



BLA 125338/S-100  
BLA 125338/S-101

**SUPPLEMENT APPROVAL**

Endo Pharmaceuticals  
Attention: Tara Chapman, Pharm.D.  
Senior Director, Regulatory Affairs  
1400 Atwater Drive  
Malvern, PA 19355

Dear Dr. Chapman:

Please refer to your Supplemental Biologics License Applications (sBLAs), dated and received April 22 and June 24, 2016, and your amendments, submitted under section 351(a) of the Public Health Service Act for XIAFLEX® (collagenase clostridium histolyticum).

We acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated, December 3, 2015.

The April 22, 2016, supplemental biologics application (S-100) provides for proposed modifications to the approved risk evaluation and mitigation strategy (REMS) for Peyronie's disease indication. This supplement is in response to our February 22, 2016, REMS Modification Notification letter.

The June 24, 2016, supplemental biologics application (S-101) includes a proposed modification to the approved REMS for the Dupuytren's contracture indication. This supplement is in response to our May 25, 2016, REMS Assessment Acknowledgment and REMS Modification Notification letter.

**APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, as described below.

### **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 none of these criteria apply to your application, you are exempt from this requirement.

### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for XIAFLEX® (collagenase clostridium histolyticum) for the treatment of Dupuytren's contracture was originally approved on February 2, 2010, modified on December 6, 2013, to add the Peyronie's disease indication, and the most recent REMS modification was approved on October 20, 2014.

#### **BLA 125338/S-101**

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. In order to minimize the burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the following REMS modifications:

- A request to remove the communication plan from the REMS
- A request to release the REMS requirements

Because the most recent assessment demonstrates that the communication plan has met its goals, we have determined that the communication plan is no longer necessary to include as an element of the approved REMS to ensure that the benefits of XIAFLEX® (collagenase clostridium histolyticum) outweigh its risks for the Dupuytren's contracture indication.

Therefore, because the communication plan is no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for XIAFLEX® (collagenase clostridium histolyticum) for the Dupuytren's contracture indication.

#### **BLA 125338/S-100**

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. In order to ensure the benefits of XIAFLEX® (collagenase clostridium histolyticum) outweigh its risks when used for the treatment of Peyronie's disease, we determined that you were required to make the following REMS modifications:

- Changes to the Prescriber Material, “*Training Guide for the Administration of Xiaflex for Peyronie’s Disease*”
- Changes to the Patient Counseling Tool, “*What You Need to Know About XIAFLEX Treatment for Peyronie’s Disease: A Patient Guide*”
- Make changes to align the Training Video with the Prescriber Material.
- Make changes to align the Xiaflex REMS Program website to align with the Prescriber Material and remove information related to the communication plan

Your proposed modified REMS, submitted on April 22, 2016, amended, 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.

There are no changes to the REMS assessment plan for the Peyronie’s disease indication as described in our September 11, 2015, letter.

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 the 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 CORRESPONDENCE**  
**(insert concise description of content in bold capital letters, e.g.,**  
**UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT**  
**METHODOLOGY**

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**  
  
**NEW SUPPLEMENT FOR BLA 125338**  
**CHANGES BEING EFFECTED IN 30 DAYS**  
**PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 125338**  
**PRIOR APPROVAL SUPPLEMENT**  
**PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 125338**  
**PRIOR APPROVAL SUPPLEMENT**  
**PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES**  
**SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR BLA 125338/SECONDARY TRACKING NUMBER  
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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

**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 Alpert, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

*{See appended electronic signature page}*

Sally Seymour, MD  
Deputy Director for Safety  
Division of Pulmonary, Allergy, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Christine P. Nguyen, MD  
Deputy Director for Safety  
Division of Bone, Reproductive, and Urologic Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURES:  
REMS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SALLY M SEYMOUR  
11/28/2016

CHRISTINE P NGUYEN  
11/28/2016