DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125338/S-84

SUPPLEMENT APPROVAL
REMS ASSESSMENT PLAN REVISION

Auxilium Pharmaceuticals, Inc.
640 Lee Road
Chesterbrook, PA 19087

Attention: Laura Grablutz
Senior Director, Regulatory Affairs

Dear Ms. Grablutz:

Please refer to your Supplemental Biologics License Application (sBLA), dated December 19, 2013, received, December 19, 2013 submitted under section 351(a) of the Public Health Service Act for XIAFLEX® (collagenase clostridium histolyticum).

We acknowledge receipt of your amendments dated February 2, August 7, 12, 28, and 21, and October 1, 10, and 15, 2014 and your risk evaluation and mitigation strategy (REMS) assessment dated April 21, 2014.

This Prior Approval supplemental biologics application proposes to revise the prescribing information to include the following change in the dosing regimen: two concurrent injections of Xiaflex into palpable cords affecting multiple joints in the same hand in adult patients with Dupuytren's contracture with finger extension procedure 24 to 72 hours after injection; the risk of skin laceration requiring skin graft in patients treated with Xiaflex; and a proposed modification to the approved REMS.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text. In addition, we have found the REMS assessment to be adequate.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the 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 to the enclosed labeling (text for the package insert, text for the Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

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

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 indications 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Xiaflex® (collagenase clostridium histolyticum) was originally approved on February 2, 2010, and modified on February 24, 2012 and December 6, 2013. The REMS for Xiaflex (collagenase clostridium histolyticum) for the treatment of Dupuytren's contracture consists of a communication plan, and a timetable for submission of assessments of the REMS. The REMS for Xiaflex (collagenase clostridium histolyticum) for the treatment of Peyronie's disease consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS for Xiaflex (collagenase clostridium histolyticum) for the treatment of Dupuytren's contracture consists of revisions to the communication plan materials (Dear Healthcare Provider Letter; Training Guide for the Administration of Xiaflex; and Xiaflex Procedure Training Video) to include:

- the following change to information in the dosing regimen: two concurrent injections of Xiaflex into palpable cords affecting multiple joints in the same hand in adult patients with Dupuytren's contracture with finger extension procedure 24 to 72 hours after injection; and
- the risk of skin laceration requiring skin graft in patients treated with Xiaflex (collagenase clostridium histolyticum).

Your proposed modified REMS, submitted on April 21, 2014 and amended on August 7 and October 15, 2014, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on December 6, 2013.

The revised REMS assessment plan for the REMS for Xiaflex (collagenase clostridium histolyticum) for the treatment of Dupuytren's contracture should include, but is not limited to, the following:

a. Post-marketing reports of the following serious adverse events of interest.
    - A summary of serious adverse events of the injected digit. The summary should include the number of new reports, number of follow-up reports, include brief narrative of each report including outcome when available.
    - A summary of new reports of anaphylaxis or hypersensitivity reactions. The summary should include the number of new reports, number of follow-up reports and for new reports provide a brief narrative of each case.

b. Healthcare provider education:
    - Number of new healthcare providers who received education
    - Method of access to educational materials and enrollment (online of other method)

c. Active healthcare providers: the number of healthcare providers ordering/injecting Xiaflex to treat Dupuytren's Contracture.

d. An evaluation of 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. Based on the information provided, an assessment and conclusion of whether the REMS is meeting its goals, and whether modifications to the REMS are needed.

f. With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal, or whether one or more such goals or such elements should be modified [per section 505-1(g)(3)].

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 the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 125338/84 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

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

BLA 125338 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125338
PROPOSED REMS MODIFICATION

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

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Michelle Jordan Garner, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH K YIM
10/20/2014
Signing for Badrul Chowdhury, M.D., Ph.D.