



BLA 125338/61

SUPPLEMENT APPROVAL

Auxilium Pharmaceuticals
Attention: Benjamin Del Tito, Jr., Ph.D.
Executive Vice President, Regulatory Affairs and Project Management
640 Lee Road
Chesterbrook, PA 19087

Dear Dr. Del Tito:

Please refer to your Supplemental Biologics License Application (sBLA) dated and received November 6, 2012, submitted under section 351 of the Public Health Service Act for XIAFLEX[®] (collagenase clostridium histolyticum).

We acknowledge receipt of your amendments dated November 7 and December 7, 2012, February 8, March 6, May 31, June 17, August 21, 26 and 27, October 16 and 31, November 7, December 3 and 5 (electronic mail communication), 2013, and your risk evaluation and mitigation strategy (REMS) assessment dated August 26, 2013.

This Prior Approval supplemental biologics application provides for a new indication for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees and proposed modifications 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.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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 (Package Insert, 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.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your November 6, 2012, submission containing final printed carton and container labels.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because Peyronie’s disease does not exist in children, and this biologic product for the Peyronie’s disease indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) 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.

We have become aware of reports of corporal fracture (penile fracture) and other serious penile injuries. These reports were obtained from data collected in the phase three clinical trials AUX-CC-802, AUX-CC-803 and AUX-CC-804 evaluating the use of XIAFLEX in the treatment of Peyronie’s disease. We consider this information to be “new safety information” as defined in section 505-1(b)(3) of the FDCA.

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 assess a known risk of serious penile injuries, or to identify an unexpected serious risk of adverse long-term outcomes after a serious penile injury.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- #1 A prospective, long-term observational study that will collect safety data, including sexual dysfunction and immunogenicity, from subjects previously treated with XIAFLEX[®] (collagenase clostridium histolyticum) who were enrolled and treated in Studies AUX-CC-802, AUX-CC-803 and AUX-CC-804.

The timetable you submitted via electronic communication on November 24, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June 2014
Study Completion:	December 2018
Final Report Submission:	June 2019

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol to your IND 5588, with a cross-reference letter to this BLA. Submit all final report to your 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 or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial 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 or clinical trials.

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 or clinical trials 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.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for XIAFLEX[®] (collagenase clostridium histolyticum), which is currently indicated for treatment of Dupuytren's contracture with palpable cord, was originally approved on February 2, 2010, and a REMS modification was approved on February 24, 2012. The REMS currently consists of a communication plan and timetable for submission of the assessments of the REMS for XIAFLEX[®] (collagenase clostridium histolyticum) in the treatment of Dupuytren's contracture.

Pursuant to 505-1(f)(1), we have determined that elements necessary to assure safe use are required as part of a REMS to mitigate the risk of corporal fracture (penile fracture) and other serious penile injuries associated with use in Peyronie's disease. The elements to assure safe use will ensure that the benefits of the drug outweigh the risk of corporal fracture (penile fracture) and other serious penile injuries by ensuring that healthcare providers who prescribe XIAFLEX[®] (collagenase clostridium histolyticum) for Peyronie's disease are specially certified, and that pharmacies or healthcare settings that dispense XIAFLEX[®] (collagenase clostridium histolyticum) for Peyronie's disease are specially certified.

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.

Your proposed modified REMS, submitted on August 26, 2013, and amended on October 16, November 7 and December 5 (via electronic communication), 2013, and appended to this letter, is approved.

The modified REMS consists of a communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the modified REMS must be revised to provide for submission of REMS Assessments to the FDA at 6 and 12 months from the date of the modified REMS approval (December 2013), and annually thereafter.

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

For Peyronie's disease:

Each assessment report should be submitted according to the above timetable with the information:

- a. A narrative summary and analysis of all cases of corporal fracture (penile fracture) and other serious penile injuries associated with the use of XIAFLEX[®] (collagenase clostridium histolyticum). Include the number of adverse events requiring surgery.
- b. An evaluation of healthcare providers understanding of: 1) the proper injection technique of XIAFLEX[®] (collagenase clostridium histolyticum) and 2) serious risks of XIAFLEX[®] (collagenase clostridium histolyticum) involving corporal fracture (penile fracture) and other serious penile injuries.
- c. An evaluation of patients understanding of: 1) the risks of corporal fracture (penile fracture) and other serious penile injury, 2) the their role in reducing these risks, 3) the conditions under which patients should promptly contact their healthcare provider, and 4) , the proper method of performing at home penile modeling activities.
- d. REMS Program Utilization Statistics - provide for the current reporting period and cumulatively:
 - Certification of healthcare providers
 - i. Include the specialty type and number of providers requesting certification, and number of providers who received certification. Stratify by provider specialty type.
 - ii. A report on the number of healthcare providers who were not certified and prescribed or administered Xiaflex, include provider specialty and the intended use.
 - Enrollment of pharmacies and healthcare settings
 - i. Number of pharmacies and healthcare settings who attempted certification
 - ii. Number of pharmacies and healthcare settings that become certified
 - iii. Number of certified healthcare settings that do not have a certified healthcare provider.
 - Dispensing/distribution activity
 - i. Number of vials shipped to each certified and noncertified pharmacy or healthcare setting
 - ii. Number of distributors contracted by Auxilium to provide drug
 - iii. Number of non-Xiaflex REMS certified pharmacies and healthcare settings that have a 25% or greater increase in vials received during the reporting period as compared to the previous year.

e. REMS Program Infrastructure and Performance

- i. A summary report of serious or critical deviations found, and corrective actions taken for any prescriber, pharmacy, and distributor audits conducted during the reporting period.
- ii. Assessment and conclusion of whether the REMS is meeting its goals, and whether additional modifications to the REMS are required.

For Dupuytren's contracture:

Each assessment report should be submitted at 6 months and then 2 and 4 years from the date of the modified REMS approval (December 2013) with the following information:

- e. 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 XIAFLEX[®] (collagenase clostridium histolyticum).
- f. 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.
- g. For serious adverse events of an injected extremity associated with administration of XIAFLEX[®] (collagenase clostridium histolyticum) injection, the analysis will include a breakdown by healthcare provider specialty, whether the healthcare provider received/participated in education on the risks and whether proper injection technique was used
- h. For hypersensitivity reactions, the analysis will include the number and temporal relationship of previous and most recent XIAFLEX[®] (collagenase clostridium histolyticum) 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.
- i. 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.
- j. An assessment of the extent of XIAFLEX[®] (collagenase clostridium histolyticum) 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[®] (collagenase clostridium histolyticum)).

- k. An evaluation of healthcare providers' understanding of proper injection technique and of the serious risks of XIAFLEX[®] (collagenase clostridium histolyticum), including the risks of tendon rupture and serious hypersensitivity reactions.
- l. An assessment and conclusion of whether the REMS is meeting its goals based on the information above, and whether other modifications to the REMS are needed

The requirements for assessments of an approved REMS under section 505-1(g)(3) include 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 1 or more such goals or such elements should be modified.

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 125338/61 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)

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>.

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

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).

In addition, as agreed to in your electronic communication dated November 20, 2013, you will conduct enhanced pharmacovigilance of XIAFLEX for the following penile-related events of special interest (PESI): corporal rupture, penile hematoma, sudden loss of penile erection, and sensation or sound of penile "popping" or "cracking." Submit expedited post-marketing reports of the PESI as 15-day Alert reports, and provide periodic summary safety reports for PESI quarterly (every 3 months) and cumulative summary since approval of the Peyronie's disease indication with the periodic safety reports. The enhanced pharmacovigilance program will be reassessed 3 years after marketing for the Peyronie's disease indication.

If you have any questions, call Eufrecina DeGuia, Senior Regulatory Health Project Manager, at (301) 796-0881.

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Deputy Director
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
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/

AUDREY L GASSMAN
12/06/2013