

Initial REMS Approved: 12/6/2013¹
Most Recent Modification: 10/2018

BLA 125338
XIAFLEX[®] (collagenase clostridium histolyticum)
Drug Class: Bacterial collagenase enzyme

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RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL

The goal of the XIAFLEX REMS is to mitigate the risks of corporal rupture (penile fracture) and other serious penile injuries associated with the use of XIAFLEX for Peyronie's disease by:

- Training healthcare providers in how to properly administer XIAFLEX.
- Informing healthcare providers about the risks of corporal rupture (penile fracture) and other serious injuries to the penis.
- Informing healthcare providers about the need to counsel patients to communicate that risks of corporal rupture and other serious penile injuries are associated with the use of XIAFLEX in treating Peyronie's disease and that patient adherence to post-injection instructions is important for the drug's safety and effectiveness.
- Ensuring that XIAFLEX is dispensed only in certified pharmacies or healthcare settings for the treatment of Peyronie's disease.
- Informing patients about the risks of corporal rupture and other serious penile injuries associated with the use of XIAFLEX in treating Peyronie's disease and that adherence to post-injection instructions is important for the drug's safety and effectiveness.

¹ The REMS for Xiaflex was originally approved on February 2, 2010 with the Dupuytren's contracture indication and released for that indication in November 2016.

II. REMS ELEMENTS

A. Elements to Assure Safe Use

1. Healthcare providers who prescribe XIAFLEX for Peyronie's disease are specially certified.

- a. Endo Pharmaceuticals will ensure that healthcare providers who prescribe² XIAFLEX for the treatment of Peyronie's disease are specially certified.
- b. To become specially certified to prescribe XIAFLEX for the treatment of Peyronie's disease, healthcare providers must:
 - i. Read the Prescribing Information for XIAFLEX.
 - ii. Complete the XIAFLEX REMS Healthcare Provider Training Program for Peyronie's disease by:
 - a. viewing the entire REMS Training Video for Administering XIAFLEX for Peyronie's disease **or**
 - b. reading the entire REMS Training Guide for Administering XIAFLEX for Peyronie's disease
 - iii. Agree to review with and provide a copy of the Patient Counseling Tool, "*What You Need to Know about XIAFLEX Treatment for Peyronie's disease: A Patient Guide*," to each patient to inform patients about the risks associated with the use of XIAFLEX and the need to follow important post-injection instructions.
 - iv. Acknowledge that my practice setting must be a certified healthcare setting, or that I will use a certified pharmacy, enrolled in the XIAFLEX REMS Program.
 - v. Complete and sign the Healthcare Provider Enrollment Form for Peyronie's disease and submit it to the XIAFLEX REMS Program.
- c. Endo Pharmaceuticals will:
 - i. Ensure that healthcare providers complete the *Healthcare Provider Training Program for Peyronie's disease* and *Healthcare Provider Enrollment Form for Peyronie's disease* before activating healthcare providers' certification in the XIAFLEX REMS Program.
 - ii. Ensure that healthcare providers are notified when they have been successfully certified by the XIAFLEX REMS Program for Peyronie's disease.

² For the purposes of this REMS, the terms "prescribe" and "prescription" include medication orders in outpatient settings or hospital settings.

- iii. Maintain a validated secure database of healthcare providers who prescribe XIAFLEX for the treatment of Peyronie's disease and their specialties in the XIAFLEX REMS Program. Endo Pharmaceuticals will ensure that the prescribers' certification requirements are met and may de-certify non-compliant prescribers until the requirements are met.
- iv. Ensure that the XIAFLEX REMS Healthcare Provider Training Program for Peyronie's disease, Healthcare Provider Enrollment Form for Peyronie's disease, and Patient Counseling Tool for Peyronie's disease are available on the XIAFLEX REMS program website at www.XIAFLEXREMS.com and from the XIAFLEX REMS Program call center (1-877-313-1235).

These materials will be available within 60 calendar days of the most recent REMS modification approval through the following distribution methods:

- Accessed through the www.XIAFLEXREMS.com website
- Hard copy is available, upon request, through the XIAFLEX REMS Program call center (1-877-313-1235).

The following materials are part of the REMS and are appended:

- REMS Training Guide for Administering XIAFLEX for Peyronie's disease
- REMS Training Video for Administering XIAFLEX for Peyronie's disease (accessed at www.XIAFLEXREMS.com)
- Healthcare Provider Enrollment Form for Peyronie's disease
- Patient Counseling Tool, *What You Need to Know About XIAFLEX Treatment for Peyronie's disease: A Patient Guide*
- XIAFLEX REMS Program website (www.XIAFLEXREMS.com), main landing page of the REMS website and Program Certification Lookup for a certified healthcare provider and healthcare setting

2. Pharmacies and healthcare settings that dispense³ XIAFLEX for Peyronie's disease are specially certified.

a. Endo Pharmaceuticals will:

- i. Ensure that XIAFLEX is only distributed to and dispensed for the treatment of Peyronie's disease from pharmacies or healthcare settings (eg, hospitals, and outpatient clinics, and healthcare providers' offices) that are specially certified.
- ii. Ensure that pharmacies or healthcare settings are recertified in the XIAFLEX REMS Program every 2 years.

³ For the purposes of this REMS, "dispense" in an outpatient setting includes dispensing for administration in a provider's office.

- iii. To become certified to dispense XIAFLEX for the treatment of Peyronie's disease, the pharmacy or healthcare setting must designate an Authorized Representative to coordinate the pharmacy or healthcare setting's activities and assure compliance with the XIAFLEX REMS Program. The Authorized Representative must agree to the following:
 - a. Complete and sign the *Pharmacy/Healthcare Setting Enrollment Form for Peyronie's disease* and submit it to the XIAFLEX REMS Program.
 - b. Put processes and procedures in place to verify, prior to dispensing XIAFLEX, that the healthcare provider prescribing XIAFLEX for Peyronie's disease is certified in the XIAFLEX REMS Program.
 - c. Maintain a record of current certified prescribers.
 - d. Agree not to loan, sell or transfer XIAFLEX to another pharmacy, healthcare setting, prescriber, institution, or distributor.
 - e. To be audited to ensure compliance with the XIAFLEX REMS Program.

The following materials are part of the REMS and are appended:

- *XIAFLEX REMS Pharmacy/Healthcare Setting Enrollment Form for Peyronie's disease*

B. Implementation System

An implementation system will be established for the XIAFLEX REMS Program to monitor and evaluate whether the elements to assure safe use are meeting the program's goals.

1. Endo Pharmaceuticals will ensure that pharmacies or healthcare settings that dispense XIAFLEX for Peyronie's disease are specially certified.
2. Endo Pharmaceuticals will maintain, monitor, and evaluate the implementation of the XIAFLEX REMS Program for Peyronie's disease.
 - a. Endo Pharmaceuticals will maintain a validated secure database of all certified pharmacies or healthcare settings.
 - b. Endo Pharmaceuticals will send confirmation of certification to each certified pharmacy or healthcare setting.
 - c. The database of certified healthcare providers who are certified to prescribe Xiaflex for the treatment of Peyronie's disease will be accessible by the Authorized Representative at a pharmacy or certified healthcare setting and by contract distributors.
 - d. Contract distributors will verify pharmacy or healthcare setting certification prior to distributing XIAFLEX.
 - e. Endo Pharmaceuticals will maintain a XIAFLEX REMS Program call center (1-877-313-1235) to respond to questions from healthcare providers, pharmacies, and healthcare settings.

- f. Endo Pharmaceuticals will ensure that within 60 calendar days of the approval of the most recent REMS modification all materials listed in or appended to the XIAFLEX REMS Program will be available through the XIAFLEX REMS Program website at www.XIAFLEXREMS.com and through the XIAFLEX REMS Program call center (1-877-313-1235).
 - g. Endo Pharmaceuticals will audit 10% of the certified pharmacies or healthcare settings annually to ensure that all processes and procedures are in place and functioning to support the requirements of the XIAFLEX REMS Program. Endo Pharmaceuticals will correct noncompliance with XIAFLEX REMS Program requirements.
 - h. Endo Pharmaceuticals will take reasonable steps to improve implementation of these elements and to maintain compliance with the XIAFLEX REMS Program requirements, as applicable.
3. Endo Pharmaceuticals will ensure that contract distributors maintain distribution records of all shipments of XIAFLEX.
4. Endo Pharmaceuticals will take reasonable steps to improve implementation of these elements and to maintain compliance with the XIAFLEX REMS Program requirements, as applicable.

C. Timetable for Submission of Assessments

Endo Pharmaceuticals will submit REMS Assessments to FDA at 6 months and 12 months from the date of the initial approval of the REMS for Peyronie's disease (12/06/2013) and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Endo Pharmaceuticals will submit each assessment so that it will be received by the FDA on or before the due date.