



BLA 125338/040

**SUPPLEMENT APPROVAL
REMOVE REMS ELEMENT**

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

Attention: Laura Grabluz
Senior Director, Regulatory Affairs

Dear Ms. Grabluz:

Please refer to your Supplemental Biologics License Application (sBLA), dated August 5, 2011, received August 5, 2011, submitted under section 351 of the Public Health Service Act for Xiaflex (collagenase clostridium histolyticum) Injection.

We acknowledge receipt of your amendments dated October 25, 2011, and January 13, and 26, 2012; and your risk evaluation and mitigation strategy (REMS) assessment dated February 1, 2011.

This Prior Approval supplement to your biologics license application proposes to modify the REMS to eliminate the requirement for the Medication Guide (MG) as an element of the approved Xiaflex (collagenase clostridium histolyticum) REMS and to modify the communication plan. It also provides for revisions to the MG to address the Agency's comment dated May 5, 2011, and includes editorial revisions to the Package Insert.

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.

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 Effectuated" (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>. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved BLA STN 125338/040.**”

Also within 14 days, amend all pending supplemental applications 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.

The SPL will be accessible via publicly available labeling repositories.

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Xiaflex (collagenase clostridium histolyticum) was originally approved on February 2, 2010. The REMS consists of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

Your proposed modification to the REMS consists of eliminating the requirement for the Medication Guide as an element of the REMS and addressing the requirements in our June 1, 2011 REMS Modification Notification letter to revise some of the communication plan materials to more effectively educate prescribers about the risks when injecting Xiaflex into a cord of the proximal interphalangeal joint of the fifth finger.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Xiaflex (collagenase clostridium histolyticum) outweigh the risks.

Therefore, we agree with your proposal, and a Medication Guide is no longer required as part of the REMS for Xiaflex (collagenase clostridium histolyticum).

Your proposed modified REMS, submitted on January 26, 2012, and appended to this letter, is approved.

The modified REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

We remind you that the Medication Guide will continue to be part of the approved labeling for Xiaflex (collagenase clostridium histolyticum) in accordance with 21 CFR 208.

The timetable for submission of assessments of the REMS will remain the same as that approved on February 2, 2010.

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

- a. Evaluation of healthcare providers understanding of proper injection and finger extension procedures and the risks of tendon rupture, serious adverse reactions affecting the injected extremity, and the potential risk of serious hypersensitivity reactions (including the potential for anaphylaxis) associated with the administration of XI AFLEX.
- b. Narrative summary and analysis of all cases of serious adverse events of the injected extremity with special attention to tendon rupture, and all cases of hypersensitivity reaction, including anaphylaxis
 - For serious adverse events of the injected extremity, the analysis will 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 will include the number and temporal relationship of previous and most recent XI AFLEX 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.
- c. 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, video, internet), and the specialty type and number of providers educated
- d. An assessment of the extent of XI AFLEX 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 XI AFLEX)
- e. An evaluation of healthcare providers' understanding of proper injection technique and of the serious risks of XI AFLEX, including the risks of tendon rupture and serious hypersensitivity reactions
- f. 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
- g. Information on the status of any postapproval study or clinical trial required under section 505(o)(3) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study,

including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. 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 material or significant updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

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.

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 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
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 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. For instruction on completing the Form FDA 2253, see page 2 of the Form. 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 Garner Jordan, Regulatory Project Manager, at (301) 796-4786.

Sincerely,

{See appended electronic signature page}

Sally Seymour, M.D.
Deputy Director for Safety
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/

SALLY M SEYMOUR
02/24/2012