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.

h) Upon complete withdrawal of the needle, apply gentle pressure at the injection site. Apply a dressing as necessary.
i) 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.
j) The second injection of each treatment cycle should be made approximately 2 to 3 mm apart from the first injection.

Penile Modeling Procedure for Peyronie's Disease

Penile modeling 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:

- Administer suitable local anesthetic, if desired.
- 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.
- 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. Hold pressure for 30 seconds then release.
- After a 30 second rest period, repeat the penile modeling technique for a total of 3 modeling attempts at 30 seconds for each attempt.

In addition to the in-office penile modeling procedure, patients should be instructed to self-perform penile modeling activities at home each day for the 6-week period following the investigator penile plaque modeling visit of each treatment cycle as follows:

- During spontaneous erections, gently attempt to straighten the penis without producing pain and hold the penis in a straightened position for 30 seconds.
- The flaccid penis should be gently stretched three times daily. Slow, gentle force should be used without producing pain.

3 DOSAGE FORMS AND STRENGTHS

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 provided 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.

4 CONTRAINDICATIONS

XIAFLEX is contraindicated in:

- the treatment of Peyronie's plaques that involve the penile urethra due to potential risk to this structure.
- patients with a history of hypersensitivity to XIAFLEX or to collagenase used in any other therapeutic application or application method *[see Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Tendon Rupture or Other Serious Injury to the Injected Finger/Hand in the Treatment of Dupuytren's Contracture

In the controlled and uncontrolled portions of clinical trials in Dupuytren's contracture, flexor tendon ruptures occurred after XIAFLEX injection *[see Adverse Reactions (6.1)]*. 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 and avoid injecting more than 4 mm distal to the palmar digital crease *[see Dosage and Administration (2.1)]*.

Other XIAFLEX-associated serious local adverse reactions included pulley rupture, ligament injury, complex regional pain syndrome (CRPS), sensory abnormality of the hand, and skin laceration (tear). In a historically controlled post-marketing trial, the incidence of skin laceration (22%) was higher for subjects treated with two concurrent injections of XIAFLEX compared with subjects treated with up to three single injections in the placebo-controlled premarketing trials (9%). Cases of skin laceration requiring skin graft after finger extension procedures have been reported post-marketing. Signs or symptoms that may reflect serious injury to the injected finger/hand should be promptly evaluated because surgical intervention may be required.

5.2 Corporal Rupture (Penile Fracture) or Other Serious Injury to the Penis in the Treatment of Peyronie's Disease

Corporal rupture was reported as an adverse reaction after XIAFLEX injections in 5 of 1044 (0.5%) XIAFLEX-treated patients in the controlled and uncontrolled clinical trials in Peyronie's disease.

In other XIAFLEX-treated patients (9 of 1044; 0.9%), a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded. These patients were managed without surgical intervention, but the long-term consequences are unknown.

Severe penile hematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical trials in Peyronie's disease *[see Adverse Reactions (6)]*.

Signs or symptoms that may reflect serious injury to the penis should be promptly evaluated in order to assess for corporal rupture or severe penile hematoma, which may require surgical intervention.

Injection of XIAFLEX into collagen-containing structures such as the corpora cavernosa of the penis may result in damage to those structures and possible injury such as corporal rupture (penile fracture). Therefore, XIAFLEX should be injected only into the Peyronie's plaque and care should be taken to avoid injecting into the urethra, nerves, blood vessels, corpora cavernosa or other collagen-containing structures of the penis.

5.3 XIAFLEX REMS Program

Because of the risks of corporal rupture (penile fracture) or other serious penile injury in the treatment of Peyronie's disease, XIAFLEX is available only through the **XIAFLEX REMS Program** *[see Warnings and Precautions (5.2)]*.

Required components of the **XIAFLEX REMS Program** include the following:

- Prescribers must be certified with the program by enrolling and completing training in the administration of XIAFLEX treatment for Peyronie's disease.
- Healthcare sites must be certified with the program and ensure that XIAFLEX is only dispensed for use by certified prescribers.

Further information is available at www.XIAFLEXREMS.com or 1-877-313-1235.

5.4 Hypersensitivity Reactions, Including Anaphylaxis

In the controlled portions of the clinical trials in Dupuytren's contracture (Studies 1 and 2), a greater proportion of XIAFLEX-treated patients (15%) compared to 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 in patients with Dupuytren's contracture.

In the double-blind, placebo-controlled portions of the clinical trials in Peyronie's disease (Studies 1 and 2), a greater proportion of XIAFLEX-treated patients (4%) compared to placebo-treated patients (1%) had localized pruritus after up to 4 treatment cycles (involving up to 8 XIAFLEX injection procedures). The incidence of XIAFLEX-associated pruritus was similar after each injection regardless of the number of injections administered.

Because XIAFLEX contains foreign proteins, severe allergic reactions to XIAFLEX can occur. Anaphylaxis was reported in a post-marketing clinical trial (Study 3) in one patient who had previous exposure to XIAFLEX for the treatment of Dupuytren's contracture. Some patients with Dupuytren's contracture 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 following XIAFLEX injections.

5.5 Risk of Bleeding in Patients with Abnormal Coagulation

In the XIAFLEX trials in Dupuytren's contracture (Studies 1 and 2), 70% and 38% of XIAFLEX-treated patients developed an ecchymosis/contusion or an injection site hemorrhage, respectively (see Table 3). In the XIAFLEX controlled trials in Peyronie's disease (Studies 1 and 2), 65.5% of XIAFLEX-treated patients developed penile hematoma, and 14.5% developed penile ecchymosis (see Table 5). Patients with abnormal coagulation (except for patients taking low-dose aspirin, e.g., up to 150 mg per day) were excluded from participating in these studies.

Therefore, the efficacy and safety of XIAFLEX in patients receiving anticoagulant medications (other than low-dose aspirin, e.g., up to 150 mg per day) within 7 days prior to XIAFLEX administration is not known. In addition, it is recommended to avoid use of XIAFLEX in patients with coagulation disorders, including patients receiving concomitant anticoagulants (except for low-dose aspirin).

5.6 Acute Post-Injection Back Pain Reactions

Acute post-injection back pain reactions have been reported in the postmarketing period in patients treated with XIAFLEX for Peyronie's disease *[see Adverse Reactions (6.4)]*. These events typically have an onset immediately or within minutes of injection. The acute lower back pain can be mild to severe in intensity and can radiate to the legs, arms and chest. Other systemic symptoms, such as chest pain, headache, and dyspnea, have been reported along with back pain episodes. None of the events were reported to occur after the patient's first XIAFLEX injection and a few were reported to occur during a second treatment course *[see Dosage and Administration (2.2)]*. Reported events typically resolved within 15 minutes, but some lasted up to 30 minutes, and one event lasted 1.5 hours. Reported events typically did not require intervention, but some required observation and treatment with analgesics.

6 ADVERSE REACTIONS

The following serious adverse reactions in patients with Dupuytren's contracture are discussed in greater detail elsewhere in the labeling:

- Tendon ruptures or other serious injury to the injected extremity *[see Warnings and Precautions (5.1)]*

The following serious adverse reactions in patients with Peyronie's disease are discussed in greater detail elsewhere in the labeling:

- Corporal rupture (penile fracture) and severe penile hematoma *[see Warnings and Precautions (5.2)]*
- In other XIAFLEX-treated patients, a combination of penile ecchymoses or hematoma, sudden penile detumescence, and/or a penile "popping" sound or sensation was reported, and in these cases, a diagnosis of corporal rupture cannot be excluded *[see Warnings and Precautions (5.2)]*

6.1 Clinical Studies Experience in Patients with Dupuytren's Contracture

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Out of 1082 patients who received 0.58 mg of XIAFLEX in the controlled and uncontrolled portions of the XIAFLEX studies (2630 XIAFLEX injections), 3 (0.3%) patients had a flexor tendon rupture of the treated finger within 7 days of the injection.

The data described below are based on two pooled randomized, double-blind, placebo-controlled trials through Day 90 in patients with Dupuytren's contracture (Studies 1 and 2). In these trials, patients were treated with up to 3 injections of 0.58 mg of XIAFLEX or placebo with approximately 4-week intervals between injections and the patients had finger extension procedures the day after injection, if needed, to facilitate disruption of the cord *[see Clinical Studies (14)]*. These trials were comprised of 374 patients of whom 249 and 125 received 0.58 mg of XIAFLEX and placebo, respectively. The mean age was 63 years, 80% were male and 20% were female, and 100% were white.

In the placebo-controlled portions of Studies 1 and 2 through Day 90, 98% and 51% of XIAFLEX-treated and placebo-treated patients had an adverse reaction after up to 3 injections, respectively. Over 95% of XIAFLEX-treated patients had an adverse reaction of the injected extremity after up to 3 injections. Approximately 81% of these local reactions resolved without intervention within 4 weeks of XIAFLEX injections. The adverse reaction profile was similar for each injection, regardless of the number of injections administered. However, the incidence of pruritus increased with more injections *[see Warnings and Precautions (5.4)]*.

The most frequently reported adverse drug reactions (≥ 25%) in the XIAFLEX clinical trials in patients with Dupuytren's contracture included edema peripheral (mostly swelling of the injected hand), contusion, injection site hemorrhage, injection site reaction, and pain in the treated extremity. Table 3 shows the incidence of adverse reactions that were reported in greater than or equal to 5% of XIAFLEX-treated patients and at a frequency greater than placebo-treated patients after up to 3 injections in the pooled placebo-controlled trials through Day 90 (Studies 1 and 2).

Table 3. Adverse Reactions Occurring in ≥ 5% of XIAFLEX-Treated Patients with Dupuytren's Contracture and at a Greater Incidence than Placebo in the Placebo-Controlled Trials Through Day 90 After Up to 3 Injections

Adverse Reaction	XIAFLEX N=249	Placebo N=125
All Adverse Reactions	98%	51%
Edema peripheral[a]	73%	5%
Contusion[b]	70%	3%
Injection site hemorrhage	38%	3%
Injection site reaction[c]	35%	6%
Pain in extremity	35%	4%
Tenderness	24%	0%
Injection site swelling[d]	24%	6%
Pruritus[e]	15%	1%
Lymphadenopathy[f]	13%	0%
Skin laceration	9%	0%
Lymph node pain	8%	0%
Erythema	6%	0%
Axillary pain	6%	0%

[a] Most of these events were swelling of the injected hand.
[b] Includes the terms: contusion (any body system) and ecchymosis.
[c] Includes the terms: injection site reaction, injection site erythema, injection site inflammation, injection site irritation, injection site pain, and injection site warmth.
[d] Includes the terms: injection site swelling and injection site edema.
[e] Includes the terms: pruritus and injection site pruritus.
[f] Includes the terms: lymphadenopathy and axillary mass.

Some patients developed vasovagal syncope after finger extension procedures.

The safety of two concurrent injections of XIAFLEX 0.58 mg into Dupuytren's cords in the same hand was evaluated in a historically-controlled, open-label multi-center trial in 715 adult subjects with Dupuytren's contracture (Study 3). In Study 3, finger extension procedures were performed approximately 24 to 72 hours after injection. The patient demographics were similar to Studies 1 and 2.

based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use.

16 HOW SUPPLIED/STORAGE AND HANDLING

XIAFLEX is available in single-use, glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder.

Sterile diluent for reconstitution is available in single-use, glass vials containing 3 mL of 0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride.

NDC Number	Package Size
66887-003-01	Single-use package: 1 carton containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent
66887-003-02	Dual-Pack (2 single-use packages): 1 box containing 2 cartons, each containing a single-use vial of XIAFLEX and a single-use vial of sterile diluent

Storage and Stability

Prior to reconstitution, the vials of XIAFLEX and diluent should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) *[see Dosage and Administration (2.1, 2.2)]*. Do not freeze.

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 *[see Dosage and Administration (2.1, 2.2)]*.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Patient Counseling for Dupuytren's Contracture

Advise patients of the following:

- Serious complications of XIAFLEX injection include tendon rupture, serious ligament damage, or skin laceration that may result in the inability to fully bend the finger and may require surgery to correct the complication.
- XIAFLEX injection is likely to result in swelling, bruising, bleeding, and/or pain of the injected site and surrounding tissue.

After the XIAFLEX injections, instruct patients:

- Not to flex or extend the fingers of the injected hand to reduce extravasation of XIAFLEX out of the cord(s).
- Not to attempt to disrupt the injected cord(s) by self-manipulation.
- To elevate the injected hand until bedtime.
- To promptly contact their physician if there is evidence of infection (e.g., fever, chills, increasing redness or edema), sensory changes in the treated finger(s), trouble bending

Medication Guide

XIAFLEX® (Zī a flex)

(collagenase clostridium histolyticum)

For injection, for intralesional use

XIAFLEX is approved for two uses: Dupuytren's contracture and Peyronie's disease. Information is provided separately for each use. Use for treating Dupuytren's contracture is described first, followed by use for treating Peyronie's disease.

Read this Medication Guide before you receive XIAFLEX for the treatment of Dupuytren's contracture 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 for the treatment of Dupuytren's contracture?

XIAFLEX may cause serious side effects, including:

1. **Tendon rupture 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.
2. **Nerve injury or other serious injury of the hand. Call your healthcare provider right away** if you get numbness, tingling, increased pain, or tears in the skin (laceration) in your treated finger or hand after your injection or after your follow-up visit.
3. **Hypersensitivity reactions, including anaphylaxis.** Severe allergic reactions can happen in people who receive 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
   - low blood pressure
   - dizziness or fainting

What is XIAFLEX?

XIAFLEX is a prescription medicine used to treat adults with Dupuytren's contracture when a "cord" can be felt.
It is not known if XIAFLEX is safe and effective in children under the age of 18.

Who should not receive XIAFLEX?

Do not receive XIAFLEX if you:

- are allergic to collagenase clostridium histolyticum, or any of the ingredients in XIAFLEX, or to any other collagenase product. See the end of this Medication Guide for a complete list of ingredients in XIAFLEX.

Talk to your healthcare provider before receiving this medicine if you have any of these conditions.

What should I tell my healthcare provider before receiving XIAFLEX?

Before receiving XIAFLEX, tell your healthcare provider if you:

- have had an allergic reaction to a XIAFLEX injection in the past
- have a bleeding problem
- have received XIAFLEX to treat another condition
- 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 or plan to breastfeed. It is not known if XIAFLEX passes into your breast milk. Talk to your 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 over-the-counter medicines, vitamins, and herbal supplements.

Using XIAFLEX with certain other medicines can cause serious side effects.

Especially tell your healthcare provider if you take:

- medicines to thin your blood (anticoagulants). 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.

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.