BLA 125338/S-121

SUPPLEMENT APPROVAL

Auxilium Pharmaceuticals, LLC
c/o Endo Pharmaceuticals, Inc.
Attention: Erin Flynn
Director, Global Regulatory Affairs
1400 Atwater Drive
Malvern, PA 19355

Dear Ms. Flynn:

Please refer to your supplemental biologics license application (sBLA) dated October 11, 2021 and received October 12, 2021, and your amendments, submitted under section 351(a) of the Public Health Service Act for Xiaflex (collagenase clostridium histolyticum) for injection.

We also refer to our letter dated June 24, 2021, notifying you, under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA), of new safety information that we believe should be included in the labeling for Xiaflex. This information pertains to the risk of skin and soft-tissue necrosis associated with the use of Xiaflex. We also refer to our August 19, 2021, approval letter for supplement 117 that provided for revisions to the labeling consistent with our safety labeling changes (SLC) letter.

This supplemental biologics license application provides for modifications to the risk evaluation and mitigation strategy (REMS) for Xiaflex to reflect the revisions to the labeling approved on August 19, 2021.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Xiaflex was originally approved on December 6, 2013, and the most recent REMS modification was approved on September 26, 2018. The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of updates to the REMS materials to reflect the safety labeling changes that were recently approved on August 19, 2021 and approved labeling regarding penile hematoma.

Your proposed modified REMS, submitted on October 11, 2021, amended on November 2, and November 19, 2021, and appended to this letter, is approved.

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

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

Health Outcomes and/or Surrogate of Health Outcomes

1. Safety Surveillance (per reporting period and cumulative)

   Provide in tabular format the number of cases of corporal fracture (penile fracture) and other serious penile injuries associated with the use of XIAFLEX as reflected in the enhanced pharmacovigilance reporting required for XIAFLEX. Include the number resulting in surgery. Provide numbers of events for the current and for each previous reporting period. Discuss any differences in cases and outcomes found compared to previous reporting periods.

   a. Include the search strategy used to identify cases and specific MedDRA terms used to identify cases of interest
   b. Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report
   c. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

Knowledge

2. An evaluation of healthcare providers understanding of:

   a. The proper injection technique of XIAFLEX (collagenase clostridium histolyticum), and

b. Serious risks of XIAFLEX (collagenase clostridium histolyticum) involving corporal rupture (penile fracture) and other serious penile injuries.

3. An evaluation of patients understanding of:
    a. The risks of corporal rupture (penile fracture) and other serious penile injury,
    b. Their role in reducing these risks,
    c. The conditions under which patients should promptly contact their healthcare provider, and
    d. The proper method of performing at home penile modeling activities.

If knowledge evaluations indicate that awareness is inadequate, specific measures to increase awareness will be proposed.

REMS Program Implementation and Operations

4. REMS Call Center (per reporting period and cumulatively)
    a. Number of contacts by stakeholder type (patient/caregiver, healthcare provider, authorized representative, pharmacy/healthcare setting staff, wholesaler/distributors staff, other)
    b. Summary of reasons for calls (e.g., enrollment question, location of a certified healthcare setting) and by reporter (e.g. authorized representative, pharmacy/healthcare setting staff, patient/caregiver, other)
    c. Summary of frequently asked questions (FAQ) by stakeholder type
    d. Summary report of REMS-related problems identified and resulting corrective actions

5. REMS Program Utilization Statistics - (per reporting period and cumulatively)
    a. Certification of healthcare providers
        i. Number of healthcare providers who requested certification, stratified by specialty, provider type, primary treatment setting, and geographic region
        ii. Number of healthcare providers who received certification stratified by, specialty, provider type, primary treatment setting, and geographic region
        iii. Number of active certified healthcare providers (who prescribed/administered Xiaflex for Peyronie's disease) stratified by, specialty, provider type, primary treatment setting, and geographic

region

b. Enrollment of pharmacies and healthcare settings

i. Number of pharmacies that requested certification by geographic region

ii. Number of healthcare settings that requested certification stratified by healthcare setting type and geographic region

iii. Number of pharmacies that received certification stratified by geographic region

iv. Number of healthcare settings that received certification stratified by healthcare setting type and geographic region

v. Number of active (i.e. have received Xiaflex) pharmacies and healthcare settings stratified by healthcare setting type and geographic region

vi. Number of pharmacy/healthcare setting recertifications expected and the number of recertifications performed.

c. Enrollment of wholesalers/distributors

i. Number of newly enrolled wholesalers/distributors

ii. Number of active (i.e. have shipped Xiaflex) wholesalers/distributors

6. Xiaflex Utilization Statistics (per reporting period and cumulatively)

i. Number of vials and shipments by distribution partner for Peyronie's disease and Dupuytren's contracture

ii. Number of vials and shipments dispensed from the specialty pharmacy channel only to REMS certified healthcare providers stratified by specialty, degree and treatment setting

iii. Number of vials and shipments dispensed by all distribution channels to REMS certified healthcare settings stratified by setting type and geographic location

iv. Number of vials shipped to each certified and noncertified pharmacy or healthcare setting

v. Number of prescriptions dispensed from certified pharmacies and certified healthcare settings stratified by:

a. Healthcare setting type

b. HCP specialty, HCP degree/credentials, geographic region

vi. Number of estimated unique patients receiving Xiaflex for each indication (Dupuytren's Contracture and Peyronie's disease)

7. Compliance with REMS Program, Infrastructure, and Performance (per

reporting period and cumulatively)

Provide a summary of non-compliance identified, including but not limited to:

a. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS.

b. Provide a copy of the audit plan for each stakeholder

c. Report of audit findings for each stakeholder (healthcare settings, pharmacies, wholesalers/distributors).

   i. The number of audits expected, and the number of audits performed.

   ii. The number and types of deficiencies noted for each group of audited stakeholders.

   iii. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.

   iv. For any that did not complete the CAPA within one month of the audit, describe actions taken.

   v. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.

   vi. Documentation of completion of training for relevant staff.

      1. The existence of documented processes and procedures for complying with the REMS

      2. Verification that each audited stakeholder's site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification.

d. Healthcare Providers (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)

   i. Number of healthcare providers who were not certified but prescribed or administered Xiaflex, include provider specialty and the intended use

e. Pharmacies and Healthcare settings (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)

   i. Number and type of pharmacy/healthcare settings for which non-compliance with the REMS is detected

ii. Number and type of non-certified pharmacy/healthcare settings that administered Xiaflex and the number of incidents for each pharmacy/healthcare setting

iii. Number of pharmacies and healthcare settings decertified for non-compliance and reasons for decertification

iv. Number of times Xiaflex was dispensed to a pharmacy/healthcare setting without verifying that the pharmacy/healthcare setting is certified

v. Number of certified pharmacies/healthcare settings that do not have a certified healthcare provider

vi. Number of certified pharmacies/healthcare settings that do not have an authorized representative

f. Wholesalers/Distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)

i. The number of authorized wholesalers/distributors for which non-compliance with the REMS is detected

ii. The number and type of non-authorized wholesalers/distributors that shipped Xiaflex and the number of incidents for each

iii. Number of times Xiaflex was distributed to a noncertified healthcare setting, non-certified pharmacy, or directly to patients.

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 one or more such goals or such elements should be modified. We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those

risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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 ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

Prominently identify any 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

or

NEW SUPPLEMENT FOR BLA 125338 S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125338 S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 125338 S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125338 S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 125338

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If

you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[1]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[2] Information and Instructions for completing the form can be found at FDA.gov.[3]

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 Meredith Hillig, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Catherine Sewell, M.D., M.P.H.
Deputy Director for Safety Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Products
Center for Drug Evaluation and Research

[1] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[2] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[3] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

ENCLOSURE

- REMS

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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/s/

CATHERINE A SEWELL
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