injection technique and of the serious risks of Xiaflex, including the risks of tendon rupture and serious hypersensitivity reactions.

e. An evaluation of patients' understanding of the serious risks of Xiaflex, including the risks of tendon rupture and hypersensitivity reactions.

f. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

g. A report on failures to adhere to Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.

h. Based on information reported, an assessment and conclusion of whether the REMS is meeting its goals, and whether modification to the REMS is needed.

Assessments of an approved REMS must include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 601.70 and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in Section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125338 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125338
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE) FOR BLA 125338
REMS ASSESSMENT
PROPOSED REMS MODIFICATION *(if included)*

If you do not submit electronically, please send five copies of REMS-related submissions.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding, and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations sent by courier or overnight mail should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4203
Silver Spring, MD 20992-0002

CONTENT OF LABELING

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the enclosed labeling (text for the package insert and Medication Guide submitted February 2, 2010) with the following minor editorial revision agreed to between you and Christopher Hilfiger from the FDA on February 2, 2010.

Delete the word [redacted] (b) (4) at the end of the package insert.

Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. The content of labeling should be submitted by updating your application by referencing the SPL file submitted to the drug establishment registration and drug listing system. To do this, place a link in your application submission that directs FDA to your SPL file. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125338**."

For additional information on submitting labeling to drug establishment registration and drug listing and to applications, see the FDA guidances at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

We remind you that pursuant to 21 CFR 201.57(x)(18) and 201.80(f)(2) the Medication Guide must be reprinted immediately following the last section of the labeling or, alternatively, accompany the prescription drug labeling.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels as soon as they are available but no more than 30 days after they are printed that are identical to the enclosed draft labels, with the following minor editorial revisions agreed to between you and Christopher Hilfiger from the FDA on February 2, 2010.

1. Delete the word [redacted] (b) (4) from the description of the diluent on the immediate-container and the carton label.

2. Delete the word [redacted] (b) (4) on the carton label.

Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125338**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this BLA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, contact the Division of Anesthesia, Analgesia, and Rheumatology Products.

If you have any questions, contact the Regulatory Project Manager, Christopher Hilfiger, at (301) 796-4131.

Sincerely,

/Curtis J. Rosebraugh, M.D., M.P.H./
Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Package Insert
Medication Guide
Carton and Immediate-Container Labels
REMS and Supporting Documents