CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125338

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	15 January 2010
To:	Bob Rappaport, M.D., Director Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Thru:	Claudia Karwoski, Pharm. D., Director Division of Risk Management (DRISK), OSE
From:	Elizabeth Donohoe, M.D., Medical Officer, DRISK Suzanne Berkman Robottom, Pharm. D., Team Leader, DRISK Kate Heinrich, MA, Health Education Reviewer, DRISK Jodi Duckhorn, MA, Senior Social Science Reviewer, DRISK
Subject:	Review of proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Collagenase Clostridium Histolyticum (Xiaflex)
Application Type/Number:	BLA 125338
Applicant/sponsor:	Auxilium Pharmaceuticals, Inc.
OSE RCM #:	2009-1022

Suzanne Robottom for C. Karwoski 1/15/10

CONTENTS

1 INTRODUCTION

This review responds to the request by the Division of Anesthetic, Analgesia and Rheumatology Products (DAARP) for the Office of Surveillance and Epidemiology's (OSE) Division of Risk Management (DRISK) to review and comment on the sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS) for collagenase clostridium histolyticum, trade name Xiaflex. The sponsor submitted a Risk Evaluation and Mitigation Strategy (REMS) on December 2, 2009 in response to the REMS notification letter of November 25, 2009. Please note that DRISK forwarded an Interim Review to DAARP addressing the REMS and Supporting Document on 12/16/09 and an Interim review #2 on the Communication Plan materials on 12/30/09. The sponsor submitted a revised REMS to DAARP on January 4, 2010, based on recommendations from the Interim Reviews and a subsequent revision on January 8, 2010 which provides the basis for this review.

DAARP also requested a consult from DRISK to review the Medication Guide (MG) which is addressed in a separate review by the Patient Labeling reviewer dated December 22, 2009. Comments on the MG subsequent to that review have been forwarded the DAARP and changes are pending.

2 BACKGROUND

Collagenase clostridium histolyticum (Xiaflex) has a proposed indication for treatment of advanced Dupuytren's disease. Xiaflex consists of two microbial collagenases and is injected into a Dupuytren's cord. The collagenase lyses the collagen-containing cord and disrupts the cord. Xiaflex is a new molecular entity and first in class biological. Dupuytren's disease is an orphan disease, usually affecting older men of European descent. Finger contractures often occur in more than one joint and may affect both hands. If approved, Xiaflex would provide the only non-surgical treatment option for this condition.

The primary safety concern is tendon rupture, which occurred in 2/249 (1%) of Xiaflex-treated patients in the two pivotal randomized controlled trials. The risk of tendon rupture is believed to be associated with inadequate provider training, particularly of the fifth digit; the clinical trials included a training program in proper injection technique to address the risk of tendon rupture. Two factors were important in bringing Xiaflex to an Arthritis Advisory Committee meeting: it is a New Molecular Entity (NME) and the possible need for a Risk Evaluation and Mitigation Strategy (REMS) to address the risks of tendon rupture.

Additionally, three mild to moderate hypersensitivity reactions (including redness, itching, and swelling at the injection site) were observed with Xiaflex treatment in 1082 patients. There is considerable potential for more serious hypersensitivity reactions, including anaphylaxis, due to the high rate of anti-product antibody formation (seen in 100% of patients after four injections), and the progressively higher antigen-specific IgE antibody titers with successive injections demonstrated in early clinical studies.

The AC meeting was held September 16, 2009. Clinicians on the AC panel included hand surgeons and rheumatologists. The primary risk management issue involved discussion about the adequacy of the sponsor's proposed training as it relates to addressing occurrence of tendon rupture. The sponsors stated at the AC that when investigators were asked what methods were preferred, the video and manual were most recommended.

The committee was asked to discuss the adequacy of the sponsor's proposed training. Some members felt the proposed training was adequate for clinicians knowledgeable of the anatomy of the hand and comfortable performing injections in the hand; members were not in agreement as to whether the proposed training was adequate for rheumatologists to perform Xiaflex injections. Members commented that a post marketing study would be helpful to address data gaps pertaining to efficacy and safety with a broader range of administering physicians, and to address questions of long-term efficacy (i.e., contracture recurrence) and safety (i.e., risks of hypersensitivity).

The panel voted unanimously 12-0 to approve Xiaflex for the treatment of patients with advanced Dupuytren's Disease. In discussion following the vote, some members stated that any restriction on the use of Xiaflex, such as a mandatory patient registry, would be onerous and the decision to inject Xiaflex should be left to each physician. The issue of hypersensitivity was also a focus of the panel's discussion. There were significant concerns raised as to the potential to cause serious allergic reactions, including anaphylaxis, with repeated use of Xiaflex. The panel was not specifically asked to vote on the requirement of a REMS or any REMS-related issue.

The discussion at the AC meeting about the importance of provider training and concern about hypersensitivity was a factor in subsequent discussion between DAARP and OSE related to the risks of tendon rupture and hypersensitivity with Xiaflex. These safety concerns prompted recommendation of a REMS with a Medication Guide (MG) and Communication Plan (CP) to help ensure that the benefits of Xiaflex outweigh the risks. To this end, a REMS Notification Letter was sent to the sponsor on November 25, 2009 which outlined the need for a REMS, components of the CP, timetable for assessments and information needed for assessments.

Access to the training materials was a major focus in developing a risk management approach for Xiaflex. Subsequent discussion between the sponsor and FDA resulted in requirement of a training guide and training video, developed by the sponsor, as a component of the CP. These training materials were to include: 1) information about the risks of Xiaflex, including tendon ruptures and hypersensitivity events (including anaphylaxis), 2) information on how to properly inject Xiaflex and perform finger extension procedures, and 3) the requirement to disseminate the Medication Guide with each Xiaflex injection. Due to concerns about hypersensitivity and potential for anaphylaxis with repeat exposure, DAARP and OSE determined that the timetable for assessments require an initial submission at one year, annually for years 2-5 after approval and at 7 years after approval.

3 MATERIAL REVIEWED

- Background Information for the September 16, 2009 Arthritis Advisory Committee (AC) meeting
    - submitted by the sponsor; and
    - submitted by DAARP
- Advisory Committee summary minutes, approved October 16, 2009.
- REMS Notification letter, sent November 25, 2009.
- Risk Evaluation and Mitigation Strategy (REMS) submitted by the sponsor:
    - December 1, 2009 (response to REMS Notification letter)
    - January 4, 2010 submission (response to comments in OSE Interim Reviews #1 and #2 of December 16 and 30, 2009, respectively)
    - January 8, 2010 submission to DAARP (response to OSE comments communicated via email of January 7, 2010 regarding language in the Supporting Document about the Adverse Event reporting forms)

4 SPONSOR'S PROPOSED REMS

The information below is provided in the sponsor's submission of January 8, 2010 to DAARP, and reflects FDA comments on the December 1, 2009 REMS submission.

4.1 Goals

The sponsor proposes the following goals:

- To inform healthcare providers about 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 XIAFLEX.
- To inform healthcare providers about how to properly inject XIAFLEX and perform finger extension procedures.
- To inform patients about the serious risks associated with XIAFLEX.

4.2 REMS Elements

The proposed REMS includes a Medication Guide, communication plan, and a timetable for submission for assessments. The information needed for assessment of the REMS is included in REMS Supporting Document. Each element is described below and the final REMS with Attachments is presented in the Addendum to this review. The Addendum is comprised of the sponsor's REMS submission of January 8, 2010.

4.2.1 Medication Guide

DRISK's review of the proposed Medication Guide was provided separately.

In accordance with 21 CFR 208.24, a Medication Guide will be attached to the Package Insert and will be provided by Auxilium Pharmaceuticals, Inc. The Medication Guide will be included in each single unit carton containing Xiaflex and dispensed in accordance with 21 CFR 208.24. The carton will include a prominent notice to authorized dispensers to "Dispense the enclosed Medication Guide to each patient." The Medication Guide will also be available through the product website (www.XIAFLEX.com), the Sponsor's toll-free medical information line (1-877-XIAFLEX; 1-877-942-3539), and Sales and/or Medical Affairs representatives.

4.2.2 Communication Plan

The sponsor will implement a communication plan to convey important information about the risks of tendon rupture and hypersensitivity and about proper training for the administration of Xiaflex. The initial audience for this CP includes healthcare providers who are likely to prescribe Xiaflex including hand surgeons, orthopedic surgeons, plastic surgeons, general surgeons, and rheumatologists.

Communication Plan materials include the Dear Healthcare Provider (DHCP) letter with the Full Prescribing Information and the Medication Guide. The letter provides information about the risks associated with Xiaflex and instructs providers on how to obtain the educational training materials. The sponsor will send these materials by direct mail within 60 days of REMS approval. Additionally, any known new provider inquiring about the use of Xiaflex will receive the Dear Healthcare Provider Letter and have access to the educational materials, including the Training Guide and Training Video.

The Training Guide and Training Video are "stand-alone" tools and although both may be used by a provider, each provides complete training instructions and information regarding the risks addressed in the REMS. The sponsor plans to make these materials available within 60 days of REMS approval through the following distribution methods: A separate REMS link accessed on the www.XIAFLEX.com website through a stand-alone webpage; Sales and Medical Affairs representatives; and Hard copy mailing, upon request, through Auxilium's toll-free medical information line (1-877-XIAFLEX; 1-877-942-3539).

The Dear Healthcare Professional Letter is in Attachment 1.

The Training Guide (Attachment 2) and the screenshots and accompanying transcript for the Training Video (Attachment 3) are also attached.

The REMS webpage is attached in Attachment 4.

4.2.3 Elements to Assure Safe Use

The REMS does not include any Elements to Assure Safe Use.

4.2.4 Implementation System

An implementation system is not a required component of the proposed REMS since there are no elements to assure safe use.

4.2.5 Timetable for Submission of Assessments

The Sponsor proposes the following timetable for submission of assessments of the Xiaflex REMS: annually for years 1 through 5, and at 7 years after the REMS is approved. The reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Each assessment will be submitted so that it will be received by the FDA on or before the due date.

4.3 REMS Assessment Plan

Information needed for assessment is not a required element of the REMS Proposal. However, the sponsor provides the following information in the REMS Supporting Document.

1) Healthcare Provider-Based Assessments will include periodic reports which will be prepared to assess:

- 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.

The periodic reports will include:

- A 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 reactions, 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 Xiaflex 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.
- 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
- An assessment of the extent of Xiaflex 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)

In order to facilitate the collection of data for any cases of tendon rupture or hypersensitivity reactions that are reported post marketing, a targeted follow up adverse event reporting form for each type of event has been developed by the sponsor. Copies of the targeted adverse event forms for tendon rupture and hypersensitivity reactions are attached to the Supporting Document. The sponsor will send the forms to the reporter when a report is made for a targeted adverse event.

2) Patient-Based Assessments will include periodic reports which will be prepared to assess:

- Patients' understanding of the serious risks of Xiaflex, including 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).
- Distribution and dispensing of the Medication Guide by the healthcare provider in accordance with 21 CFR 208.24
- Failures to adhere to distribution and dispensing requirements and corrective actions taken to address noncompliance

3) Assessment protocols for the Healthcare Provider-Based and Patient-Based Assessments described above will be submitted to FDA at least 90 days before the assessments are conducted.

4) Based on the information reported, an assessment and conclusion of whether the REMS is meeting its goals, and whether modification to the REMS is needed will be generated at each interval.

In the proposed REMS, the sponsor also included some information about the planned approach to survey assessments; the DRISK Assessment Team has reviewed this information and provides comments to the sponsor at the end of this review.

5 DISCUSSION

The sponsor's proposed REMS addresses the requirements stipulated by FDA in the November 24, 2009 REMS notification letter. The sponsor has proposed a REMS with a MG and CP; the CP includes the DHCP letter, educational materials, a description of the intended audience and a schedule for distribution of the educational materials. Also, the sponsor plans to provide access to the Xiaflex REMS materials through a webpage.

The proposed Xiaflex REMS requires that providers have access to training materials addressing proper injection technique. The proposed training guide and video each provide thorough instructions for use of Xiaflex. The sponsor addresses information about safety concerns and the requirement for a REMS in the beginning of the materials which emphasizes the importance of the training. Both the Guide and the Video include review of hand anatomy and demonstration of appropriate storage, handling, preparation and the injection technique for use of Xiaflex. Illustration of correct needle placement within the hand is also included as is demonstration of proper finger extension exercise technique. There are also answers to frequently asked questions which address the REMS, the risks of Xiaflex and reporting of adverse events (AEs). Specific questionnaires targeted to follow-up reports of the AE of tendon/ligament rupture as well as hypersensitivity will be utilized and the sponsor will include information obtained from those questionnaires in their planned assessments.

While not required to restrict distribution through the REMS via elements to assure safe use (ETASU), the sponsor has made the business decision to require providers to complete training prior to accessing Xiaflex and all access will be directly through the sponsor. Also, DRISK acknowledges that additional data will be submitted through required post-marketing requirements the review division has outlined; planned studies will address hypersensitivity reactions including assessment of whether repeated treatment courses of Xiaflex injection result in specific antibody responses. Information from future safety data may impact the scope and focus of the REMS for Xiaflex.

6 CONCLUSION AND RECOMMENDATIONS

The Division of Risk Management and the OSE Xiaflex review team find the proposed REMS for Xiaflex to be acceptable.

The REMS materials applicable for this review include the REMS document (Addendum) with the following Attachments: the DHCP Letter (Attachment 1), the Training Guide (Attachment 2), the Training Video (Attachment 3 with stillshots and transcript) and the REMS webpage (Attachment 4) accessible through the link from the product website (www.XIAFLEX.com).

Note: At the time this review was completed, the sponsor had not submitted the final REMS submission. The pending final version is to include changes to the Medication Guide (MG). There are also minor changes to Prescribing Information. These changes will affect the Training Guide and Video with the following correction: removal of (b) (4)' from the sentence: (b) (4)

OSE recommends approval of the Xiaflex REMS as submitted on January 8, 2010 with the comments below.

We have the following comments for the sponsor:

1. Please ensure that all communication materials accurately reflect the most recent language used in labeling.

2. Regarding the Patient and Prescriber Surveys:

   The submitted methodologies lack sufficient detail to complete a review.

   Submit for review the detailed plans that will be used to evaluate patients' and healthcare providers' understanding about the risks associated with and safe use of XIAFLEX. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence", and should include all methodology and instruments that will be used in the evaluations. We have the following recommendations you should consider when designing your methodology:

   a. Recruit respondents using a multi-modal approach. For example, patients might be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.

      Explain how non-respondent follow-up or reminders will be completed and the planned frequency.

      Explain how incentive or honorarium will be offered and the intended amount.

      Explain how sites will be selected.

      Submit for review any recruitment advertisements.

   b. Define the sample size and confidence associated with that sample size.

   c. Define the expected number of healthcare providers and patients to be surveyed, and how the samples will be determined (selection criteria)

   d. Explain the inclusion criteria; that is, who is an eligible respondent. For example, a *patient* respondent might be:
      - Age 18 or older
      - Currently taking XIAFLEX or have taken in past 3 months
      - Not currently participating in a clinical trial involving XIAFLEX
      - Not a healthcare provider

      Submit any screener instruments, and if any quotas will be used.

   e. Explain how and how often surveys will be administered.

      Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy patient population. For example, surveys could be completed online, in writing or by mail, over the phone, or in person.

      Explain how surveyors will be trained.

   f. Explain controls used to compensate for the limitations or bias associated with the methodology

   g. The patient sample should be demographically representative of the patients who use XIAFLEX.

The healthcare provider sample should be demographically representative of the healthcare providers who prescribe or administer XIAFLEX.

If possible and appropriate, sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geographically

h. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.

Potential respondents should be told that their answers will not affect their ability to receive or take (patients) or prescribe or administer (healthcare providers) XIAFLEX, and that their answers and personal information will be kept confidential and anonymous.

i. Respondents should not be eligible for more than one wave of the survey.

j. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).

k. Data may be stratified by any relevant demographic variable, and presented in aggregate. We encourage you to submit with your required assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

With regard to the patient assessment:

l. The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating patients' knowledge of the serious risks associated with the use of XIAFLEX. The assessment is not to evaluate consumer comprehension of the Medication Guide.

Respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.

m. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.

n. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.

Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about XIAFLEX?" section of the Medication Guide

The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.

The order of the multiple choice responses should be randomized on each survey.

o. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

p. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.

q. Just prior to the questions about receipt of the Medication Guide, include text explaining what is a Medication Guide. For example,

Now we are going to ask you some questions about the Medication Guide you may have received with XIAFLEX. The Medication Guide is a paper handout that contains important information about the risks associated with use of XIAFLEX and how to use XIAFLEX safely. Medication Guides always include the title "Medication Guide".

r. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

- Who gave you the Medication Guide for XIAFLEX? (Select all that apply)
  a) My doctor or someone in my doctor's office
  b) My pharmacist or someone at the pharmacy
  c) Someone else - please explain: _____
  d) I did not get a Medication Guide for XIAFLEX
- Did you read the Medication Guide?
  - All,
  - Most,
  - Some,
  - None
- Did you understand what you read in the Medication Guide?
  - All,
  - Most,
  - Some,
  - None
- Did someone offer to explain to you the information in the Medication Guide?
  - Yes, my doctor or someone in my doctor's office
  - Yes, my pharmacist or someone at the pharmacy
  - Yes, someone else – please explain: _____
  - No
- Did you accept the offer? Yes or No
- Did you understand the explanation that was given to you?
  - All,
  - Most,
  - Some,
  - None
- Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

With regard to the healthcare provider assessment:

s. The assessment is to evaluate the effectiveness of the REMS in achieving the goal by evaluating healthcare providers' knowledge of: the serious risks associated with use of

XIAFLEX, how to properly inject XIAFLEX, and how to perform finger extension procedures. The assessment is not to evaluate healthcare providers' comprehension of the educational materials.

Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, videos, etc.) again prior to taking the survey.

t. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.

u. The healthcare provider knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials. These include the risk 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. Questions should also address administration technique conveyed in the educational materials. These include proper injection and finger extension procedures.

Questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.

The order of the multiple choice responses should be randomized on each survey.

v. The order of the survey questions should be such that the risk-specific questions are asked first, followed by questions about proper injection and finger extension procedures, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.

Respondents should not have the opportunity or ability to go back to previous questions in the survey.

Explain if and when any education will be offered for incorrect responses.

w. Use the following (or similar) questions to assess receipt and use of the educational materials.

- Prior to today, which of the following were you aware of or received with regard to XIAFLEX? (Select all that apply)

Educational Material	Aware	Received
Full Prescribing Information	☐	☐
Medication Guide	☐	☐
Dear Healthcare Provider Letter	☐	☐
Training Guide for the Administration of XIAFLEX	☐	☐
XIAFLEX Procedure Training Video	☐	☐

Something else - please explain:	□	□
None of the above	□	□

- Did you read the Full Prescribing Information?
  - All,
  - Most,
  - Some,
  - None
  - I did not receive the XIAFLEX Full Prescribing Information
- Did you read the Medication Guide?
  - All,
  - Most,
  - Some,
  - None
  - I did not receive the XIAFLEX Medication Guide
- Did you read the Dear Healthcare Provider Letter?
  - All,
  - Most,
  - Some,
  - None
  - I did not receive the XIAFLEX Dear Healthcare Provider Letter
- Did you read the Training Guide for the Administration of XIAFLEX?
  - All,
  - Most,
  - Some,
  - None
  - I did not receive the Training Guide for the Administration of XIAFLEX
- Did you watch the XIAFLEX Procedure Training Video?
  - All,
  - Most,
  - Some,
  - None
  - I did not access the XIAFLEX Procedure Training Video
- Do you have any questions about any of the educational materials related to XIAFLEX? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

Please let us know if you have any questions.

DRISK Xiaflex REMS Addendum 01-15-10

RISK EVALUATION AND MITIGATION STRATEGY (REMS) for XIAFLEX™ (collagenase clostridium histolyticum), under BLA 125338

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

Contact Information:

(b) (4)

I. GOALS

To inform healthcare providers about 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 XIAFLEX.

To inform healthcare providers about how to properly inject XIAFLEX and perform finger extension procedures.

To inform patients about the serious risks associated with XIAFLEX.

II. REMS ELEMENTS

A. MEDICATION GUIDE

In accordance with 21 CFR 208.24, a Medication Guide will be attached to the Package Insert and will be provided by Auxilium Pharmaceuticals, Inc.

- The Medication Guide will be included in each single unit carton containing XIAFLEX and dispensed in accordance with 21 CFR 208.24.
- The carton will include a prominent notice to authorized dispensers to "Dispense the enclosed Medication Guide to each patient."
- The Medication Guide will also be available through the product website (www.XIAFLEX.com), the Sponsor's toll-free medical information line (1-877-XIAFLEX; 1-877-942-3539), and Sales and/or Medical Affairs representatives.

Please refer to the appended Medication Guide (Appendix A).

B. COMMUNICATION PLAN

In accordance with FDCA 505-1(e)(3), Auxilium will implement a Communication Plan to convey important information about the risks associated with XIAFLEX [tendon rupture, serious adverse reactions affecting the injected extremity, and the potential risk of serious hypersensitivity reactions (including the potential for anaphylaxis)] and to disseminate education materials about how to properly inject XIAFLEX and perform finger extension procedures.

The initial target audience for this Communication Plan will include healthcare providers who are likely to prescribe XIAFLEX including hand surgeons, orthopedic surgeons, plastic surgeons, general surgeons, and rheumatologists.

Elements of the communication plan:

1. A Dear Healthcare Provider Letter (Attachment 1) will be distributed via hardcopy mailings at the time of first marketing, within 60 days of the REMS approval. Full Prescribing Information and a copy of the Medication Guide will also be distributed in this communication. This letter will also include information about how to obtain the

educational materials (see below). In addition, any known new provider inquiring about the use of XIAFLEX will also receive the Dear Healthcare Provider Letter and have access to the educational materials, including the Training Guide and Training Video.

2. Educational Materials include:
   - Training Guide for the Administration of XIAFLEX (Attachment 2)
   - XIAFLEX Procedure Training Video (see Attachment 3 for Training Video screenshots and transcript)

   The Training Guide and Training Video are "stand-alone" tools and although both may be used by a provider, each provides complete training instructions and information regarding the risks addressed in the REMS. These materials will be available within 60 days of REMS approval through the following distribution methods:
   - A separate REMS link accessed through the www.XIAFLEX.com website (Attachment 4)
   - Sales and Medical Affairs representatives
   - Hard copy mailing, upon request, through Auxilium's toll-free medical information line (1-877-XIAFLEX; 1-877-942-3539)

C. ELEMENTS TO ASSURE SAFE USE

Elements to Assure Safe Use are not required.

D. IMPLEMENTATION SYSTEM

An Implementation System is not required.

E. TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Auxilium will submit REMS Assessments to FDA annually for years 1 through 5 and at 7 years from the date of the approval of the REMS. 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 days before the submission date for that assessment. Auxilium will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix A

Medication Guide

75 Pages Withheld as b(4) Trade Secret/Confidential

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA, ANALGESIA, AND RHEUMATOLOGY PRODUCTS

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

DATE:	November 24, 2009
BLA #:	BLA 125338
PRODUCT:	Xiaflex (collagenase clostridium histolyticum)
FROM:	Curtis Rosebraugh, M.D., M.P.H., Director, Office of Drug Evaluation II, Center of Drug Evaluation and Research

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

The pre-marketing clinical review of the new molecular entity Xiaflex (collagenase clostridium histolyticum) determined that serious risks were observed with the use of Xiaflex in clinical trials. The serious risks associated with Xiaflex (collagenase clostridium histolyticum) included tendon ruptures and other serious adverse events affecting the injected extremity. In addition, the premarketing clinical review suggests potential serious risks of hypersensitivity reactions and anaphylaxis associated with Xiaflex (collagenase clostridium histolyticum). No serious adverse events of hypersensitivity or anaphylaxis were observed in the Xiaflex (collagenase clostridium histolyticum) clinical trials. However, based on a high rate of anti-product antibody formation, including high titers of antigen-specific IgE antibodies observed in early

clinical studies, the potential for serious hypersensitivity events, including anaphylaxis, remains a concern.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS will be necessary to ensure that the benefits of Xiaflex (collagenase clostridium histolyticum) outweigh the risk of tendon rupture and the potential risk of serious hypersensitivity reactions. In reaching this determination, we considered the following:

A. It has been estimated that over 9 million patients have the diagnosis of Dupuytren's Disease, although it is likely that less than 200,000 patients have severe contractures that would potentially be treated with Xiaflex (collagenase clostridium histolyticum).

B. Advanced Dupuytren's contracture is a debilitating and deforming disorder for which there are currently no effective treatments other than surgery.

C. Xiaflex (collagenase clostridium histolyticum) injection resulted in almost complete contracture reduction for 60% of Xiaflex (collagenase clostridium histolyticum) treated patients in the two pivotal randomized controlled trials, compared to 6% of placebo-treated patients.

D. The expected duration of therapy with Xiaflex (collagenase clostridium histolyticum) is episodic. For a single Dupuytren's lesion, up to 3 injections may be required, given at 30-day intervals. Because of the underlying disorder associated with Dupuytren's Disease, recurrence of nodules and contractures requiring additional treatment would be anticipated.

E. During the review of the Xiaflex (collagenase clostridium histolyticum) application, we have identified signals of serious risks observed with use of Xiaflex (collagenase clostridium histolyticum), including tendon rupture, which occurred in 2/249 (1%) of Xiaflex-treated patients in the two pivotal randomized controlled trials. Three mild to moderate hypersensitivity reactions (including redness, itch, and swelling at the injection site) were observed with Xiaflex (collagenase clostridium histolyticum) treatment in 1082 patients; however the potential for more serious hypersensitivity reactions, including anaphylaxis, remains a concern due to the high rate of anti-product antibody formation (seen in 100% of patients after four injections), and the progressively higher antigen-specific IgE antibody titers with successive injections demonstrated in early clinical studies. The background incidence of tendon ruptures and hypersensitivity events would be lower in Dupuytren's patients in the absence of Xiaflex (collagenase clostridium histolyticum) treatment. In addition to the risks of tendon ruptures and hypersensitivity reactions, Xiaflex (collagenase clostridium histolyticum) has been associated with other adverse effects to the injected hand such as edema, contusion, injection site hemorrhage, pain, swelling, and hypo-/paresthesia. Xiaflex (collagenase clostridium histolyticum) should be used with caution in patients receiving anticoagulation therapy.

F. Xiaflex is a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Xiaflex (collagenase clostridium histolyticum). FDA has determined that Xiaflex (collagenase clostridium histolyticum) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Xiaflex (collagenase clostridium histolyticum). FDA has determined that Xiaflex (collagenase clostridium histolyticum) is a product that has serious risks (relative to the benefits) of which patients should be made aware because information concerning these risks could affect patients' decisions to use Xiaflex (collagenase clostridium histolyticum).

The elements of the REMS will be a Medication Guide, a communication plan consisting of: 1) information about the risks of Xiaflex (collagenase clostridium histolyticum), including tendon ruptures and hypersensitivity events (including potential for anaphylaxis) and 2) information on how to properly inject Xiaflex (collagenase clostridium histolyticum) and perform finger extension procedures,; and a timetable for the submission of the assessments of the REMS.

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