HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIAFLEX safely and effectively. See full prescribing information for XIAFLEX.

XIAFLEX® (collagenase clostridium histolyticum)
for injection, for intralesional use
Initial U.S. Approval: 2010

----------INDICATIONS AND USAGE----------

XIAFLEX is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord. (1)

---------- DOSAGE AND ADMINISTRATION----------

- XIAFLEX should be administered by a healthcare provider experienced in injection procedures of the hand and in the treatment of Dupuytren's contracture. (2.1)
- Reconstitute XIAFLEX lyophilized powder with only the supplied diluent prior to use. (2.1, 2.2)
- Inject 0.58 mg of XIAFLEX into a palpable Dupuytren's cord with a contracture of a metacarpophalangeal (MP) joint or a proximal interphalangeal (PIP) joint according to the injection procedure. (2.1,2.4)
- Approximately 24 hours following an injection, perform a finger extension procedure if a contracture persists. (2.1,2.5)
- Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals. (2.1)
- Inject only one cord at a time. If a patient has other cords with contractures, inject each cord in sequential order. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Single-use glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilized powder for reconstitution. Sterile diluent for reconstitution is also provided in a single-use glass vial. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Tendon rupture or serious injury to the injected extremity: Avoid injecting XIAFLEX into tendons, nerves, blood vessels, or other collagen-containing structure of the hand. Injection into these structures may result in possible permanent injury, such as tendon rupture or ligament damage. (5.1)
- Allergic reactions: Healthcare providers should be prepared to address severe allergic reactions following XIAFLEX injections. (5.2)
- Patients with abnormal coagulation: Use with caution, including in patients who have received anticoagulant medications other than low-dose aspirin within 7 days of the injection. (5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported in ≥ 25% of patients treated with XIAFLEX and at an incidence greater than placebo were edema peripheral (e.g., swelling of the injected hand), contusion, injection site hemorrhage, injection site reaction, and pain in the injected extremity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Auxilium Pharmaceuticals, Inc. at 1-877-663-0412 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised:07/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XIAFLEX is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Overview

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

XIAFLEX, supplied as a lyophilized powder, **must be reconstituted with the provided diluent prior to use** *[see Dosage and Administration (2.2)]*. The dose of 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 *[see Dosage and Administration (2.4)]*. Table 1 displays an overview of the volumes of sterile diluent for reconstitution and the reconstituted XIAFLEX solution to be used in the intralesional injection *[*see *Dosage and Administration (2.2, 2.4)]*. Approximately 24 hours after injection, perform a finger extension procedure if a contracture persists to facilitate cord disruption *[*see *Dosage and Administration (2.5)]*.

Table 1. Volumes Needed for Reconstitution and Administration

	For cords affecting MP joints	For cords affecting PIP joints
Sterile Diluent for Reconstitution		
Volume	0.39 mL	0.31 mL
Reconstituted XIAFLEX Solution to be Injected[1]		
Volume	0.25 mL	0.20 mL

[1] The reconstituted XIAFLEX solution to be used in the intralesional injection contains 0.58 mg of XIAFLEX.
Note: The entire reconstituted XIAFLEX solution contains 0.9 mg of XIAFLEX. Reconstituted XIAFLEX solution remaining in the vial after the injection should be discarded.

Four weeks after the XIAFLEX injection and finger extension procedure, 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 may be repeated (approximately 24 hours after injection). Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.

Inject only one cord at a time. If a patient has other palpable cords with contractures of MP or PIP joints, these cords may be injected with XIAFLEX in a sequential order.

2.2 Reconstitution of the Lyophilized Powder

a) Before use, remove the vial containing the lyophilized powder of XIAFLEX and the vial containing the diluent for reconstitution from the refrigerator and allow the two

vials to stand at room temperature for at least 15 minutes and no longer than 60 minutes. Visually inspect the vial containing XIAFLEX. The cake of lyophilized powder should be intact and white in color.

b) After removal of 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).

c) Use only the supplied diluent for reconstitution. The diluent contains calcium which is required for the activity of XIAFLEX.

d) Using a 1 mL syringe that contains 0.01 mL graduations with a 27-gauge ½-inch needle (not supplied), withdraw a volume of the **diluent supplied**, as follows:

- **0.39 mL for cords affecting a MP joint or**
- **0.31 mL for cords affecting a PIP joint**.

e) Inject the diluent slowly into the sides of the vial containing the lyophilized powder of XIAFLEX. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilized powder has gone into solution.

f) The reconstituted XIAFLEX solution can be kept at room temperature (20º to 25ºC/68º to 77ºF) for up to one hour or refrigerated at 2º to 8°C (36º to 46°F) for up to 4 hours prior to administration. If the reconstituted XIAFLEX solution is refrigerated, allow this solution to return to room temperature for approximately 15 minutes before use.

g) Discard the syringe and needle used for reconstitution and the diluent vial.

2.3 Preparation Prior to Injection

a) 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.

b) Administration of a local anesthetic agent prior to injection is not recommended, as it may interfere with proper placement of the XIAFLEX injection.

c) If injecting into a cord affecting the PIP joint of the fifth finger, care should be taken to inject as close to the palmar digital crease as possible (as far proximal to the digital PIP joint crease), and the needle insertion should not be more than 2 to 3 mm in depth. Tendon ruptures occurred after XIAFLEX injections near the digital PIP joint crease *[see Warnings and Precautions (5.1)]*.

d) Reconfirm the cord to be injected. The site chosen for injection should be the area where the contracting cord is maximally separated from the underlying flexor tendons and where the skin is not intimately adhered to the cord.

e) Apply an antiseptic at the site of the injection and allow the skin to dry.

2.4 Injection Procedure

a) Using a new 1 mL hubless syringe that contains 0.01 mL graduations with a permanently fixed, 27-gauge ½-inch needle (not supplied), withdraw a volume of **reconstituted solution (containing 0.58 mg of XIAFLEX)** as follows:

- **0.25 mL for cords affecting a MP joint or**
- **0.20 mL for cords affecting a PIP joint.**

b) With your non-dominant hand, secure the patient's hand to be treated while simultaneously applying tension to the cord. With your dominant hand, place the needle into the cord, using caution to keep the needle within the cord. Avoid having the needle tip pass completely through the cord to help minimize the potential for injection of XIAFLEX into tissues other than the cord *[see Warnings and Precautions (5.1)]*. 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. 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 cord.

c) If the needle is in the proper location, there will be some resistance noted during the injection procedure. After confirming that the needle is correctly placed in the cord, inject approximately one-third of the dose.

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

e) Again withdraw the needle tip from the cord and reposition it a third time proximal to the initial injection (approximately 2 to 3 mm) and inject the final portion of the dose into the cord.

f) Wrap the patient's treated hand with a soft, bulky, gauze dressing.

g) Instruct the patient to limit motion of the treated finger and to keep the injected hand elevated until bedtime.

h) Instruct the patient not to attempt to disrupt the injected cord by self-manipulation and to return to the provider's office the next day for follow-up and a finger extension procedure, if needed.

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

2.5 Finger Extension Procedure

a) **At the follow-up visit the day after the injection**, if a contracture remains, perform a passive finger extension procedure (as described below) to facilitate cord disruption.

b) Local anesthesia may be used. Avoid direct pressure on the injection site as it will likely be tender. Care should be taken during release of contracture, as some patients may experience skin splitting. If this occurs, cover the area with gauze and apply gentle pressure until bleeding stops. Standard wound care with regular dressings should be applied.

c) While the patient's wrist is in the 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.

d) If the first finger extension procedure does not result in disruption of the cord, a second and third attempt can be performed at 5- to 10-minute intervals. However, no more than 3 attempts are recommended to disrupt a cord.

e) If the cord has not been disrupted after 3 attempts, a follow-up visit may be scheduled in approximately 4 weeks. If, at that subsequent visit, the contracted cord persists, an additional XIAFLEX injection with finger extension procedures may be performed *[*see *Dosage and Administration (2.1)]*.

f) Following the finger extension procedure(s), fit patient with a splint and provide instructions for use at bedtime for up to 4 months to maintain finger extension. Also, instruct the patient to perform finger extension and flexion exercises several times a day for several months.

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

None.

5 WARNINGS AND PRECAUTIONS

5.1 Tendon Rupture or Other Serious Injury to the Injected Extremity

In the controlled and uncontrolled portions of the clinical trials, 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 (2.3, 2.4)]*.

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.

5.2 Allergic Reactions

In the controlled portions of the clinical trials (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.

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. 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 following XIAFLEX injections.

5.3 Patients with Abnormal Coagulation

In the XIAFLEX trials (Studies 1 and 2), 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, e.g., up to 150 mg per day) within 7 days prior to XIAFLEX administration is not known. Therefore, XIAFLEX should be used with caution in patients with coagulation disorders including patients receiving concomitant anticoagulants (except for low-dose aspirin).

6 ADVERSE REACTIONS

The following serious adverse reactions 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 most frequently reported adverse drug reactions (≥ 25%) in the XIAFLEX clinical trials included edema peripheral (mostly swelling of the injected hand), contusion, injection site hemorrhage, injection site reaction, and pain in the treated extremity.

6.1 Clinical Studies Experience

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 (5.2)]*.

Table 2 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 2. Adverse Reactions Occurring in ≥ 5% of XIAFLEX-Treated Patients 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.

Immunogenicity
During clinical studies, patients with Dupuytren's contracture were tested at multiple time points for antibodies to the protein components of XIAFLEX (AUX-I and AUX-II). At 30 days post the first injection of XIAFLEX 0.58 mg, 92% of patients had antibodies detected against AUX-I and 86% of patients had antibodies detected against AUX-II. After the fourth injection of XIAFLEX, every XIAFLEX-treated patient developed high titers of antibodies to both AUX-I and AUX-II. Neutralizing antibodies to AUX-I or AUX-II, were detected in 10% and 21%, respectively, of patients treated with XIAFLEX. However, there was no apparent correlation of antibody frequency, antibody titers, or neutralizing status to clinical response or adverse reactions.

Since the protein components in XIAFLEX (AUX-I and AUX-II) have some sequence homology with human matrix metalloproteinases (MMPs), anti-product antibodies could theoretically interfere with human MMPs.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to collagenase clostridium histolyticum with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

Anticoagulant drugs: XIAFLEX should be used with caution in patients receiving concomitant anticoagulants (except for low-dose aspirin) *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category B
There are no adequate and well-controlled studies of XIAFLEX in pregnant women. Human pharmacokinetic studies showed that XIAFLEX levels were not quantifiable in the systemic circulation following injection into a Dupuytren's cord *[see Clinical Pharmacology (12.3)]*. Reproduction studies have been performed in rats with intravenous doses up to 0.13 mg (approximately 45 times the human dose of XIAFLEX on a mg/kg basis, if administered intravenously) and have revealed no evidence of impaired fertility or harm to the fetus due to collagenase clostridium histolyticum. Almost all patients develop anti-product antibodies (anti-AUX-I and anti-AUX-II) after treatment with XIAFLEX, and the clinical significance of anti-product antibody formation on a developing fetus is not known *[see Adverse Reactions (6.1)]*. Because animal reproduction studies are not always predictive of human response, XIAFLEX should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether collagenase clostridium histolyticum is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XIAFLEX is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of XIAFLEX in pediatric patients less than 18 years old have not been established.

8.5 Geriatric Use

Of the 249 XIAFLEX-treated patients in the double-blind, placebo-controlled, clinical trials (Studies 1 and 2), 104 (42%) were 65 years of age or older and 9% were 75 years of age or older. No overall differences in safety or effectiveness of XIAFLEX were observed between these patients and younger patients.

10 OVERDOSAGE

The effects of overdose of XIAFLEX are unknown. It is possible that multiple simultaneous or excessive doses of XIAFLEX may cause more severe local effects including serious adverse reactions (e.g., tendon ruptures) than the recommended doses. Supportive care and symptomatic treatment are recommended in these circumstances.

11 DESCRIPTION

XIAFLEX contains purified collagenase clostridium histolyticum, consisting of two microbial collagenases in a defined mass ratio, Collagenase AUX-I and Collagenase AUX-II, which are isolated and purified from the fermentation of *Clostridium histolyticum* bacteria.

Collagenase AUX-I is a single polypeptide chain consisting of approximately 1000 amino acids of known sequence. It has an observed molecular weight of 114 kiloDaltons (kDa). It belongs to the class I *Clostridium histolyticum* collagenases.

Collagenase AUX-II is a single polypeptide chain consisting of approximately 1000 amino acids of deduced sequence. It has an observed molecular weight of 113 kDa. It belongs to the class II *Clostridium histolyticum* collagenases.

XIAFLEX is supplied as a sterile lyophilized powder (white cake) intended for reconstitution with 0.39 mL (for a MP joint) or 0.31 mL (for a PIP joint) of the supplied sterile diluent (0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride) prior to intralesional injection into a Dupuytren's cord.

XIAFLEX is available in single-use, glass vials containing 0.9 mg of collagenase clostridium histolyticum. Each vial also contains 0.5 mg of hydrochloric acid, 18.5 mg of sucrose, and 1.1 mg of tromethamine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Collagenases are proteinases that hydrolyze collagen in its native triple helical conformation under physiological conditions, resulting in lysis of collagen deposits. Injection of XIAFLEX into a Dupuytren's cord, which is comprised mostly of collagen, may result in enzymatic disruption of the cord.

Results of *in vitro* studies suggest that the collagenases (AUX-I and AUX-II) worked synergistically to provide hydrolyzing activity towards collagen. However, there are no clinical data regarding the relative contributions of the individual collagenases (AUX-I or AUX-II) to the efficacy of XIAFLEX in the treatment of Dupuytren's contracture.

12.3 Pharmacokinetics

Following administration of a single XIAFLEX dose of 0.58 mg into a Dupuytren's cord in 20 patients, no quantifiable levels of XIAFLEX (AUX-I or AUX-II) were detected in plasma up to 30 days post injection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies to evaluate the carcinogenic potential of collagenase clostridium histolyticum have not been conducted.

Purified collagenase clostridium histolyticum was not mutagenic in *Salmonella typhimurium* (AMES test) and was not clastogenic in both an *in vivo* mouse micronucleus assay and an *in vitro* chromosomal aberration assay in human lymphocytes.

Collagenase clostridium histolyticum did not impair fertility and early embryonic development when administered intravenously in rats at doses up to 0.13 mg/dose (approximately 45 times the human dose on a mg/kg basis).

14 CLINICAL STUDIES

The efficacy of 0.58 mg of XIAFLEX was evaluated in two randomized, double-blind, placebo-controlled, multi-centered trials in 374 adult patients with Dupuytren's contracture (Studies 1 and 2). At study entry, patients must have had: (1) a finger flexion contracture with a palpable cord of at least one finger (other than the thumb) of 20° to 100° in a metacarpophalangeal (MP) joint or 20° to 80° in a proximal interphalangeal (PIP) joint and (2) a positive "table top test" defined as the inability to simultaneously place the affected finger(s) and palm flat against a table top. Patients could not have received a surgical treatment (e.g., fasciectomy, fasciotomy) on the selected primary joint within 90 days before the first injection of study medication and patients could not have received anticoagulation medication (except for up to 150 mg of aspirin per day) within 7 days before the first injection of study medication.

The cord affecting the selected primary joint received up to 3 injections of 0.58 mg of XIAFLEX or placebo on Days 0, 30, and 60. About 24 hours after each injection of study medication, if needed, the investigator manipulated (extended) the treated finger in an attempt to facilitate rupture of the cord (finger extension procedure). Following manipulation, patients were fitted with a splint, instructed to wear the splint at bedtime for up to 4 months, and instructed to perform a series of finger flexion and extension exercises each day.

See Table 3 for the baseline disease characteristics of patients with Dupuytren's contracture in Studies 1 and 2.

Table 3. Baseline Disease Characteristics of Patients with Dupuytren's Contracture

	Study 1	**Study 2**
Proportion of patients with prior surgery for Dupuytren's contracture[1]	38%	53%
Proportion of patients with prior surgery for Dupuytren's contracture on the same finger as the primary joint[1]	8%	18%
Mean number of affected joints	3.0	3.3

[1] Prior surgery for Dupuytren's contracture included fasciotomy and fasciectomy

In Studies 1 and 2, the primary endpoint was to evaluate the proportion of patients who achieved a reduction in contracture of the selected primary joint (MP or PIP) to within 0° to 5° of normal, 30 days after the last injection of that joint on Days 30, 60, or 90 **(after up to 3 injections)**. A greater proportion of XIAFLEX-treated patients compared to placebo-treated patients achieved the primary endpoint (see Table 4).

Table 4. Percentage of Patients Who Achieved Reduction in Contracture of the Primary Joint to 0° to 5° After Up to 3 Injections in Studies 1 and 2[a]

Treated Joint	Study 1		Study 2	
	XIAFLEX[b]	Placebo	XIAFLEX[b]	Placebo
All Joints (MP and PIP)[c,d]	N=203	N=103	N=45	N=21
Difference (CI[e])	**64%** 57% (47%, 67%)	**7%** -	**44%** 40% (14%, 62%)	**5%** -
MP Joints[c]	N=133	N=69	N=20	N=11
Difference (CI[e])	**77%** 69% (57%, 79%)	**7%** -	**65%** 56% (19%, 83%)	**9%** -
PIP Joints[d]	N=70	N=34	N=25	N=10
Difference (CI[e])	**40%** 34% (14%, 52%)	**6%** -	**28%** 28% (-10%, 61%)	**0%** -

[a] Patients may have received up to 3 injections of study medication into the cords associated with contracture of the primary joints on Days 0, 30, and 60. Assessments were made 30 days after the last injection (on Days 30, 60, or 90).
[b] For XIAFLEX-treated patients, the mean (±SD) number of injections given to the cord associated with the contracture was 1.7 (±0.8) in the 90-day controlled period in each trial.
[c] MP joints are metacarpophalangeal joints
[d] PIP joints are proximal interphalangeal joints
[e] 95% confidence interval

The proportion of patients who achieved a contracture reduction of the primary joint to 0° to 5° **after the first injection** was 39% and 1% in Study 1 and 27% and 5% in Study 2 in the XIAFLEX and placebo groups respectively.

XIAFLEX-treated patients, compared to placebo-treated patients, showed a greater increase from baseline in the range of motion of MP and PIP joints (see Table 5).

Table 5. Mean Increase in Range of Motion from Baseline in Degrees After Up to 3 Injections in Studies 1 and 2[a]

Treated Joint	Study 1		Study 2	
	XIAFLEX	Placebo	XIAFLEX	Placebo
All Joints[b,c]	**N=196**	**N=102**	**N=45**	**N=21**
Baseline	44 (20)	45 (19)	40 (15)	44 (16)
Final	80 (20)	50 (22)	76 (18)	52 (20)
Increase	36 (21)	4 (15)	35 (18)	8 (15)
MP Joints[b]	**N=129**	**N=68**	**N=20**	**N=11**
Baseline	43 (20)	46 (19)	40 (12)	41 (21)
Final	83 (16)	50 (21)	80 (11)	50 (22)
Increase	41 (20)	4 (13)	40 (13)	9 (15)
PIP Joints[c]	**N=67**	**N=34**	**N=25**	**N=10**
Baseline	46 (20)	44 (18)	41 (18)	47 (10)
Final	75 (24)	49 (24)	73 (21)	54 (18)
Increase	28 (22)	5 (19)	32 (20)	7 (16)

[a] Patients may have received up to 3 injections of study medication into the cords associated with contracture of the primary joints on Days 0, 30, and 60. Assessments were made 30 days after the last injection (on Days 30, 60, or 90). Baseline and final range of motion degree values are expressed in mean (SD).
[b] MP = Metacarpophalangeal joint
[c] PIP = Proximal interphalangeal joint
Range of Motion = Degrees of Full Flexion minus Degrees of Fixed Extension
Not all patients had range of motion values at both time points.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each single-use vial of XIAFLEX is packaged with a single-use vial of sterile diluent in an outer carton. The National Drug Code is:

- NDC 66887-003-01

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.

Storage and Stability
Prior to reconstitution, the vials of XIAFLEX and diluent should be stored in a refrigerator at 2º to 8ºC (36º to 46ºF) *[see Dosage and Administration (2.2)]*. Do not freeze.

The reconstituted XIAFLEX solution can be kept at room temperature (20º to 25ºC/68º to 77ºF) for up to one hour or refrigerated at 2º to 8˚C (36º to 46°F) for up to 4 hours prior to administration *[see Dosage and Administration (2.2)]*.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Advise patients of the following:

- Serious complications of XIAFLEX injection include tendon rupture or serious ligament damage 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.
- Not to attempt to disrupt the injected cord 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, or trouble bending the finger after the swelling goes down (symptoms of tendon rupture).
- To return to their healthcare provider's office the next day for an examination of the injected hand and for a possible finger extension procedure to disrupt the cord.

Following the finger extension procedure(s) and fitting patient with a splint, instruct patients:

- Not to perform strenuous activity with the injected hand until advised to do so.
- To wear the splint at bedtime for up to 4 months.
- To perform a series of finger flexion and extension exercises each day.

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