CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125338

REMS

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:
Auxilium Pharmaceuticals, Inc.
Tel: 484-321-5900

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

MEDICATION GUIDE
XIAFLEX™ (Zī a flex)
(collagenase clostridium histolyticum)

Read this Medication Guide before you receive XIAFLEX and each time you get an injection. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about XIAFLEX?

XIAFLEX can cause serious side effects, including:

- **Tendon or ligament damage.** Receiving an injection of XIAFLEX may cause damage to a tendon or ligament in your hand and cause it to break or weaken. This could require surgery to fix the damaged tendon or ligament. Call your healthcare provider right away if you have trouble bending your injected finger (towards the wrist) after the swelling goes down or you have problems using your treated hand after your follow-up visit.

- **Nerve injury or other serious injury of the hand.** Call your healthcare provider if you get numbness, tingling, or increased pain in your treated finger or hand after your injection or after your follow-up visit.

- **Allergic Reactions.** Allergic reactions can happen in people who take XIAFLEX because it contains foreign proteins.

  Call your healthcare provider right away if you have any of these symptoms of an allergic reaction after an injection of XIAFLEX:

  - hives
  - swollen face
  - breathing trouble
  - chest pain

What is XIAFLEX?

XIAFLEX is a prescription medicine used to treat adults with Dupuytren's contracture when a "cord" can be felt.

In people with Dupuytren's contracture, there is thickening of the skin and tissue in the palm of your hand that is not normal. Over time, this thickened tissue can form a cord in your palm. This causes one or more of your fingers to bend toward the palm, so you can not straighten them.

XIAFLEX should be injected into a cord by a healthcare provider who is skilled in injection procedures of the hand and treating people with Dupuytren's contracture. The proteins in XIAFLEX help to "break" the cord of tissue that is causing the finger to be bent.

It is not known if XIAFLEX is safe and effective in children under the age of 18.

What should I tell my healthcare provider before starting treatment with XIAFLEX?

XIAFLEX may not be right for you. Before receiving XIAFLEX, tell your healthcare provider if you:

- have had an allergic reaction to a previous XIAFLEX injection.
- have a bleeding problem.
- have any other medical conditions.
- are pregnant or plan to become pregnant. It is not known if XIAFLEX will harm your unborn baby.
- are breastfeeding. It is not known if XIAFLEX passes into your breast-milk. Talk to healthcare provider about the best way to feed your baby if you receive XIAFLEX.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you use:

- a blood thinner medicine such as aspirin, clopidogrel (PLAVIX®), prasugrel hydrochloride (EFFIENT®), or warfarin sodium (COUMADIN®). If you are told to stop taking a blood thinner before your XIAFLEX injection, your healthcare provider should tell you when to restart the blood thinner.

How will I receive XIAFLEX?

- Your healthcare provider will inject XIAFLEX into the cord that is causing your finger to bend.
- After an injection of XIAFLEX, your affected hand will be wrapped with a bandage. You should limit moving and using the treated finger after the injection.
    - Do not bend or straighten the fingers of the injected hand until your healthcare provider says it is okay. This will help prevent the medicine from leaking out of the cord.
    - Do not try to straighten the treated finger yourself.
- Keep the injected hand elevated until bedtime.
- Call your healthcare provider right away if you have
    - signs of infection after your injection, such as fever, chills, increased redness, or swelling
    - numbness or tingling in the treated finger
    - trouble bending the injected finger after the swelling goes down
- Return to your healthcare provider's office as directed on the day after your injection. During this first follow-up visit, if you still have the cord, your healthcare provider may try to extend the treated finger to "break" the cord and try to straighten your finger.

- Your healthcare provider will provide you with a splint to wear on the treated finger. Wear the splint as instructed by your healthcare provider at bedtime to keep your finger straight.
- Do finger exercises each day, as instructed by your healthcare provider.
- Follow your healthcare provider's instructions about when you can start doing your normal activities with the injected hand.

What are the possible side effects of XIAFLEX?

XIAFLEX can cause serious side effects. See "What is the most important information I should know about XIAFLEX?".

Common side effects with XIAFLEX include:

- swelling of the injection site or the hand
- bleeding or bruising at the injection site
- pain or tenderness of the injection site or the hand
- swelling of the lymph nodes (glands) in the elbow or underarm
- itching
- breaks in the skin
- redness or warmth of the skin
- pain in the underarm

These are not all of the possible side effects with XIAFLEX. Tell your healthcare provider about any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088**.**

General information about XIAFLEX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about XIAFLEX. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider for information about XIAFLEX that is written for health professionals. For more information visit www.XIAFLEX.com or call 1-877-663-0412.

What are the ingredients in XIAFLEX?

Active ingredient: collagenase clostridium histolyticum.

Ingredients: hydrochloric acid, sucrose, and tromethamine. The diluent contains: calcium chloride dihydrate in 0.9% sodium chloride.

Manufactured and distributed by:
Auxilium Pharmaceuticals, Inc.
Malvern, PA 19355
USA

Revised February 2010

This Medication Guide has been approved by the U.S. Food and Drug Administration.

US License No. 1816

PL-1109-001.a

Attachment 1

DHCP Letter

XIAFLEX™
collagenase clostridium histolyticum

IMPORTANT DRUG WARNING

Dear Healthcare Provider,

The purpose of this letter is to inform you of important safety information about XIAFLEX™ (collagenase clostridium histolyticum), a new biologic medication which has been approved by the Food and Drug Administration (FDA) for the treatment of adult patients with Dupuytren's contracture with a palpable cord. XIAFLEX is administered by intra-lesional injection into a palpable Dupuytren's cord by a healthcare provider experienced in injection procedures of the hand and in the treatment of patients with Dupuytren's contracture.

The FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for XIAFLEX to ensure that the benefits of XIAFLEX outweigh its risks of tendon rupture and other serious adverse reactions of the injected extremity, and its potential risk of serious hypersensitivity reactions (including the potential for anaphylaxis).

Auxilium has worked with the FDA to develop materials to communicate about the proper preparation and injection of XIAFLEX and about finger extension procedures to facilitate cord disruption about 24 hours after XIAFLEX injections. **Training materials are available at www.XIAFLEX.com or by calling 1-877-XIAFLEX (1-877-942-3539).**

Important Safety Information

Tendon Rupture or Other Serious Injury to the Injected Extremity

- Injection of XIAFLEX, a collagenase, into collagen-containing structures such as tendons or ligaments of the hand may result in damage to those structures and possible permanent injury such as tendon rupture or ligament damage.
- Out of 1082 XIAFLEX-treated patients in the XIALFEX studies, serious adverse events of the injected extremity occurred in 11 (1%) patients including 3 (0.3%) patients who had flexor tendon ruptures and other events of the injected extremity (pulley rupture, ligament injury, recurrence of complex regional pain syndrome, tendonitis, sensory abnormality of the hand). The incidence of XIAFLEX-associated serious adverse events of the injected extremity including tendon ruptures in clinical practice may be different than the incidence seen in the clinical studies.

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- To reduce the risk of serious injury to the injected extremity, XIAFLEX should be injected only into a palpable Dupuytren's cord with a MP or PIP joint contracture, and care should be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. When injecting XIAFLEX into a Dupuytren's cord affecting a PIP joint of the fifth finger, special precautions should be taken (refer to the FDA-approved label).

Theoretical Risk of Severe Hypersensitivity Reactions

- Although there were no severe allergic reactions observed in the XIAFLEX studies (e.g., those associated with respiratory compromise, hypotension, or end-organ dysfunction), severe reactions including anaphylaxis could occur following XIAFLEX injections because XIAFLEX is a foreign protein and allergic reactions were observed in XIAFLEX-treated patients.
- In the controlled portions of the clinical XIAFLEX trials, a greater proportion of XIAFLEX-treated patients (15%) compared with placebo-treated patients (1%) had mild allergic reactions (pruritus) after up to 3 injections. The incidence of XIAFLEX-associated pruritus increased after more XIAFLEX injections.
- Healthcare providers should be prepared to address severe hypersensitivity reactions (including anaphylaxis) following XIAFLEX injections.

Healthcare Providers Should

- Review training materials (procedure training video, training guide) and the FDA-approved label on the proper preparation and injection of XIAFLEX and on finger extension procedures to facilitate cord disruption. **Training materials are available at www.XIAFLEX.com or by calling 1-877-XIAFLEX (1-877-942-3539).**
- Counsel and communicate with patients about the potential risks associated with XIAFLEX before treatment.
- Dispense a MEDICATION GUIDE to each patient before each injection. This MEDICATION GUIDE contains information that can be used to facilitate discussions about the potential risks of XIAFLEX.

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Reporting Adverse Events

If you have a patient that develops a tendon rupture, another serious adverse event of the injected extremity, or a severe hypersensitivity event following a XIAFLEX injection, it is important that you report the case even if you do not think there is a causal relationship. To report adverse events, please contact either

- Auxilium Drug Information Center at 1-877-663-0412; or
- FDA MedWatch reporting system by telephone (1-800-FDA-1088), facsimile (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/) or by mail, using the postage-paid MedWatch Voluntary Reporting Form 3500, to the FDA Safety Information and Adverse Event Reporting Program, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD, 20852-9787

Read the accompanying FDA-approved full prescribing information for XIAFLEX for a complete understanding of the benefits and risks of XIAFLEX in the treatment of adult patients with Dupuytren's contracture with a palpable cord.

Sincerely,

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

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Attachment 2
Training Guide

XIAFLEX™

collagenase clostridium histolyticum

TRAINING GUIDE FOR THE ADMINISTRATION OF XIAFLEX™

This Training Guide is required and approved by the FDA as part of the XIAFLEX Risk Evaluation and Mitigation Strategy (REMS). A REMS is a strategy to manage known or potential serious risks associated with a drug and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

Auxilium has worked with the FDA to develop this Training Guide to inform healthcare providers about the risks of XIAFLEX including tendon rupture and other serious adverse events of the injected extremity and the possible risks of severe hypersensitivity events. This Training Guide also provides instructions on the proper preparation and administration of XIAFLEX to reduce the risks of serious adverse events of the injected extremity.

Please see Full Prescribing Information and MEDICATION GUIDE.

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Please see Full Prescribing Information and MEDICATION GUIDE.

Overview

Dupuytren's contracture, a slowly progressive fibroproliferative disease of the palmar fascia in the hand, is characterized by increased collagen production and deposition which commonly results in cord formation. The Dupuytren's cord(s) may cause the affected fingers to bend or contract toward the palm of the hand resulting in the inability to fully extend the affected fingers and a reduced range of motion.

XIAFLEX™ (collagenase clostridium histolyticum) is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord. XIAFLEX consists of 2 microbial collagenases that are isolated and purified from the fermentation of *Clostridium histolyticum*. The collagenases work in a complementary fashion to provide hydrolyzing activity to collagen in the Dupuytren's cords.

This guide demonstrates the steps necessary to prepare and administer XIAFLEX. It also outlines the finger extension procedure(s) that may be required approximately 24 hours after injection to help disrupt the cord.

XIAFLEX should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.

XIAFLEX Dosing

- XIAFLEX™ (collagenase clostridium histolyticum), supplied as a lyophilized powder, **must be reconstituted with the supplied sterile diluent in the appropriate volume prior to use**
- The dose for XIAFLEX is 0.58 mg per injection into a palpable cord with a contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint, according to the injection procedure
- XIAFLEX treatment of cords associated with contractures of distal interphalangeal (DIP) joints or the joints of the thumb has not been evaluated in clinical trials
- Finger extension procedure(s) may be performed approximately 24 hours after injection in the event the cord has not spontaneously ruptured
- Four weeks after the XIAFLEX injection and finger extension procedure(s), if a MP or PIP contracture remains, the cord may be re-injected with a single dose of 0.58 mg of XIAFLEX and the finger extension procedure(s) may be repeated (approximately 24 hours after re-injection)

Please see Full Prescribing Information and MEDICATION GUIDE.

- Injection and finger extension procedure(s) may be administered up to **3 times per cord at approximately 4-week intervals**
- Inject only 1 cord at a time. If patients have multiple MP or PIP joint contractures with palpable cords, treatment of each cord should be undertaken in a sequential order with only 1 cord receiving XIAFLEX at a time

XIAFLEX Preparation for Administration

This section summarizes the procedure for reconstitution of the lyophilized XIAFLEX™ (collagenase clostridium histolyticum) powder.

Important Considerations

- Prior to reconstitution, the vials of lyophilized XIALFEX powder and sterile diluent should be stored in a refrigerator at 2° to 8°C (36° to 46°F)
- If the vials have stood at room temperature for more than 60 minutes, they should not be used and should be destroyed
- The preparation procedure varies slightly depending on whether the palpable cord is associated with a MP or PIP joint contracture and is described in detail below
- Visually inspect the vial containing XIAFLEX. The cake of lyophilized powder should be intact and white in color. If the cake has been eroded, it should not be used

Please see Full Prescribing Information and MEDICATION GUIDE.

XIAFLEX is supplied in a single-use glass vial containing 0.9 mg of a sterile, lyophilized powder for reconstitution. The vial of lyophilized XIAFLEX powder should be reconstituted with the sterile diluent (0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride) provided in a single-use vial in the package. Syringes are not included in the package.

Before Use

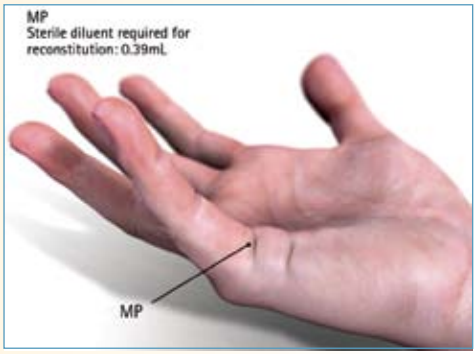
Before removing the vials from the refrigerator, confirm that the joint to be treated has a palpable cord. This is important particularly when performing a second or third XIAFLEX injection.

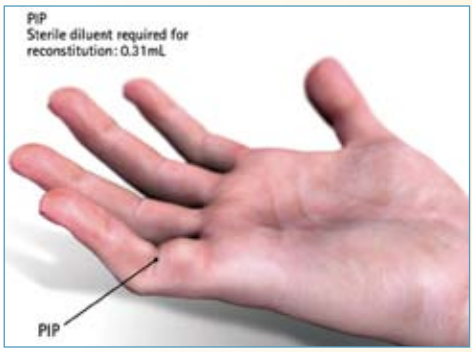
The vial containing the lyophilized XIAFLEX powder and the vial containing the sterile diluent for reconstitution should be removed from the refrigerator and allowed to stand at room temperature for at least 15 minutes but no longer than 60 minutes prior to reconstitution.

Using an aseptic technique, the following procedure for reconstitution should be followed.

XIAFLEX Preparation for Administration (continued)

1. Identify the joint contracture that is associated with the palpable cord (ie, MP or PIP)—the volume of sterile diluent required for reconstitution is determined by the type of joint contracture





2. Remove the protective covering from both vials

3. Using sterile alcohol, swab the rubber stopper and surrounding surface of the vial containing lyophilized XIAFLEX powder and the vial containing the sterile diluent for reconstitution

Please see Full Prescribing Information and MEDICATION GUIDE.

4. Using a syringe that contains 0.01 mL graduations with a 27-gauge ½-inch needle (not supplied), withdraw the appropriate amount of **sterile diluent required for reconstitution** as follows:
   - **0.39 mL for a cord affecting a MP joint or**
   - **0.31 mL for a cord affecting a PIP joint**

5. When reconstituting XIAFLEX powder, inject the sterile diluent slowly into the sides of the vial containing the lyophilized XIAFLEX powder

XIAFLEX Preparation for Administration (continued)

6. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into the solution. Do not shake the solution because it can denature the proteins

7. The reconstituted XIAFLEX solution is now ready for injection (see "XIALFEX Injection Procedure" for the appropriate injection volumes)

8. Discard the sterile diluent vial and the syringe and needle used for reconstitution

Please see Full Prescribing Information and MEDICATION GUIDE.

Important Considerations

- The reconstituted XIAFLEX solution should be clear. Inspect the solution for particulate matter and discoloration prior to administration. If the solution contains particulates, is cloudy, or is discolored, do not inject it

XIAFLEX is the trade name for the investigational product AA4500.

- Reconstituted XIAFLEX solution can be kept at room temperature (20°-25°C/68°-77°F) for up to 1 hour or refrigerated (2°-8°C/36°-46°F) for up to 4 hours prior to administration. If refrigerated, the reconstituted XIAFLEX solution should be allowed to return to room temperature for approximately 15 minutes before use

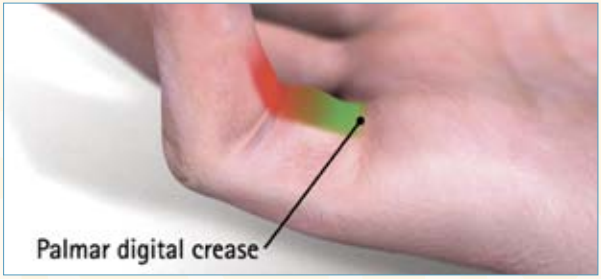
XIAFLEX Injection Procedure

This section outlines the procedure for injecting the reconstituted XIAFLEX™ (collagenase clostridium histolyticum) solution into the Dupuytren's cord.

Important Considerations

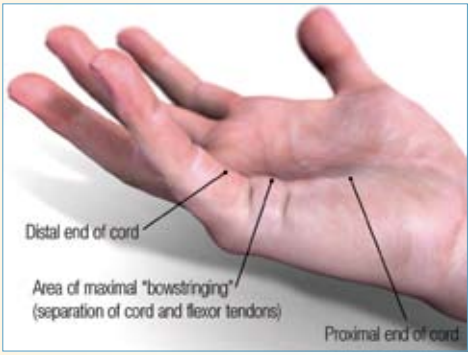
- XIAFLEX should be injected into the cord at the point of maximal separation between the cord and the underlying tendon to prevent accidental injection into the tendon or surrounding tissue
- Care must be taken to place the needle in the cord and not through the cord
- Special care also should be taken when treating the PIP of the little finger (see below)

If injecting into a cord affecting the PIP joint of the fifth finger, the needle insertion should not be more than 2 to 3 mm in depth and care should be taken to inject as close to the palmar digital crease as possible (as far proximal to the digital PIP joint crease). Tendon ruptures have occurred after XIAFLEX injections near the digital PIP joint crease.



Please see Full Prescribing Information and MEDICATION GUIDE.

Administration of a local anesthetic agent prior to injection of XIAFLEX is not recommended because it may interfere with proper injection placement.

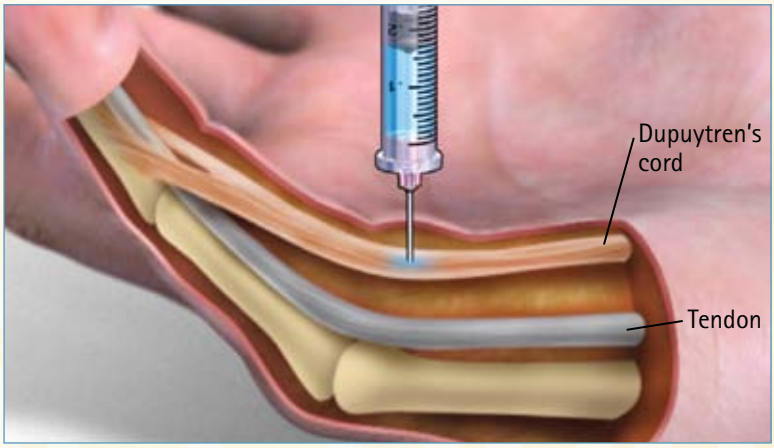


1. Reconfirm the cord and site chosen for injection. It should be the area where the contracting cord is separated maximally from the underlying flexor tendons and where the skin is not adhered intimately to the cord
2. Instruct patient to remove any jewelry from the hand to be treated
3. Prepare the skin with an antiseptic and allow it to dry

procedure

XIAFLEX Injection Procedure (continued)

4. Withdraw the volume of **reconstituted XIAFLEX solution**[1] required for injection using a hubless syringe with 0.01-mL graduations and a permanently fixed, 27-gauge ½-inch needle
   - **Cord affecting MP joint:**
     Withdraw 0.25 mL of the reconstituted solution
   - **Cord affecting PIP joint:**
     Withdraw 0.20 mL of the reconstituted solution
5. Secure the patient's hand to be treated while simultaneously applying tension to the cord. Place the needle into the cord, using caution to keep the needle within the cord, which has a gritty and gristly consistency. Avoid passing the needle tip completely through the cord to minimize the potential for injection of XIAFLEX into other tissues



Please see Full Prescribing Information and MEDICATION GUIDE.

6. After needle placement, if there is any concern that the needle is in the flexor tendon, apply a small amount of passive motion at the distal interphalangeal (DIP) joint to ascertain that the needle does not move with finger tip motion. If insertion of the needle into a tendon is suspected or paresthesia is noted by the patient, withdraw the needle and reposition it into the Dupuytren's cord

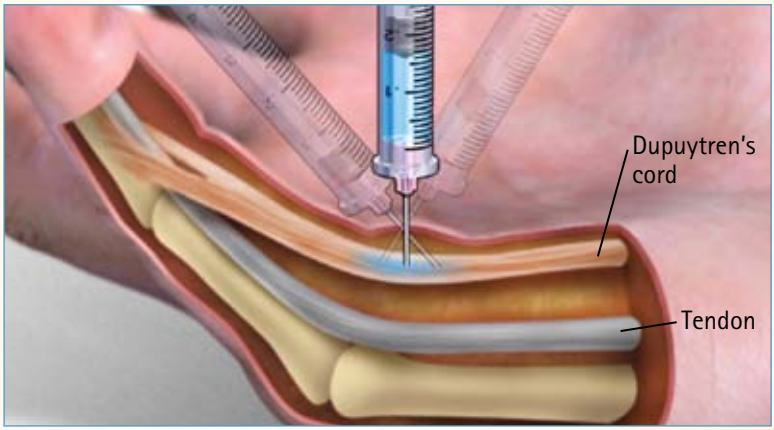
7. After confirming that the needle is placed correctly in the cord, inject approximately one-third of the dose. It is important to stabilize the needle while pushing the plunger to prevent accidental injection through the cord

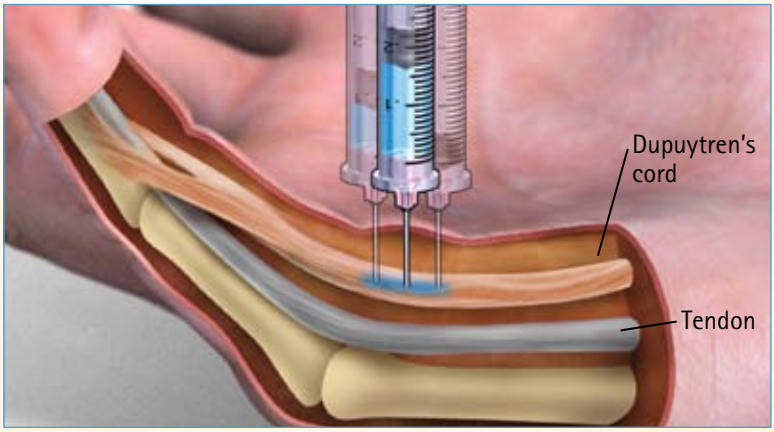
8. Withdraw the needle tip from the cord and reposition it in a slightly more distal location to the initial injection in the cord (approximately 2-3 mm) and inject another one-third of the dose

1. Each reconstituted volume withdrawn will contain the required dose of 0.58 mg of XIAFLEX. The entire reconstituted XIAFLEX solution contains 0.9 mg of XIAFLEX. Reconstituted XIAFLEX solution remaining in the vial after the injection should be discarded.

XIAFLEX Injection Procedure (continued)

9. Again, withdraw the needle tip from the cord and reposition it proximal to the initial injection (approximately 2-3 mm) and inject the final portion of the dose into the cord





An alternate method of injection may be used, in which the needle is completely withdrawn from the skin when being repositioned in the cord (approximately 2-3 mm to each side of the initial injection).

Please see Full Prescribing Information and MEDICATION GUIDE.

10. After the injections are completed, wrap the patient's treated hand with a soft, bulky gauze dressing. Instruct the patient that the dressing may be removed at bedtime, but he/she must return the next day and should keep the treated hand elevated until bedtime

11. Patients should be informed that the injection may result in swelling, bruising, or pain at the injection site and surrounding tissue. Patients should be instructed to limit motion of the injected finger and promptly contact their physician if there is evidence of infection, sensory changes, or trouble bending the finger after swelling has gone down

Important Considerations

- Discard the unused portion of the reconstituted solution after injection
- Do not store, pool, or use any vials with unused, reconstituted solution

Finger Extension Procedure(s)

This section describes the finger extension procedure(s) that are usually performed 24 hours after the XIAFLEX™ (collagenase clostridium histolyticum) injection to rupture the Dupuytren's cord.

1. Determine if the contracture has resolved at the follow-up visit the day after XIAFLEX injection

2. If a contracture remains, a passive finger extension procedure should be undertaken in an attempt to disrupt the cord

3. Local anesthesia may be used during the finger extension procedure since the procedure can be painful for the patient

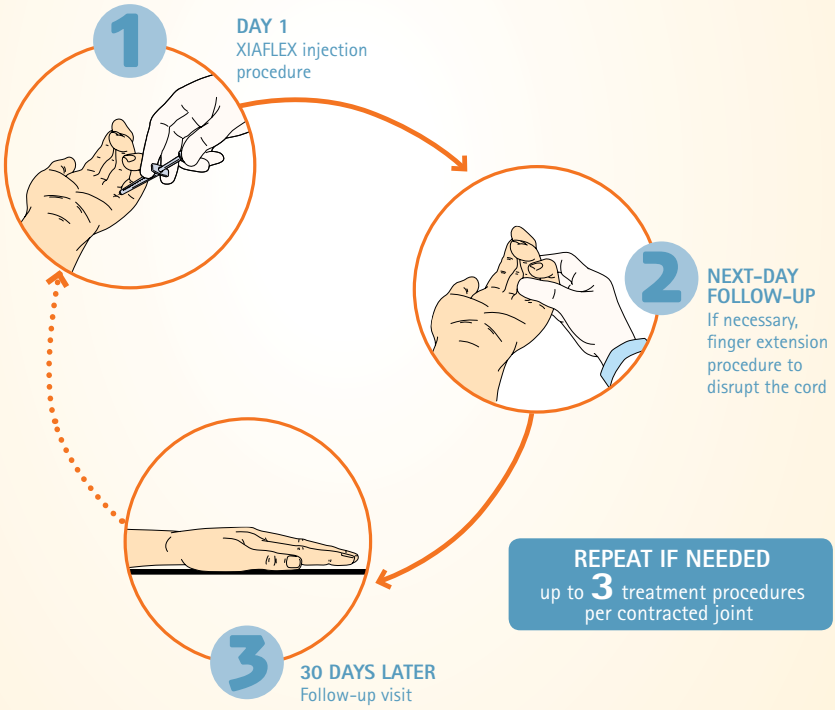
Please see Full Prescribing Information and MEDICATION GUIDE.

4. With the patient's wrist in a flexed position, apply moderate stretching pressure to the injected cord by extending the finger for approximately 10 to 20 seconds. For cords affecting the PIP joint, perform the finger extension procedure when the MP joint is in the flexed position. Do not jerk the finger to attempt to disrupt the cord, as this may contribute to tendon rupture

5. During this visit (approximately 24 hours after the XIAFLEX injection), if the first finger extension procedure does not result in rupture of the cord, a second and third attempt can be performed in 5- and 10-minute intervals. However, no more than 3 attempts to rupture a cord are recommended during this visit

Finger Extension Procedure(s) (continued)

6. If the cord has not ruptured after 3 attempts of extension, a follow-up visit should be scheduled in approximately 4 weeks. If the contracted cord persists at that subsequent visit, an additional XIAFLEX injection and subsequent finger extension procedure(s) may be repeated



In 2 XIAFLEX clinical trials, 64% and 44% of the XIAFLEX-treated patients, compared to 7% and 5% of the placebo-treated patients, achieved reduction in contracture of the primary joint (MP or PIP) to 0° to 5° after up to 3 injections.

Please see Full Prescribing Information and MEDICATION GUIDE.

7. During release of contracture, some patients may experience skin splitting. If this occurs, standard wound care with regular dressings should be applied

8. Following the finger extension procedure(s), patients should be fitted with a splint and provided instructions for use at bedtime for up to 4 months to maintain finger extension. Instruct the patient to perform finger extension and flexion exercises several times a day for several months. Patients can be instructed to resume normal activities but should not perform strenuous activity with the injected hand until instructed to do so

XIAFLEX Indication and Important Safety Information

INDICATION

XIAFLEX™ (collagenase clostridium histolyticum) is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

IMPORTANT SAFETY INFORMATION

XIAFLEX should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture.

In the controlled and uncontrolled portions of the clinical trials, flexor tendon ruptures occurred after XIAFLEX injection. Injection of XIAFLEX into collagen-containing structures such as tendons or ligaments of the hand may result in damage to those structures and possible permanent injury such as tendon rupture or ligament damage. Therefore, XIAFLEX should be injected only into the collagen cord with a MP or PIP joint contracture, and care should be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. When injecting a cord affecting a PIP joint of the fifth finger, the needle insertion should not be more than 2 to 3 mm in depth. Avoid injecting more than 4 mm distal to the palmar digital crease.

Other XIAFLEX-associated serious local adverse reactions in the controlled and uncontrolled portions of the studies

Please see Full Prescribing Information and MEDICATION GUIDE.

included pulley rupture, ligament injury, complex regional pain syndrome (CRPS), and sensory abnormality of the hand.

XIAFLEX contains foreign proteins and patients developed IgE anti-drug antibodies in greater proportions and higher titers with successive XIAFLEX injections. Healthcare providers should be prepared to address severe allergic reactions including potential for anaphylaxis immediately following XIAFLEX injections.

In XIAFLEX trials (Studies 1 and 2 in XIAFLEX Prescribing Information), 70% and 38% of XIAFLEX-treated patients developed an ecchymosis/contusion or an injection site hemorrhage, respectively. The efficacy and safety of XIAFLEX in patients receiving anticoagulant medications (other than low dose aspirin) within 7 days prior to XIAFLEX administration is unknown. Use with caution in patients with abnormal coagulation, including patients receiving anticoagulant medications (except for low-dose aspirin).

The most common adverse reactions reported in ≥25% of patients treated with XIAFLEX and at an incidence greater than placebo in the XIAFLEX clinical trials were: edema peripheral (e.g., swelling of the injected hand), contusion, injection site reaction, injection site hemorrhage, and pain in the injected extremity.

XIAFLEX Indication and Important Safety Information

Read the FDA-approved Full Prescribing Information for XIAFLEX for an understanding of the benefits and risks of XIAFLEX in the treatment of adult patients with Dupuytren's contracture with a palpable cord.

Distribute the XIAFLEX MEDICATION GUIDE to your patients and counsel each on the associated risks of treatment.

If you have product-related questions, please contact the Auxilium Drug Information Center at 1-877-663-0412.

To report adverse events, please contact either of the following

- Auxilium Drug Information Center at 1-877-663-0412
- FDA MedWatch reporting system by telephone (1-800-FDA-1088), fax (1-800-FDA-0178), online (https://www.accessdata.fda.gov/scripts/medwatch/), or by mail using the postage-paid MedWatch Voluntary Reporting Form 3500.
  Please mail to:

  FDA Safety Information and Adverse Event Reporting Program
  Food and Drug Administration
  5600 Fishers Lane
  Rockville, MD, 20852-9787

Please see Full Prescribing Information and MEDICATION GUIDE.

nt safety

Frequently Asked Questions

1. What are the risks of XIAFLEX™ (collagenase clostridium histolyticum) use?

In the XIAFLEX clinical studies, serious injury of the injected extremity including flexor tendon ruptures occurred after XIAFLEX injection. Injection of XIAFLEX into collagen-containing structures, such as tendons or ligaments of the hand, may result in damage to those structures and possible permanent injury, such as tendon rupture or ligament damage. Therefore, XIAFLEX should be injected only into the collagen cord causing a MP or PIP joint contracture, and care should be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. Other events of the injected extremity included pulley rupture, ligament injury, recurrence of complex regional pain syndrome, tendonitis, and sensory abnormality of the hand.

Since XIAFLEX is a biologic that contains foreign proteins, severe hypersensitivity reactions, including anaphylaxis, could occur following XIAFLEX injections. Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX injections. For additional information concerning XIAFLEX use, please see Full Prescribing Information.

Please see Full Prescribing Information and MEDICATION GUIDE.

2. Why is a Risk Evaluation and Mitigation Strategy (REMS) program required for XIAFLEX?

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. The FDA has determined that a REMS is necessary to help mitigate the risks associated with XIAFLEX.

Auxilium has worked with the FDA to develop the XIAFLEX REMS program to inform healthcare providers and patients about the potential risks with XIAFLEX. The XIAFLEX REMS materials for healthcare providers, including this Training Guide and the Training Video, were designed to reduce the risk of tendon rupture and other serious adverse events.

3. What is the likelihood of tendon rupture?

Of the 1,082 patients who received 0.58 mg of XIAFLEX in the controlled and uncontrolled portions of the XIAFLEX studies (2,630 XIAFLEX injections), 3 (0.3%) patients had a flexor tendon rupture of the injected finger. The incidence of XIAFLEX-associated tendon ruptures in clinical practice may be different than the incidence seen in the XIAFLEX clinical studies.

Frequently Asked Questions (continued)

4. Were there any allergic reactions to XIAFLEX?

In the controlled portions of the clinical trials (Studies 1 and 2), a greater proportion of XIAFLEX-treated patients (15%) compared with placebo-treated patients (1%) had mild hypersensitivity reactions (pruritus) after up to 3 injections. The incidence of XIAFLEX-associated pruritus increased after more XIAFLEX injections.

Although there were no severe allergic reactions observed in the XIAFLEX studies (e.g., those associated with respiratory compromise, hypotension, or end-organ dysfunction), severe reactions including anaphylaxis could occur following XIAFLEX injections because XIAFLEX is a foreign protein and mild allergic reactions were observed in XIAFLEX-treated patients.

5. What is my responsibility when I prescribe/ administer XIAFLEX?

You should read the Full Prescribing Information. The Prescribing Information and training materials include important information regarding proper injection of XIAFLEX and the finger extension procedure(s) designed to mitigate the risks of tendon rupture and other serious adverse events of the injected extremity. Secondly, a

Please see Full Prescribing Information and MEDICATION GUIDE.

MEDICATION GUIDE should be dispensed to each patient receiving XIAFLEX. This MEDICATION GUIDE contains information that can be used to facilitate discussions about the potential risks of XIAFLEX. It is important to counsel patients about the risks associated with XIAFLEX including tendon rupture, other serious adverse events of the injected extremity and the potential risk of serious hypersensitivity reactions (including the potential for anaphylaxis).

The Full Prescribing Information and the MEDICATION GUIDE will be included in the product packaging and also can be found at www.XIAFLEX.com. For additional information, visit www.XIAFLEX.com or contact the toll-free medical information line (1-877-XIAFLEX; 1-877-942-3539).

To report adverse events, please contact either of the following: Auxilium Drug Information Center at 1-877-663-0412 or the FDA MedWatch reporting system by telephone (1-800-FDA-1088), fax (1-800-FDA-0178), or online (https:// www.accessdata.fda.gov/scripts/medwatch/).

Access to XIAFLEX

XIAFLEX™ (collagenase clostridium histolyticum) is only available through a managed distribution program called XIAFLEX Xperience.

The enrollment process consists of 3 steps

1. Review the training materials
2. Complete, sign, and fax the physician enrollment form
3. Complete, sign, and fax the site enrollment form to register site(s) for shipping

More details can be found at www.XIAFLEX.com.

Please see Full Prescribing Information and MEDICATION GUIDE.

AUXILIUM

Innovations for Life™

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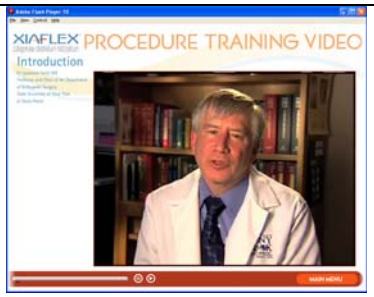
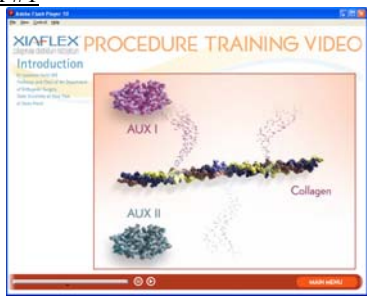
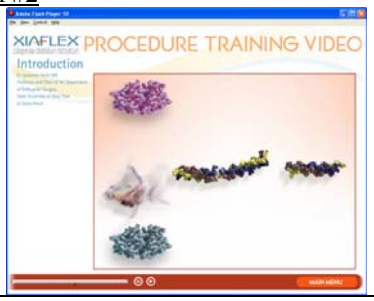
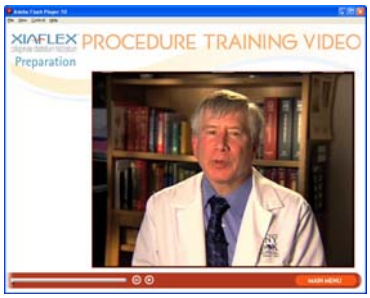
Attachment 3

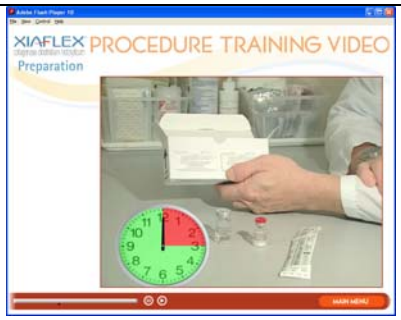
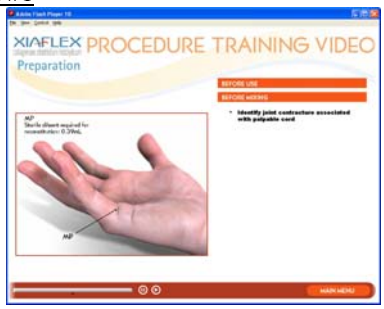
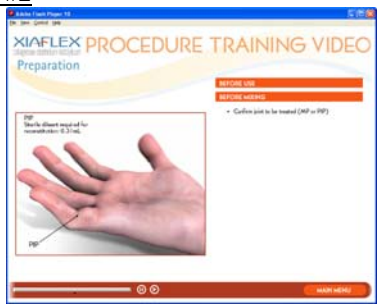
Training Video- Screenshots and Transcript

XIAFLEX Training Video

NARRATIVE	VISUAL
OPENING	
Narrator: Welcome to the XIAFLEX training video. XIAFLEX, or collagenase clostridium histolyticum is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord. **PI/p2/Indications and Usage** XIAFLEX should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture. **PI/p1/c1/"Dosage and Administration"/bullet 1**	
INTRODUCTION	
[TRANSITION SLIDE]	
KOL: Hello, I'm Dr. Lawrence Hurst, Professor and Chair of the Department of Orthopedic Surgery at the State University of New York at Stony Brook.	

	
KOL: In the early 1980s, researchers established the central role of collagen in the pathogenesis of Dupuytren's disease. Dr Marie Badalamente and I felt that collagen would be a serious therapeutic target and began investigating the role of a clostridial collagenase that could be injected into the cords that cause Dupuytren's disease. XIAFLEX contains 2 different classes of clostridial collagenase which break down collagen at different locations along the collagen fiber. **[panel #1] PI/p10/"Description" and "Clinical Pharmacology"** Once the collagen is broken into these smaller, disorganized units, endogenous enzymes are able to assist in further breaking down the fibrous material. **[panel #2]**	Panel #1  Panel #2 
KOL: Since collagen also exists in tissues other than the cords that cause Dupuytren's disease, it is vitally important that XIAFLEX be injected properly. This video will demonstrate the proper injection technique, preparation and follow-up finger-extension procedure used to disrupt the Dupuytren's cord after the administration of XIAFLEX. Also, there is important safety information at the end of the video that should be reviewed carefully.	

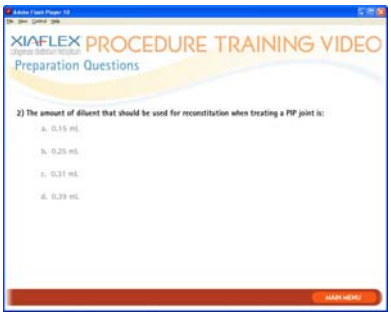
PREPARATION	
[TRANSITION SLIDE]	
KOL: In the next section, we will discuss how to properly prepare XIAFLEX for injection. It is important to note that preparation will be slightly different depending on whether you are treating an MP or PIP joint.	
Narrator: XIAFLEX is supplied in a single-use glass vial containing 0.9 mg of a sterile, lyophilized powder for reconstitution. The vial of lyophilized XIAFLEX powder should be reconstituted only with the sterile diluent provided in a single-use glass vial in the package. **PI/p5/"Dosage Forms and Strengths"; PI/p3/"Reconstitution of the Lyophilized Powder"/c** Preparation will require a syringe with 0.01 mL graduations with a 27 gauge, ½-inch needle. **PI/p3/"Reconstitution of the Lyophilized Powder"/d; p4/"Injection Procedure"/a** Syringes are not included in the package. Prior to reconstitution, the vials of lyophilized XIAFLEX powder and sterile diluent should be stored in the upright position in a refrigerator **[panel #1]**. Before removing the vials from the	Panel #1 Panel #2

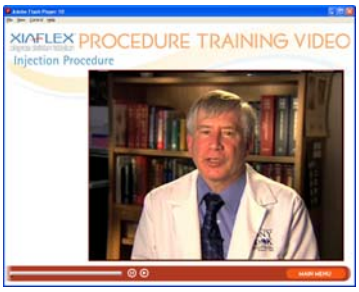
refrigerator, confirm that the joint to be treated has a palpable cord. This is particularly important when performing a 2nd or 3rd XIAFLEX injection. Once a palpable cord has been identified, both vials should be removed from the refrigerator and allowed to stand at room temperature for at least 15 minutes and no longer than 60 minutes **[panel #2]**. **PI/p3/"Reconstitution of the Lyophilized Powder"/a** If the vials have accidentally been allowed to stand at room temperature for over 60 minutes, they should not be used and should be destroyed. Visually inspect the vial containing XIAFLEX. The cake of lyophilized powder should be intact and white in color. If the cake has been eroded, it should not be used. **[panel #3]**	 Panel #3
Narrator: To begin preparing the solution, first identify the joint contracture that is associated with the palpable cord as the volume of sterile diluent required for reconstitution is determined by the type of joint contracture. For a cord affecting a MP joint use 0.39 mL of diluent for reconstitution **[panel #1]** and for a cord affecting a PIP joint use 0.31 mL **[panel #2]**. **PI/p2/Table 1**	Panel #1  Panel #2 

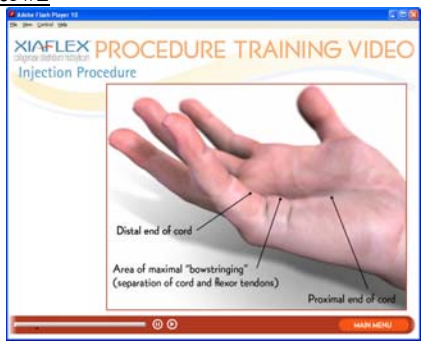
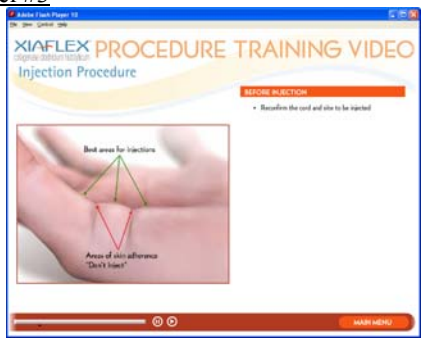
Narrator: Next, remove the protective covering from both vials… **PI/p3/"Reconstitution of the Lyophilized Powder"/b**	
Narrator: … and swab the rubber stopper and surrounding surface of both vials with sterile alcohol. No other antiseptics should be used. **PI/p3/"Reconstitution of the Lyophilized Powder"/b**	
Narrator: Using a syringe that contains 0.01 mL graudations, with a 27 gauge ½ inch needle, withdraw the appropriate amount of sterile diluent required for reconstitution. Again, for a cord affecting a MP joint use 0.39 mL of diluent **[panel #1]** and for a cord affecting a PIP joint use 0.31 mL **[panel #2]**. **PI/p3/"Reconstitution of the Lyophilized Powder"/d**	Panel #1 Panel #2

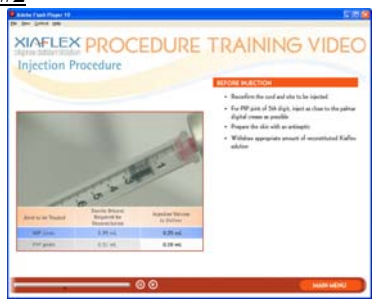
Narrator: Then, inject the diluent slowly into the sides of the vial containing the lyophilized powder of XIAFLEX. **PI/p3/"Reconstitution of the Lyophilized Powder"/e**	
Narrator: Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution **[panel #1]**. **PI/p3/"Reconstitution of the Lyophilized Powder"/e** Do not shake the solution because it can denature the proteins. The reconstituted XIAFLEX solution should be clear. Inspect the solution visually for particulate matter and discoloration prior to administration. If the solution contains particulates, is cloudy, or is discolored, do not inject it **[panel #2]**. **PI/p3/"Reconstitution of the Lyophilized Powder"/e** If particulate matter is detected, call the drug information center to report it as a product complaint.	Panel #1 Panel #2
Narrator: As a final step you can discard the sterile diluent vial and the syringe and needle used for reconstitution. **PI/p3/"Reconstitution of the Lyophilized Powder"/g**	

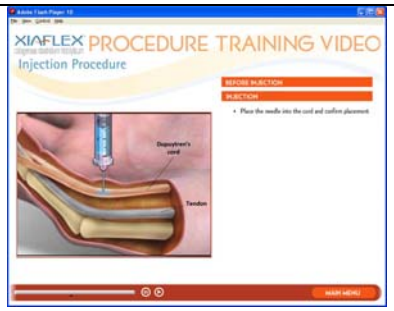
Narrator: The solution is now ready for injection. **[panel #1]** Reconstituted XIAFLEX solution can be kept at room temperature for up to one hour or refrigerated for up to 4 hours prior to administration **[panel #2]**. If refrigerated, the reconstituted XIAFLEX solution should be allowed to return to room temperature for approximately 15 minutes before use. **PI/p3/"Reconstitution of the Lyophilized Powder"/f**	Panel #1 Panel #2
[Self-Learning Versions] *Narrator:* This completes the section on Preparation of the XIAFLEX injection. To confirm understanding of the key points in this section, please answer the following self-test questions. After answering these questions you may continue to the next section.	

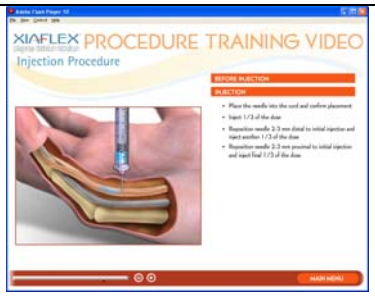
	 XIAFLEX PROCEDURE TRAINING VIDEO Preparation Questions 2) The amount of diluent that should be used for reconstitution when treating a PIP joint is: a. 0.15 mL b. 0.25 mL c. 0.31 mL d. 0.39 mL MAIN MENU

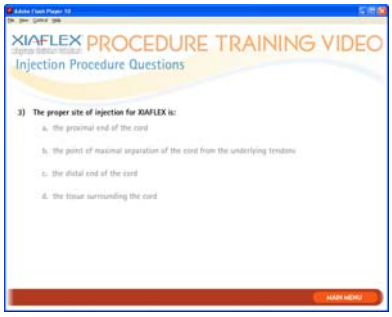
INJECTION PROCEDURE	
[TRANSITION SLIDE]	
KOL: In the next section, we will discuss how to properly inject XIAFLEX into the cord. There are three very important points that I wanted to stress here: First, XIAFLEX should be injected into the cord at the point of maximal separation between the cord and the underlying flexor tendon in order to prevent accidental injection into the flexor tendon sheath. Second, care must be taken to place the needle in the cord, and not through the cord. And third, special care should also be taken when injecting the PIP joint of the fifth finger. Let's now look at the procedure in more detail.	
Narrator: As you prepare for injection, first reconfirm the cord to be injected **[panel #1]**. The site chosen for injection should be the area where the contracting cord is maximally separated from the underlying flexor tendons **[panel #2]** and where the skin is not intimately adhered to the cord **[panel #3]**. **PI/p3/"Preparation Prior to Injection"/d**	<u>Panel #1</u>

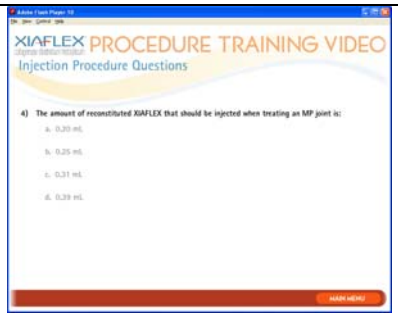
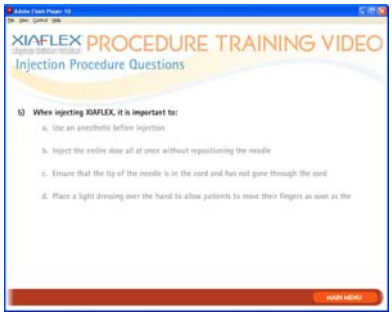
	 Panel #2  Panel #3 
Narrator: If injecting into a cord affecting the PIP joint of the fifth finger, the needle insertion should not be more than 2 to 3 mm in depth and care should be taken to avoid injecting more than 4 mm distal to the palmar digital crease. Tendon ruptures have occurred after XIAFLEX injections near the digital PIP joint crease. **PI/p3/"Preparation Prior to Injection"/c**	

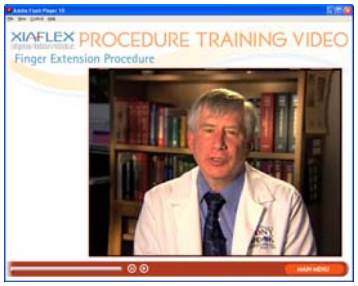
Narrator: Begin by preparing the skin with an antiseptic and allowing it to dry. **PI/p3/"Preparation Prior to Injection"/e** Make sure that any jewelry on the affected hand has been removed. Administration of a local anesthetic agent prior to injection of XIAFLEX is not recommended, as it may interfere with proper placement of the injection. **PI/p3/"Preparation Prior to Injection"/b** It is also not recommended because it may be just as painful as the injection of XIAFLEX.	
Narrator: Next, using a new 1 mL hubless syringe with 0.01 mL graduations and a permanently fixed, 27 gauge, ½-inch needle, withdraw the volume of reconstituted XIAFLEX solution required for injection. For a cord affecting a MP joint, withdraw 0.25 mL **[panel #1]** and for a cord affecting a PIP joint withdraw 0.20 mL **[panel #2]**. **PI/p4/"Injection Procedure"/a**	Panel #1 Panel #2 
Narrator: After withdrawing the correct volume of reconstituted XIAFLEX, carefully place the needle into the cord **[panel #1]**. The cord has a gritty, gristly consistency. It is important to keep the needle within the cord and not allow the needle tip to pass completely through the cord **[panel #2]**. This	Panel #1

will help minimize the potential for injection of XIAFLEX into tissues other than the cord. After needle placement, if there is any concern that the needle is in the flexor tendon, apply a small amount of passive motion at the distal interphalangeal joint to ascertain that the needle does not move with finger tip motion. If insertion of the needle into a tendon is suspected or paresthesia is noted by the patient, withdraw the needle and reposition it into the Dupuytren's cord. **PI/p4/"Injection Procedure"/b**	 Panel #2
Narrator: After confirming that the needle is correctly placed in the cord, inject approximately one-third of the dose. **PI/p4/"Injection Procedure"/c** When injecting, it is important to stabilize the needle while pushing the plunger to prevent accidental injection through the cord.	
Narrator: Next, withdraw the needle tip from the cord, reposition it in the cord approximately 2-3 mm distal to the initial injection and inject another one-third of the dose **[panel #1]**. **PI/p4/"Injection Procedure"/d** For ease of repositioning, it may be helpful to not completely withdraw the needle tip from the skin **[panel #2]**.	Panel #1 Panel #2

Narrator: Withdraw the needle tip from the cord again and reposition it in the cord, this time approximately 2-3 mm proximal to the initial injection and inject the final portion of the dose. **PI/p4/"Injection Procedure"/e**	
Narrator: An alternate method of injection may be used in which the needle is completely withdrawn from the skin when being repositioned in the cord.	
Narrator: After the injections are completed, wrap the patient's treated hand with a soft, bulky, gauze dressing **PI/p4/"Injection Procedure"/f** The dressing may be removed at bedtime. Instruct the patient to return the next day and to keep the hand elevated until bedtime. **PI/p14/"Patient Counseling Information"**	
Narrator: Patients should be informed that the injection may result in swelling, bruising,	<u>Panel #1</u>

or pain at the injection site and surrounding tissue. **[panel #1]** They should be instructed to limit motion of the injected finger until the return visit, usually the following day. **[panel #2]** Patients should also be instructed to promptly contact their physician if there is evidence of infection, sensory changes, or trouble bending the finger after the swelling goes down. **PI/p14/"Patient Counseling Information"**	 Panel#2
[Self-Learning Versions] *Narrator:* This completes the section on the proper injection procedure for the XIAFLEX injection. To confirm understanding of the key points in this section, please answer the following self-test questions. After answering these questions you may continue to the next section.	 

	 XIAFLEX PROCEDURE TRAINING VIDEO Injection Procedure Questions 4) The amount of reconstituted XIAFLEX that should be injected when treating an MP joint is: a. 0.20 mL b. 0.25 mL c. 0.31 mL d. 0.39 mL MAIN MENU  XIAFLEX PROCEDURE TRAINING VIDEO Injection Procedure Questions 5) When injecting XIAFLEX, it is important to: a. Use an anesthetic before injection b. Inject the entire dose all at once without repositioning the needle c. Ensure that the tip of the needle is in the cord and has not gone through the cord d. Place a light dressing over the hand to allow patients to move their fingers as soon as the MAIN MENU

FINGER EXTENSION PROCEDURE	
[TRANSITION SLIDE]	
KOL: This final section will briefly describe the finger extension procedure that should be used to disrupt the Dupuytren's cord. It should be performed on the follow-up visit, which usually occurs the next day after the injection. In some patients, the cord may rupture on its own. If this is not the case, the following procedure should be followed.	
Narrator: Determine if the contracture has resolved at the follow-up visit the day after XIAFLEX injection. **[panel #1]** If a contracture remains on the follow-up visit, a passive finger extension procedure should be undertaken in an attempt to disrupt the cord. **PI/p4/"Finger Extension Procedure"/a** Local anesthesia may be used during the finger extension procedure since the procedure can be painful for the patient. **PI/p4/"Finger Extension Procedure"/b** With the patient's wrist in a flexed position, apply moderate stretching pressure to the injected cord by extending the finger for approximately 10 to 20 seconds. For cords affecting the PIP joint, perform the finger extension procedure when the MP joint is in the flexed position. **PI/p4/"Finger Extension Procedure"/c** Do not jerk the finger to attempt to disrupt the cord as this may contribute to	Panel #1 Panel #2

tendon rupture. Sometimes, disruption of the cord might not occur. In other instances, the cord will be disrupted without a sound. Additionally, there may be cases in which there will be an audible "pop" when the cord is disrupted **[panel #2]**.

During this visit, approximately 24 hours after the XIAFLEX injection, if the first finger extension procedure does not result in rupture of the cord, a second and third attempt can be performed in 5- and 10-minute intervals. However, no more than 3 attempts to rupture a cord are recommended during this visit. **[panel #3] PI/p5/"Finger Extension Procedure"/d**

If the cord has not disrupted after 3 attempts of extension, a follow-up visit should be scheduled in approximately 4 weeks **[panel #4]**. If, at that subsequent visit the contracted cord persists, an additional XIAFLEX injection and subsequent finger extension procedure, or procedures, may be repeated **[panel #5]**. **PI/p5/"Finger Extension Procedure"/e**

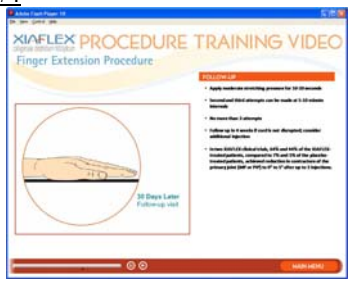
It is not unusual for patients to require more than one injection, and in fact, they can receive up to 3 injections per cord at 4 week intervals **[panel #6]**. **PI/p2/"Dosing Overview"/paragraph 3**

During release of contracture, some patients may experience skin splitting. If this occurs, standard wound care with regular dressings should be applied.

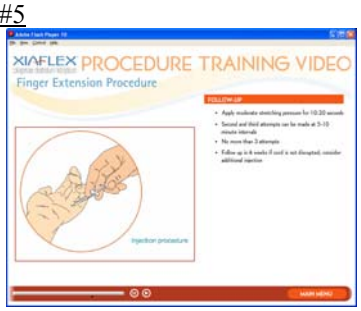
Following the finger extension procedure, or procedures, patients should be fitted with a splint and provided instructions for use at bedtime for up to 4 months to maintain finger extension **[panel #7]**. **PI/p5/"Finger Extension Procedure"/f** Instruct the patient to perform finger extension and flexion exercises several times a day for several months. Patients can be instructed to resume normal

Panel #3

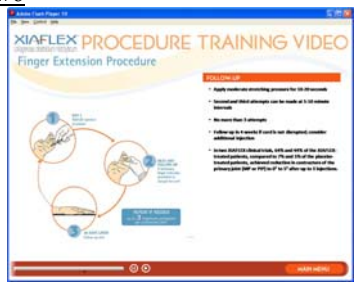
Panel #4



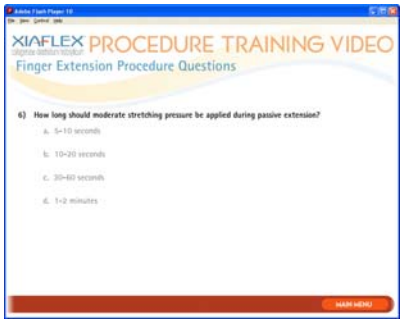
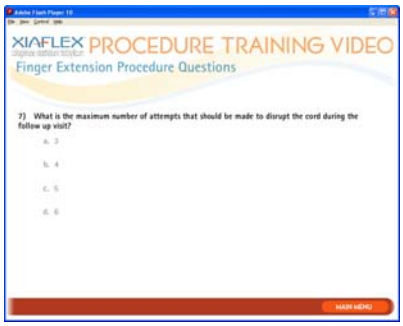
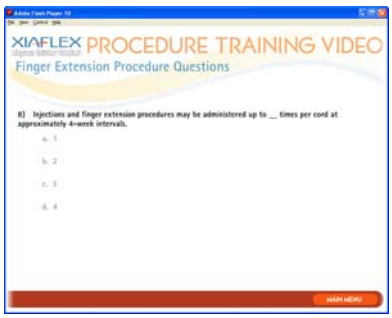
Panel #5

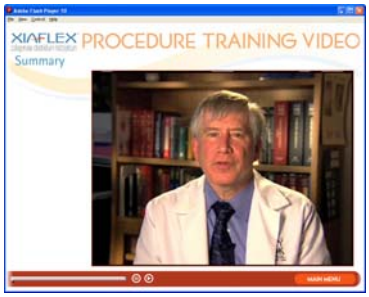


Panel #6



Panel #7

activities, but should not perform strenuous activity with the injected hand until told to do so. **PI/p14/"Patient Counseling Information"**	
[Self-Learning Versions] *Narrator:* This concludes the section on finger extension. To confirm understanding of the key points in this section, please answer the following self-test questions. After answering these questions you may continue to the next section.	  

SUMMARY	
[TRANSITION SLIDE]	
KOL: Thank you for taking time out to learn about the preparation and injection of XIAFLEX. Here's a recap of some key points.	
Narrator: **Preparation stage** • Before preparing XIAFLEX, allow vials to stand at room temperature for at least 15 minutes and no longer than 60 minutes **[panel #1] PI/p3/"Reconstitution of the Lyophilized Powder"/a** • Identify the joint contracture that is associated with the palpable cord as the volume of sterile diluent required for reconstitution is determined by the type of joint contracture. For a cord affecting a MP joint use 0.39 mL of diluent for reconstitution **[panel #2]** and for a cord affecting a PIP joint use 0.31 mL. **[panel #3] PI/p2/Table 1** **Injection procedure** • Withdraw and inject the volume of	**Include visuals for each point as follows:** Panel #1

reconstituted XIAFLEX solution required for injection. For a cord affecting a MP joint, withdraw 0.25 mL **[panel #4]** and for a cord affecting a PIP joint withdraw 0.20 mL **[panel #5] PI/p2/Table 1**

- Inject XIAFLEX at the site of maximal separation of the cord from underlying tendons **[panel #6] PI/p3/"Preparation Prior to Injection"/d**
- When injecting a cord affecting a PIP joint of the fifth finger, the needle insertion should not be more than 2 to 3 mm in depth and avoid injecting more than 4 mm distal to the palmar digital crease. **[panel #7] PI/p3/"Preparation Prior to Injection"/c**
- Confirm that the needle tip is placed in the cord **[panel #8] PI/p4/"Injection Procedure"/b**
- To maximize contact with the cord, XIAFLEX should be injected into the cord at 3 adjacent locations with one-third of the total dose being injected at each location **[panels #9, 10] PI/p4/"Injection Procedure"/c,d,e**

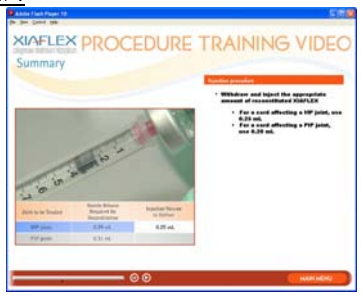
Finger extension procedure

- For finger extension, apply moderate stretching pressure for 10-20 seconds, waiting 5-10 minutes between attempts **[panel #11] PI/p4/"Finger Extension Procedure"/c; p5/"Finger Extension Procedure"/d**
- No more than 3 attempts should be made in a single visit **PI/p5/"Finger Extension Procedure"/d**
- Following the finger extension procedure, patients should be fitted with a splint **[panel #12] PI/p5/"Finger Extension Procedure"/f**

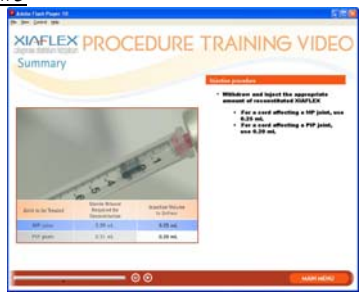
Panel #2

Panel #3

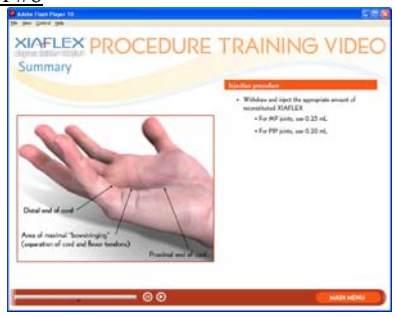
Panel #4



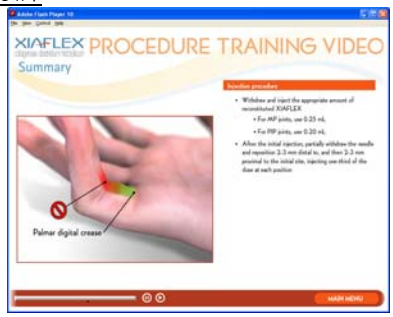
Panel #5



Panel #6

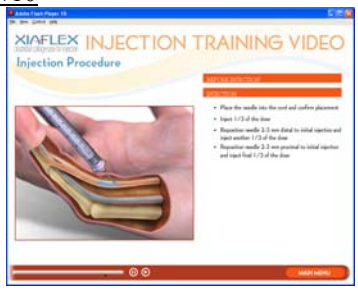


Panel #7



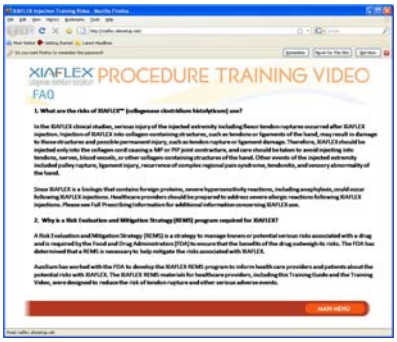
Panel #8

Panel #9

	Panel #10  Panel #11 Panel #12

IMPORTANT SAFETY INFORMATION	
Narrator: XIAFLEX is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord. **PI/p2/Indications and Usage** **IMPORTANT SAFETY INFORMATION** XIAFLEX should be administered by a health care provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture. In the controlled and uncontrolled portions of the clinical trials, flexor tendon ruptures occurred after XIAFLEX injection. Injection of XIAFLEX into collagen-containing structures such as tendons or ligaments of the hand may result in damage to those structures and possible permanent injury such as tendon rupture or ligament damage. Therefore, XIAFLEX should be injected only into the collagen cord with a MP or PIP joint contracture, and care should be taken to avoid injecting into tendons, nerves, blood vessels, or other collagen-containing structures of the hand. When injecting a cord affecting a PIP joint of the fifth finger, the needle insertion should not be more than 2 to 3 mm in depth. Avoid injecting more than 4 mm distal to the palmar digital crease. Other XIAFLEX-associated serious local adverse reactions in the controlled and uncontrolled portions of the studies included pulley rupture, ligament injury, complex regional pain syndrome (CRPS), and sensory abnormality of the hand. XIAFLEX contains foreign proteins and patients developed IgE anti-drug antibodies in greater proportions and higher titers with successive XIAFLEX injections. Healthcare providers should be prepared to address severe allergic reactions including potential for	

anaphylaxis immediately following XIAFLEX injections. In XIAFLEX trials (Studies 1 and 2 in XIAFLEX Prescribing Information), 70% and 38% of XIAFLEX-treated patients developed an ecchymosis/contusion or an injection site hemorrhage, respectively. The efficacy and safety of XIAFLEX in patients receiving anticoagulant medications (other than low dose aspirin) within 7 days prior to XIAFLEX administration is unknown. Use with caution in patients with abnormal coagulation, including patients receiving anticoagulant medications (except for low-dose aspirin). The most common adverse reactions reported in ≥ 25% of patients treated with XIAFLEX and at an incidence greater than placebo in the XIAFLEX clinical trials were: edema peripheral (e.g., swelling of the injected hand), contusion, injection site reaction, injection site hemorrhage, and pain in the injected extremity.	

FREQUENTLY ASKED QUESTIONS	
	  

	XIAFLEX PROCEDURE TRAINING VIDEO FAQ 5. What is my responsibility when I prescribe/administer XIAFLEX? You should read the Full Prescribing Information. The Prescribing Information and training materials include important information regarding proper injection of XIAFLEX and the finger extension procedure(s) designed to mitigate the risks of tendon rupture and other serious adverse events of the injected extremity. Secondly, a MEDICATION GUIDE should be dispensed to each patient receiving XIAFLEX. This MEDICATION GUIDE contains information that can be used to facilitate discussions about the potential risks of XIAFLEX. It is important to counsel patients about the risks associated with XIAFLEX including tendon rupture, other serious adverse events of the injected extremity and the potential risk of serious hypersensitivity reactions (including the potential for anaphylaxis). The Full Prescribing Information and the MEDICATION GUIDE will be included in the product packaging and also can be found at www.XIAFLEX.com. For additional information, visit www.XIAFLEX.com or contact the toll-free medical information line (1-877-XIAFLEX; 1-877-942-3339). To report adverse events, please contact either of the following: Auxilium Drug Information Center at 1-877-663-0432 or the FDA MedWatch reporting system by telephone (1-800-FDA-1088), fax (1-800-FDA-0178), or online (http://www.accessdata.fda.gov/scripts/medwatch/). MAIN MENU

CONTACT US	

Attachment 4
Website Landing Page

XIAFLEX
collagenase clostridium histolyticum

Risk Evaluation and Mitigation Strategy

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks. In order for Auxilium to communicate certain risks to ensure that XIAFLEX is injected properly, Auxilium has worked with the FDA to develop materials to communicate the risks of tendon rupture and hypersensitivity reactions. The REMS program is designed to inform health care providers and patients about the potential risks with XIAFLEX. To learn more about serious risks of XIAFLEX, read the important safety information provided in this link, including the Medication Guide, and discuss it with your patients.

The goals of the XIAFLEX REMS are:

- 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.

To access training materials on how to properly administer XIAFLEX click here:

- Procedure Training Video
- Training Guide for the Administration of XIAFLEX (pdf)

Please see the Dear Healthcare Provider Letter for more information about XIAFLEX, its use and details on accessing the XIAFLEX Xperience procedure training program.

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Please see **Full Prescribing Information** and **MEDICATION GUIDE**.

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