REMS Training Guide for Administering Xiaflex for Peyronie's Disease

This guide discusses:

- the Xiaflex REMS and the risks of penile fracture or other serious injury to the penis
- the steps necessary to prepare and administer Xiaflex
- the in-office penile modeling procedure that is part of each Xiaflex treatment cycle
- the daily, at-home penile modeling activities that are performed by the patient for approximately 6 weeks after each treatment cycle
- counseling your patient with the Xiaflex Patient Counseling Tool

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Background

What is the Xiaflex REMS (Risk Evaluation and Mitigation Strategy)?

A REMS is a strategy to manage known or potential risks associated with a drug, and is required by the FDA to ensure that the benefits of the drug outweigh its risks. Xiaflex is only available under a restricted distribution program called the Xiaflex REMS because of the risks of penile fracture and other serious penile injury associated with using Xiaflex in treating Peyronie's Disease.

This training guide is part of the Xiaflex REMS program. This guide discusses:

- the steps necessary to prepare and administer Xiaflex
- the in-office penile modeling procedure that is part of each Xiaflex treatment cycle
- the daily, at-home penile modeling activities that are performed for 5 to 6 weeks after each treatment cycle
- counseling your patient with the Xiaflex Patient Counseling Tool

Peyronie's Disease

Peyronie's disease is a localized connective tissue disorder characterized by changes in collagen composition in the tunica albuginea.[1] These changes cause an abnormal scar formation known as Peyronie's plaque, which is typically a palpable bump under the skin.[2-4] The Peyronie's plaque is composed predominantly of collagen, and replaces the normally elastic fibers of the tunica albuginea. Microvascular trauma resulting from excessive bending or injury to the penis (possibly during sexual activity) is thought to be an important trigger for the inflammatory response and plaque development characteristic of Peyronie's disease. Genetic predisposition and autoimmunity may also play a role in its development.

One of the hallmarks of Peyronie's disease is penile curvature deformity. Peyronie's disease may also cause other types of deformities, including narrowing, indentation, and shortening of the penis.

Indication

Xiaflex is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy. Xiaflex is also indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord. Use of Xiaflex for Dupuytren's contracture is covered under the REMS, but with separate requirements. (A separate letter to healthcare providers describing Important Drug Warnings for use in Dupuytren's contracture is available at www.XIAFLEXREMS.com or by calling 1-877-313-1235.)

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Xiaflex contains 2 different types of purified collagenase clostridium histolyticum (AUX-I and AUX-II), in a defined mass ratio. Injection of Xiaflex into a Peyronie's plaque, which is composed mostly of collagen, may result in enzymatic disruption of the collagen found in Peyronie's plaque. Following this disruption of the collagen-containing plaque, penile curvature deformity may improve while Patient-Reported Bother may be reduced.

Xiaflex should be administered by a healthcare provider experienced in the treatment of male urological diseases, **who has completed required training for use of Xiaflex in the treatment of Peyronie's disease.**

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Xiaflex Treatment Overview

- Xiaflex, supplied as a lyophilized powder, **must be reconstituted with the provided diluent prior to use**
- The dose of Xiaflex is 0.58 mg per injection administered into a Peyronie's plaque. If more than one plaque is present, inject into the plaque causing the curvature deformity
- A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of 2 Xiaflex injection procedures and one in-office penile modeling procedure. The second Xiaflex injection procedure occurs 1 to 3 days after the first. The in-office penile modeling procedure is performed 1 to 3 days after the second injection of the treatment cycle. (See diagram on next page.) It is necessary to identify the treatment area prior to each treatment cycle
- Healthcare providers must counsel patients on:
  - the risks of penile fractures or other serious injuries of the penis
  - how to perform the at-home penile modeling activities as appropriate
- After the third office visit of each treatment cycle, the patient performs approximately 6 weeks of daily, at-home penile modeling activities

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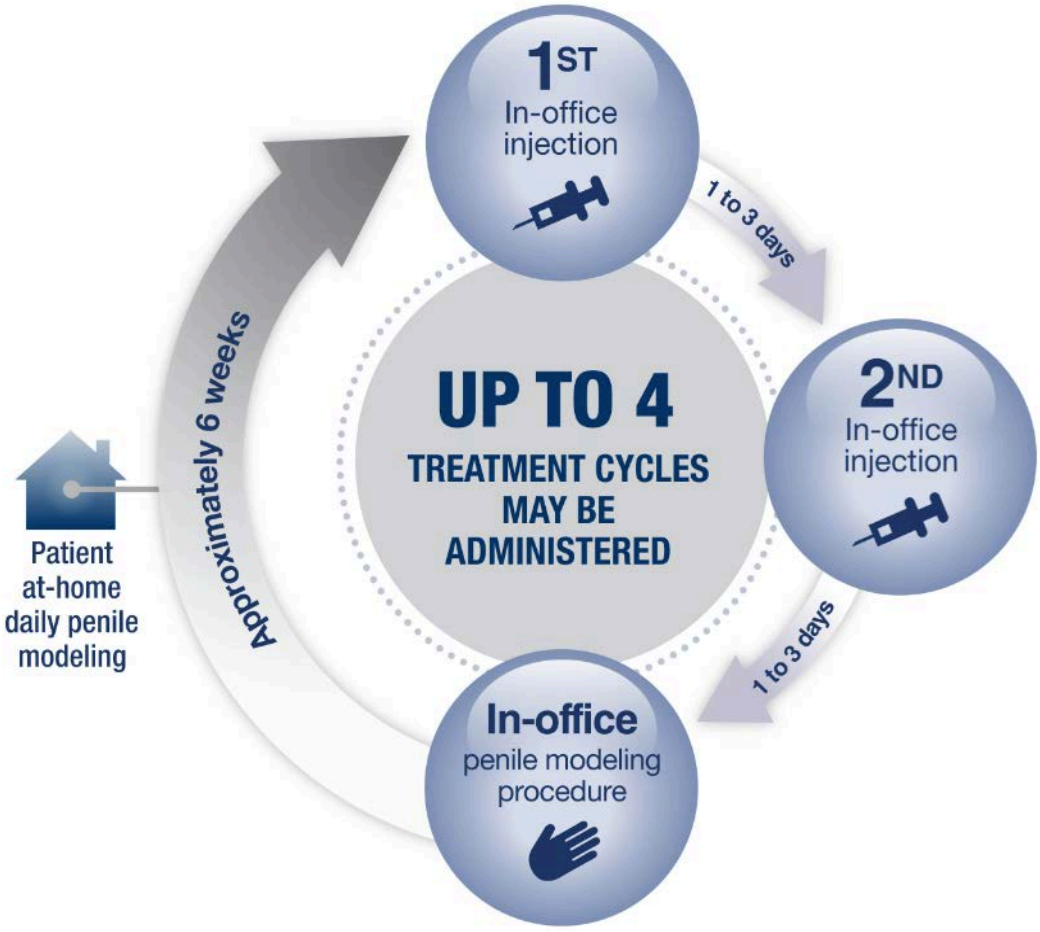
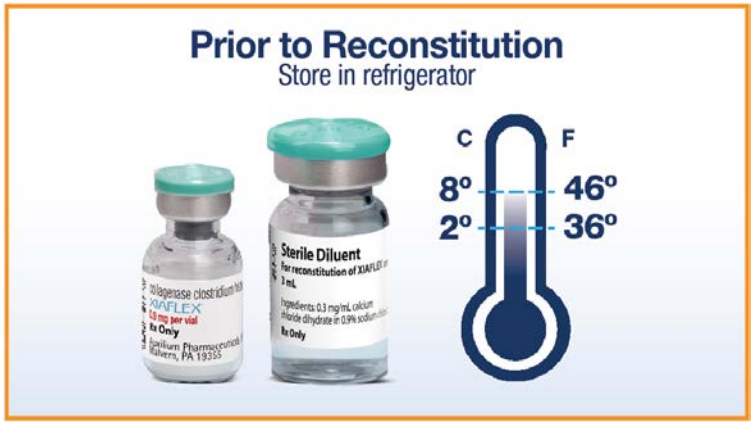
- Up to 4 treatment cycles (for a total of 8 injection procedures and 4 modeling procedures) may be administered per plaque causing the curvature deformity. If the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if the healthcare provider determines that further treatment is not clinically indicated, then the subsequent treatment cycles should not be administered
- The safety of more than one treatment course of Xiaflex (comprising 4 treatment cycles) is not known



Preparing for Administration

This section summarizes the procedure for reconstituting the lyophilized powder of Xiaflex.

Xiaflex is supplied in single-use glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. Sterile diluent for reconstitution is supplied in the package in a single-use glass vial containing 3 mL of 0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride. **Xiaflex must be reconstituted with the provided diluent prior to use.**



Prior to reconstitution, the vials of lyophilized powder of Xiaflex and sterile diluent should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze.

Before Use

1. Remove the vial containing the lyophilized powder of Xiaflex and the vial containing the diluent for reconstitution from the refrigerator and check the labels on both the diluent vial and the lyophilized powder vial to make sure they have not expired. Allow the 2 vials to stand at room temperature for at least 15 minutes but no longer than 60 minutes.

2. 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 and should be reported to Auxilium by calling 1-877-663-0412.

3. After removing the flip-off cap from each vial, using aseptic technique swab the rubber stopper and surrounding surface of the vial containing Xiaflex and the vial containing the diluent for reconstitution with sterile alcohol (no other antiseptics should be used). Use only the supplied diluent for reconstitution. The diluent contains calcium, which is required for the activity of Xiaflex.

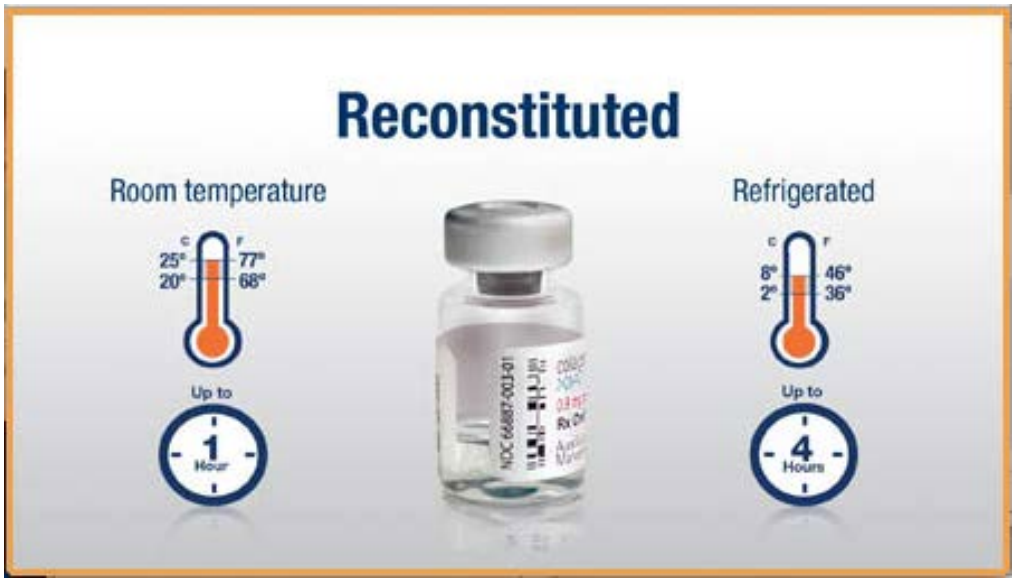
4. Using a 1-mL syringe with 0.01-mL graduations with a 27-gauge ½-inch needle (not supplied), withdraw a volume of 0.39 mL of the **diluent supplied**.

5. Inject the diluent slowly into the sides of the vial containing the lyophilized powder of Xiaflex.

6. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into the solution. Do not use if opaque particles, discoloration, or other foreign particles are present.

7. The reconstituted Xiaflex solution is now ready for injection.

8. The reconstituted Xiaflex solution can be kept at room temperature (20°C to 25°C [68°F to 77°F]) for up to 1 hour or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 4 hours prior to administration. If the reconstituted Xiaflex solution is refrigerated, allow the solution to return to room temperature for approximately 15 minutes before use and no longer than 60 minutes.



9. Do not recap the needle. Discard the syringe, needle, and diluent used for reconstitution using medical waste disposal procedures.

Self-Test Questions

1. Before use, for how long should the vials containing Xiaflex and the diluent be left to stand at room temperature?

   a) Five to ten minutes
   b) At least fifteen but no more than sixty minutes
   c) Sixty to ninety minutes
   d) At least two hours

2. The amount of diluent that should be used for reconstituting the lyophilized powder of Xiaflex is:

   a) 0.15 mL
   b) 0.25 mL
   c) 0.31 mL
   d) 0.39 mL

3. The reconstituted Xiaflex solution can be kept at room temperature for up to 1 hour or refrigerated for up to:

   a) Two hours
   b) Three hours
   c) Four hours
   d) Five hours

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Answers to Self-Test Questions

1. Before use, for how long should the vials containing Xiaflex and the diluent be left to stand at room temperature?

   a) Five to ten minutes
   b) At least fifteen but no more than sixty minutes
   c) Sixty to ninety minutes
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   b) Three hours
   c) Four hours
   d) Five hours

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Identifying the Treatment Area and Injecting Xiaflex

This section outlines the procedures for identifying the treatment area and injecting the reconstituted Xiaflex solution into the Peyronie's plaque.

NOTE: Prior to administering Xiaflex and as part of every treatment-related visit, use the Patient Counseling Tool, *What You Need to Know About Xiaflex Treatment for Peyronie's Disease* to discuss important information with each patient. Patients should be given this counseling tool to take home for reference along with a Medication Guide. See page 25 for details.

Identifying the Treatment Area

Prior to each treatment cycle, identify the treatment area as follows:

1. Induce a penile erection. A single intracavernosal injection of 10 mcg or 20 mcg of alprostadil may be used for this purpose. Apply antiseptic at the site of injection and allow the skin to dry prior to the intracavernosal injection.

2. Locate the plaque at the point of maximum concavity (or focal point) in the bend of the penis.

3. Mark the point with a surgical marker. This indicates the target area in the plaque for Xiaflex deposition.

4. The penis should be in a flaccid state before Xiaflex is injected.

Injection Procedure

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 the reconstituted solution.

1. Apply antiseptic at the site of the injection and allow the skin to dry. Administer suitable local anesthetic, if desired.

2. Using a new hubless syringe containing 0.01-mL graduations with a permanently fixed 27-gauge ½-inch needle (not supplied), withdraw a volume of 0.25 mL of **reconstituted solution (containing 0.58 mg of Xiaflex)**. There will be reconstituted solution left in the vial.

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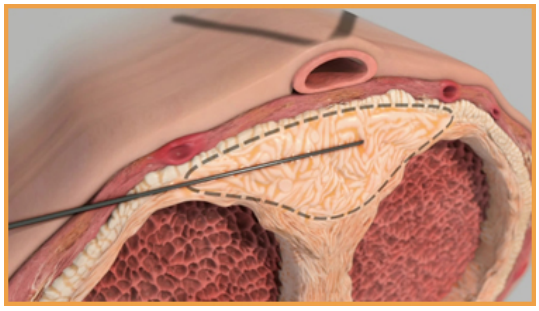
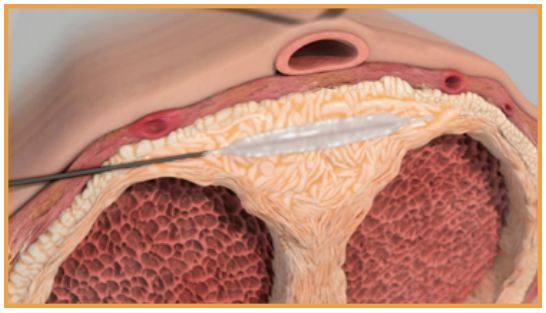
3. The penis should be in a flaccid state before Xiaflex is injected. Place the needle tip on the side of the target plaque in alignment with the point of maximal concavity. Orient the needle so that it enters the plaque from the side, NOT downwards or perpendicularly towards the corpora cavernosum.

4. Insert and advance the needle transversely through the width of the plaque, towards the opposite side of the plaque without passing completely through it. Proper needle position is confirmed by carefully noting resistance to minimal depression of the syringe plunger.





5. With the tip of the needle placed within the plaque, initiate the injection, maintaining steady pressure to slowly inject the drug into the plaque. Withdraw the needle slowly, so as to deposit the full dose along the needle track within the plaque. For plaques that are only a few millimeters in width, the distance of withdrawal of the syringe may be very minimal. The goal is always to deposit the full dose entirely within the plaque.

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6. Upon complete withdrawal of the needle, apply gentle pressure at the injection site. Apply a dressing as necessary.

7. Discard the unused portion of the reconstituted solution and diluent after each injection. Do not store, pool, or use any vials containing unused reconstituted solution or diluent.

8. The second injection of each treatment cycle should be made approximately 2 mm to 3 mm apart from the first injection and within the plaque.

At each patient visit, counsel the patient as appropriate on the following:

- The risks of penile fracture and other serious injury to the penis
- That their penis may appear bruised and/or swollen
- That they may have mild-to-moderate penile pain that can be relieved by taking over-the-counter pain medications
- To promptly contact their physician if, at any time, they have any of these symptoms:
  - a popping sound or sensation in an erect penis
  - sudden loss of the ability to maintain an erection
  - severe purple bruising and swelling of the penis
  - difficulty urinating or blood in the urine
  - severe pain in the penis

  These symptoms may indicate penile fracture, and may require surgery.

- To return to their healthcare provider's office when directed for further injection(s) and/or penile modeling procedure(s)
- **To wait 2 weeks after the <u>second</u> injection of each treatment cycle before resuming sexual activity, provided pain and swelling have subsided**

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Self-Test Questions

1. The proper site of injection for Xiaflex is:

   a) Laterally into the distal two-thirds of the penis
   b) At the point of minimal concavity in the bend of the penis
   c) At the point of maximal concavity in the bend of the penis
   d) Two millimeters from the base of the erect penis

2. The amount of reconstituted Xiaflex that should be injected into the Peyronie's plaque is:

   a) 0.20 mL
   b) 0.25 mL
   c) 0.31 mL
   d) 0.39 mL

3. When marking the treatment area the penis should be:

   a) flaccid or
   b) erect

4. When injecting Xiaflex the penis should be:

   a) flaccid or
   b) erect

5. The needle needs to be inserted in which direction into the plaque?

   a) Perpendicular to
   b) Transversely through the width of
   c) Parallel to
   d) Adjacent to, but not within

6. The goal of injection is always to deposit the full dose of drug:

   a) Entirely within the plaque
   b) Mostly within the plaque
   c) Entirely outside of the plaque
   d) Both inside and outside of the plaque

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Answers to Self-Test Questions

1. The proper site of injection for Xiaflex is:

   a) Laterally into the distal two-thirds of the penis
   b) At the point of minimal concavity in the bend of the penis
   c) At the point of maximal concavity in the bend of the penis
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Penile Modeling (In-Office and At-Home)

This section outlines the in-office penile modeling procedure, which, in conjunction with Xiaflex, helps relieve curvature deformity and straighten the penile shaft. At a follow-up visit 1 to 3 days after the second injection of each treatment cycle, perform a penile modeling procedure (as described below) on the flaccid penis to stretch and elongate the treated plaque.

This section also outlines instructions to give to patients on how to perform daily, at-home penile modeling activities for 5 to 6 weeks following each treatment cycle.

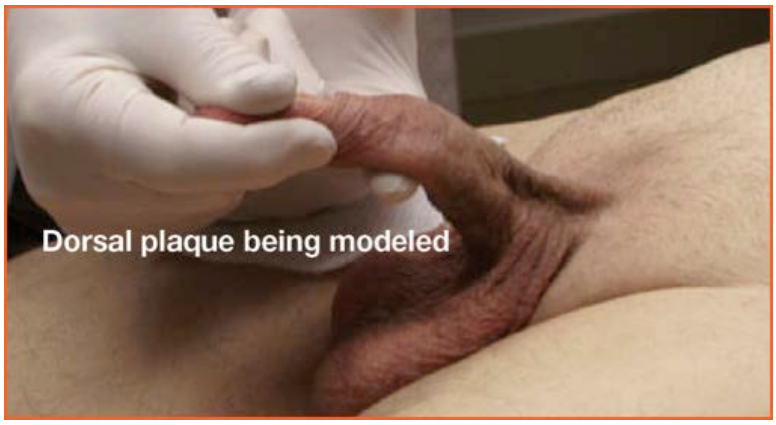
NOTE: Prior to administering Xiaflex and as part of every treatment-related visit, use the Patient Counseling Tool, *What You Need to Know About Xiaflex Treatment for Peyronie's Disease* to discuss important information with each patient. See page 21 for details.

In-Office Penile Modeling Procedure

1. Administer suitable local anesthetic, if desired.

2. Wearing gloves, grasp the plaque or indurated portion of the flaccid penis about 1 cm proximal and distal to the injection site. Avoid direct pressure on the injection site.

3. Using the target plaque as a fulcrum point, use both hands to apply firm, steady pressure to elongate and stretch the plaque. The goal is to gradually create bending opposite to the patient's penile curvature, with stretching to the point of moderate resistance.



4. Hold pressure for 30 seconds, then release.

5. After a 30-second rest period, repeat the penile modeling technique for a total of 3 modeling attempts at 30 seconds for each attempt.

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At-Home Penile Modeling Activities

There are 2 types of at-home penile modeling activities. One is a gentle stretching activity; the other is a gentle straightening activity. Discuss with patients the best time to perform these activities. Patients will do these for approximately 6 weeks after each treatment cycle.

Patients should perform the penis-stretching activity daily, three times per day, with a nonerect penis.

For the **stretching activity**, instruct the patient to:

1. Grasp the tip of the penis with the fingers of one hand and hold the base of the penis with the fingers of the other.
2. **Gently** pull the penis away from the body to its full length.
3. Hold the stretch for 30 seconds.
4. Let go and allow the penis to return to its normal, unstretched length.

Side view of penis stretching activity

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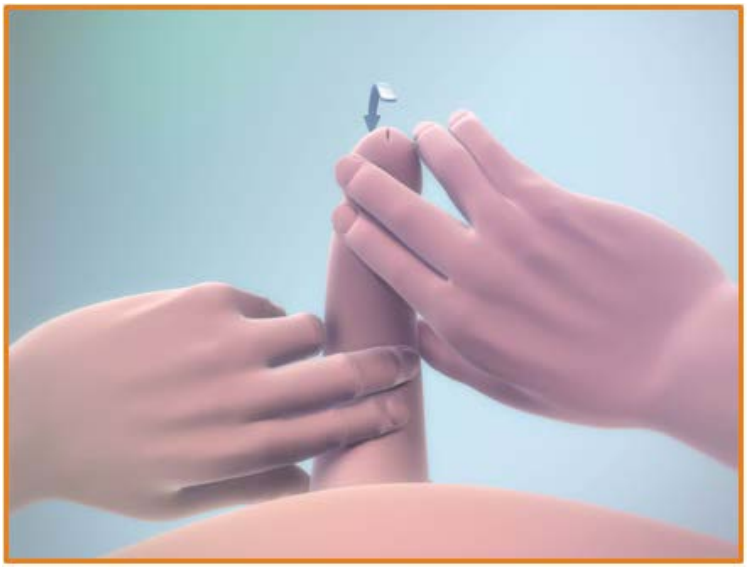
Patients should perform the penis-straightening activity no more than once per day only if a spontaneous erection occurs. If the patient does not have a spontaneous erection, he should not attempt the penis straightening.

For the **straightening activity**, instruct the patient to:

1. **Gently** attempt to bend the shaft of the erect penis in the opposite direction of the curve, but not so forcefully as to produce significant pain or discomfort.

2. Hold the penis in this more straightened position for 30 seconds, then let go.

3. Perform this no more than once per day, if a spontaneous erection unrelated to sexual activity occurs.



Top view of penis straightening activity

Self-Test Questions

1. How soon should the in-office penile modeling procedure be performed after the second injection of each treatment cycle?

   a) Immediately
   b) Fifteen to sixty minutes
   c) One to three days
   d) Five to seven days

2. When performing in-office penile modeling procedure, hold the pressure for thirty seconds and rest for thirty seconds for a total of:

   a) Two times
   b) Three times
   c) Five times
   d) Ten times

3. The patient should be instructed to perform at-home penile straightening activity on a spontaneous erection unrelated to sexual activity no more than once daily for thirty seconds. How often should the patient perform the stretching activity on the flaccid penis?

   a) At no time
   b) Once daily for a total of one minute
   c) Five times daily for thirty seconds at a time
   d) Three times daily for thirty seconds at a time

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Answers to Self-Test Questions

1. How soon should the in-office penile modeling procedure be performed after the second injection of each treatment cycle?

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   c) One to three days
   d) Five to seven days

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   a) At no time
   b) Once daily for a total of one minute
   c) Five times daily for thirty seconds at a time
   d) Three times daily for thirty seconds at a time

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Patient Counseling

A Patient Counseling Tool is a part of the Xiaflex REMS Program. This Tool called *What You Need to Know About Xiaflex Treatment for Peyronie's Disease: A Patient Guide* must be given to the patient at each visit. The Tool contains the following information that you should discuss with each patient:

- The risks of corporal rupture (penile fracture) and other serious penile injury
- Precautions related to the patient's actions to reduce these adverse outcomes (eg, advising patients to wait two weeks until after the second injection of each treatment cycle before resuming sexual activity)
- Symptoms to look for and conditions under which patients should promptly contact their healthcare provider
- Clear instructions on at-home penile modeling activities

The patient must be given a copy of the Patient Counseling Tool to take home.

In addition, provide a Medication Guide to each patient prior to each injection of Xiaflex.

To obtain copies of the Patient Counseling Tool,

- Visit www.XIAFLEXREMS.com
- Call 1-877-XIAFLEX (1-877-942-3539)
- Or contact your Xiaflex sales representative

Convenient tear pads are also available for your office.

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Self-Test Questions

1. A Peyronie's patient receiving Xiaflex should be advised to wait how long following the second injection of each treatment cycle before resuming sexual activity?

   a. 1-2 days
   b. 2 weeks
   c. 3 weeks
   d. 2 months

2. True or False. The Patient Counseling Tool, *"What You Need to Know About Xiaflex Treatment for Peyronie's Disease: A Patient Guide*," must be given to the patient at EACH visit.

   a. True
   b. False

3. True or False. The Medication Guide should be provided to each patient PRIOR to EACH injection of Xiaflex.

   a. True
   b. False

Answers to Self-Test Questions

1. A Peyronie's patient receiving Xiaflex should be advised to wait how long following the second injection of each treatment cycle before resuming sexual activity?

   a. 1-2 days
   b. 2 weeks
   c. 3 weeks
   d. 2 months

2. True or False. The Patient Counseling Tool, "*What You Need to Know About Xiaflex Treatment for Peyronie's Disease: A Patient Guide*," must be given to the patient at EACH treatment visit.

   a. True
   b. False

3. True or False. The Medication Guide should be provided to each patient PRIOR to EACH injection of Xiaflex.

   a. True
   b. False

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References: 1. Hellstrom WJ. Medical management of Peyronie's disease. *J Androl.* 2009;30(4):397-405. **2.** Ralph D, Gonzalez-Cadavid N, Mirone V, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. *J Sex Med.* 2010;7(7):2359-2374. **3.** Moreland RB, Nehra A. Pathophysiology of Peyronie's disease. *Int J Impot Res.* 2002;14(5):406-410. **4.** Bella AJ, Perelman MA, Brant WO, Lue TF. Peyronie's disease (CME). *J Sex Med.* 2007;4(6):1527-1538.

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