

# PRODUCT INFORMATION

## XIAFLEX<sup>®</sup> (collagenase clostridium histolyticum) Lyophilised powder for injection 900 micrograms/vial

### NAME OF THE MEDICINE

Active: collagenase clostridium histolyticum

CAS: *Clostridium histolyticum* gene colG isoenzyme AUX-I: 955089-04-0

CAS: *Clostridium histolyticum* gene colH isoenzyme AUX-II: 955089-06-2

Pharmacotherapeutic group: Other Drugs for Disorders of the Musculo-Skeletal System – Enzymes.

### DESCRIPTION

XIAFLEX is a lyophilised product for intralesional administration. 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. A collagenase is an enzyme that recognises and binds to collagen in its native conformation and cleaves the peptide bonds resulting in collagen breakdown. 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 known sequence. It has an observed molecular weight of 113 kDa. It belongs to the class II *Clostridium histolyticum* collagenases.

XIAFLEX is supplied in single-use, glass vials containing 0.9 mg of collagenase clostridium histolyticum as a sterile, lyophilised powder for reconstitution. Each vial also contains approximately 0.5 mg of hydrochloric acid, 18.5 mg of sucrose, and 1.1mg of trometamol. The reconstituted drug product has a pH of 7.5 – 8.5.

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.

### PHARMACOLOGY

#### Pharmacodynamic Properties

##### ***Mechanism of Action***

Collagenases are proteinases that hydrolyse 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.

The signs and symptoms of Peyronie's disease are caused by a collagen plaque. Injection of XIAFLEX into a Peyronie's plaque, which is comprised mostly of collagen, may result in enzymatic disruption of the plaque. Following this disruption of the plaque, penile curvature deformity and patient bother caused by Peyronie's disease are reduced.

Results of *in vitro* studies, including those of explant tissues containing Peyronie's plaques, suggest that XIAFLEX disrupts the predominant collagen found in plaques (Types I and III). At higher doses and longer incubation times, non-fibrillar Type IV collagen was affected causing collagen lysis in small veins, but did not cause structural damage to arteries, nerves or large veins which contain Type IV collagen in *in vitro* or *in vivo* studies.

Results of *in vitro* studies suggest that the collagenases (AUX-I and AUX-II) worked synergistically to provide hydrolysing 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 or Peyronie's disease.

Collagen fragments generated from clostridial collagenase have been shown to generate increased vascular permeability, inflammatory responses, and regenerative changes. However, the effects of the formation of the collagen fragments derived from the collagen plaque are unknown.

## **Pharmacokinetics**

### ***Absorption and Distribution***

#### Dupuytren's Contracture

Following administration of a single dose of 0.58 mg of XIAFLEX into a cord in patients with Dupuytren's contracture, or two concurrent injections of 0.58 mg of XIAFLEX into Dupuytren's cords in the same hand of patients with Dupuytren's contracture, no quantifiable levels of XIAFLEX were detected in plasma up to 30 days post injection.

#### Peyronie's Disease

Following each of two intralesional administrations, separated by 24 hours, of XIAFLEX 0.58 mg into the penile plaque of 19 patients with Peyronie's disease, plasma levels of AUX-I and AUX-II in patients with quantifiable levels (79% and 40% for AUX-I and AUX-II, respectively) were minimal and short-lived. The maximal plasma concentrations of AUX-I and AUX-II were <29 ng/mL and <71 ng/mL, respectively, and were observed approximately within 10 minutes after injection. All plasma levels were below the limits of quantification within 30 minutes following dosing. There was no evidence of accumulation following two sequential injections of XIAFLEX administered 24 hours apart. No patients had quantifiable plasma levels 15 minutes after modeling of plaque on Day 3 (i.e., 24 hours after Injection 2 on Day 2).

### ***Biotransformation and Elimination***

Because XIAFLEX is not a substrate for cytochrome P450 or other medicinal product metabolising enzyme pathways, and because no active metabolites are expected, no metabolism studies have been performed.

Because there is no quantifiable systemic exposure following a single injection of XIAFLEX in patients with Dupuytren's contracture and minimal and short-lived systemic exposure in patients with Peyronie's disease, no formal studies on elimination have been performed.

## **CLINICAL TRIALS**

### **Dupuytren's Contracture**

The efficacy of XIAFLEX 0.58 mg was evaluated in two pivotal randomised, double-blind, placebo-controlled studies, CORD-I (AUX-CC-857), and CORD-II (AUX-CC-859), in adult patients with Dupuytren's contracture.

At study entry, patients in the clinical studies 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 MP joint, or 20° to 80° in 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.

The cord affecting a selected primary joint received up to 3 injections of 0.58 mg of XIAFLEX or placebo. A finger extension procedure was performed if needed, approximately 24 hours after injection to facilitate disruption of the cord. Each injection was separated by approximately 4 weeks.

The primary endpoint of each study was to evaluate the proportion of patients who achieved a reduction in contracture of the selected primary joint (MP or PIP) to 5° or less, approximately 4 weeks after the last injection of that joint.

Other endpoints included ≥50% reduction from baseline in degree of contracture, percent change from baseline in degree of contracture, change from baseline in range of motion, subject global assessment of treatment satisfaction and physician global assessment of severity.

XIAFLEX demonstrated a clinically significant benefit compared to placebo in the proportion of patients achieving the primary endpoint of a reduction in the contracture of all joints treated to 5° or less, approximately 4 weeks after the last injection (MP plus PIP, MP only, PIP only). The mean number of injections required was 1.5.

See Table 1 for the baseline disease characteristics of patients with Dupuytren's contracture in CORD-I and CORD-II.

**Table 1: Demographic and Baseline Characteristics, Phase 3 double-blind, placebo-controlled studies (CORD-I, CORD-II)**

Variable	XIAFLEX (N=249)	Placebo (N=125)
Age (years)		
mean	62.7	64.2
Age category (years), n (%)		
<45	9 (3.6)	5 (4.0)
45 - 54	33 (13.2)	17 (13.6)
55 - 64	103 (41.4)	44 (35.2)
65 - 74	82 (33.0)	40 (32.0)
≥75	22 (8.8)	19 (15.2)
Gender, n (%)		
Male	210 (84.3)	91 (72.8)
Female	39 (15.7)	34 (27.2)
Family History of Dupuytren's Disease, n (%)		
Yes	107 (43.0)	62 (49.6)
No	142 (57.0)	63 (50.4)
Physician Rating of Severity at Baseline		
Mild	38 (15.4%)	21 (16.8%)
Moderate	148 (59.9%)	71 (56.8%)
Severe	61 (24.7%)	33 (26.4%)
Missing <sup>1</sup>	2 (0.8%)	-

Note: Includes all patients who received at least 1 injection of double-blind study medicinal product (XIAFLEX 0.58 mg or placebo).

<sup>1</sup> Not used to calculate physician rating of severity at baseline percentage – actual denominator of N=247 used.

**Table 2: Percentage of Patients who Achieved Reduction in Contracture to 5° or Less (last injection)**

Treated Primary Joints	CORD-I		CORD-II	
	XIAFLEX	Placebo	XIAFLEX	Placebo
All joints Difference (CI <sup>d</sup> )	N=203 <sup>c</sup>	N=103 <sup>c</sup>	N=45	N=21
	64.0% 57% (47%, 67%)	6.8% -	44.4% 40% (14%, 62%)	4.8% -
MP Joints <sup>a</sup> Difference (CI <sup>d</sup> )	N=133	N=69	N=20	N=11
	76.7% 69% (57%, 79%)	7.2% -	65.0% 56% (19%, 83%)	9.1% -
PIP Joints <sup>b</sup> Difference (CI <sup>d</sup> )	N=70	N=34	N=25	N=10
	40.0% 34 % (14%, 52%)	5.9% -	28.0% 28% (-10%, 61%)	0.0% -

<sup>a</sup> Metacarpophalangeal joint; <sup>b</sup> Proximal interphalangeal joint; <sup>c</sup> Two (2) primary joints were excluded from the efficacy analysis (1 joint from the placebo group was not evaluated and 1 joint from the XIAFLEX-treated group had a baseline contracture of 0 degrees before treatment) <sup>d</sup> 95% confidence intervals.

**Table 3: Mean Increase in Range of Motion from Baseline (Last Injection)**

Treated Primary Joints	CORD-I		CORD-II	
	XIAFLEX	Placebo	XIAFLEX	Placebo
<b>All Joints</b>	N=197 <sup>c</sup>	N=102 <sup>c</sup>	N=45	N=21
Mean Baseline (SD)	43.9 (20.1)	45.3 (18.7)	40.3 (15.2)	44.0 (16.5)
Mean Final (SD)	80.7 (19.0)	49.5 (22.1)	75.8 (17.7)	51.7 (19.6)
Mean Increase (SD)	36.7 (21.0)	4.0 (14.8)	35.4 (17.8)	7.6 (14.9)
<b>MP Joints<sup>a</sup></b>	N=130	N=68	N=20	N=11
Mean Baseline (SD)	42.6 (20.0)	45.7 (19.2)	39.5 (11.8)	41.4 (20.8)
Mean Final (SD)	83.7 (15.7)	49.7 (21.1)	79.5 (11.1)	50.0 (21.5)
Mean Increase (SD)	40.6 (20.0)	3.7 (12.6)	40.0 (13.5)	8.6 (14.7)
<b>PIP Joints<sup>b</sup></b>	N=67	N=34	N=25	N=10
Mean Baseline (SD)	46.4 (20.4)	44.4 (17.9)	41.0 (17.7)	47.0 (10.3)
Mean Final (SD)	74.9 (23.1)	49.1 (24.4)	72.8 (21.3)	53.5 (18.3)
Mean Increase (SD)	29.0 (20.9)	4.7 (18.5)	31.8 (20.1)	6.5 (15.8)

<sup>a</sup> Metacarpophalangeal joint; <sup>b</sup> Proximal interphalangeal joint; <sup>c</sup> Two (2) primary joints were excluded from the efficacy analysis (1 joint from the placebo group was not evaluated and 1 joint from the XIAFLEX-treated group had a baseline contracture of 0 degrees before treatment).

All p-values < 0.001 for all comparisons between XIAFLEX and placebo, except for PIP joints in Study CORD-II which was not eligible for statistical testing due to a hierarchical testing procedure.

Physician-rated change in contracture severity was reported as very much improved or much improved in 86% and 80% of the subjects in the XIAFLEX group compared to 3% and 5% of subjects in the placebo group for the CORD-I and CORD-II studies, respectively ( $p < 0.001$ ). Based on the Patient Global Assessment of Treatment Satisfaction, more than 85% of subjects in the CORD-I and CORD-II studies reported either being quite satisfied or very satisfied with their treatment with XIAFLEX versus approximately 30% treated with placebo ( $p < 0.001$ ). Greater patient satisfaction was correlated with improved range of motion ( $r = 0.51$ ,  $p < 0.001$ ).

#### Treatment of two concurrent injections

An open-label, historically-controlled study (AUX-CC-867) was conducted in 715 patients to assess the safety and efficacy of two concurrent injections of XIAFLEX into one hand in adults with multiple Dupuytren's contractures with palpable cords. Two concurrent injections were administered into cords affecting MP and/or PIP joints on the same or different fingers in the selected hand.

The primary efficacy endpoint was fixed flexion contracture in the treated joint pair subgroup. A significant mean improvement (74.4%) from baseline to Day 31 was observed overall in fixed flexion contracture following administration of two concurrent injections of XIAFLEX 0.58 mg (one injection per joint) in the same hand, see Table 4.

Improvement was observed regardless of joint type or finger involvement (range: 60.5% to 83.9%). Improvement of the total fixed flexion contracture was also observed irrespectively of the time of finger extension, 24, 48 or 72 hours after injection, with a mean improvement at Day 31 of 75.2%, 74.8% and 72.4% respectively. An improvement from baseline was also seen in range of motion at Day 31 for all the treated joint pair subgroups, see Table 4.

**Table 4: Total fixed flexion contracture and range of motion following administration of two concurrent injections of XIAFLEX 0.58 mg in the same hand, mITT population, study AUX-CC-867 (first treatment cycle)**

	<b>Same Finger, 1 MP, 1 PIP (n=350)</b>	<b>Different Fingers, Both MPs (n=244)</b>	<b>Different Fingers, Both PIPs (n=72)</b>	<b>Different Fingers, 1 MP, 1 PIP (n=58)</b>	<b>Total (n=724)</b>
<b>Total FFC (°)</b>					
Baseline, mean (SD)	102 (31)	89 (31)	109 (37)	96 (28)	98 (32)
Day 31, mean (SD)	30 (27)	17 (28)	47 (39)	31 (29)	27 (30)
Change, mean (SD)	72 (29)	72 (29)	62 (32)	65 (34)	70 (30)
% Change, mean (SD)	72 (22)	84 (23)	60 (29)	68 (27)	74 (25)
<b>Total ROM (°)</b>					
Baseline, mean (SD)	87 (31)	92 (34)	93 (36)	92 (29)	90 (33)
Day 31, mean (SD)	154 (29)	163 (30)	148 (42)	155 (31)	156 (31)
Change, mean (SD)	67 (30)	71 (34)	55 (28)	63 (37)	67 (32)

FFC = Fixed flexion contracture  
ROM = Range of motion

Clinical success (a reduction of contracture to  $\leq 5^\circ$  within 30 days) after two concurrent injections of XIAFLEX (one per joint) in the same hand was achieved for the majority of MP joints (64.6%) compared with 28.6% of PIP joints following a single injection per affected joint. Time of finger extension after injection had no impact on the rate of clinical success for either MP or PIP joints. Clinically meaningful improvement in hand function as determined by the URAM (Unite´ Rhumatologique des Affections de la Main) score was observed at Day 31 (-11.3) and Day 61 (-12.3).

Long-term efficacy and safety

A long term, non-treatment, Year 2 to Year 5 follow-up study (AUX-CC-860) was undertaken to evaluate recurrence of contracture in subjects who received up to 8 single injections of XIAFLEX 0.58mg in a previous Phase 3 open-label or double-blind with open-label extension study. Recurrence was assessed in successfully treated joints (i.e., subjects had a reduction in contracture to  $5^\circ$  or less at the Day 30 evaluation after the last injection of XIAFLEX in a previous study) and was defined as an increase in joint contracture by at least  $20^\circ$  in the presence of a palpable cord, or the joint underwent medical or surgical intervention primarily to correct a new or worsening Dupuytren’s contracture in that joint. Data on the long term recurrence rates following successful treatment with XIAFLEX are provided in Table 5.

**Table 5: Long Term Recurrence Rates for Joints Treated Successfully with XIAFLEX**

Follow-up Interval (days)	N (%) of Joints in Each Interval <sup>a</sup>	N (%) of Recurrent Joints in Each Interval <sup>b</sup>	Cumulative Nominal Recurrence by Joint Type (%)		Cumulative Nominal Recurrence Rate (%) <sup>c</sup>	Nominal Change in Recurrence Rate vs Previous Year (%)
			MP	PIP		
0-365	20 (3.2)	19 (6.3)	1.8	6.4	3.0	-
366-730	114 (18.3)	103 (33.9)	14.2	33.7	19.6	16.6
731-1095	125 (20.1)	97 (31.9)	27.1	56.4	35.2	15.6
1096-1460	85 (13.6)	45 (14.8)	34.8	62.2	42.4	7.2
1461-1825	169 (27.1)	27 (8.9)	39.5	65.7	46.7	4.3
> 1825	110 (17.7)	13 (4.3)	41.9	66.9	48.8	2.1

MP=Metacarpophalangeal joint; PIP= Proximal interphalangeal joint

- <sup>a</sup> A joint was considered in an interval if the duration of assessment falls in the interval. The duration of assessment started at the day of success (visit after the last injection where the 0° to 5° measurement was first recorded). The duration of assessment ended at the last available measurement or at the day of medical intervention for joints that did not recur and the recurrence day for recurrent joints.
- <sup>b</sup> A recurrent joint was a joint evaluated by the investigator as having a worsening Dupuytren's contracture due to a palpable cord. The recurrence day was the visit where the recurrence was reported or the day of intervention if a joint was treated for a worsening Dupuytren's contracture. For joints reported as recurring in a previous study, the day of recurrence was the first visit with a fixed flexion contracture measurement of 20° or greater following the report of recurrence.
- <sup>c</sup> The nominal rate of recurrence was the total number of recurrences occurring prior to the last day of the interval divided by the total number of joints (x100).

### Retreatment of Recurrent Contractures

Clinical efficacy in Study AUX-CC-862 was similar to that reported in studies CORD-I and CORD-II. In Study AUX-CC-862, 64.5% of recurrent MP joints and 45.0% of recurrent PIP joints achieved clinical success after retreatment with up to three injections of XIAFLEX.

### Peyronie's Disease

The efficacy of XIAFLEX was evaluated in two randomised, double-blind, placebo-controlled studies, Study 1 (AUX-CC-803) and Study 2 (AUX-CC-804), in adult males with Peyronie's disease. At study entry, patients must have had penile curvature deformity of at least 30 degrees and had disease present for at least 12 months prior to enrolment. Patients were excluded if they had a penile curvature greater than 90°, a ventral curvature deformity, an isolated hourglass deformity or a calcified plaque that could have interfered with the injection technique. At baseline, penile pain was either not present or was mild in most (98%) patients.

In these studies, patients were given up to 4 treatment cycles of XIAFLEX or placebo (weeks 0, 6, 12, 18), and were followed in a non-treatment follow-up period (weeks 24 -52). In each treatment cycle, two injections of XIAFLEX or two injections of placebo were administered 1 to 3 days apart. A penile modeling procedure was performed on patients at the study site 1 to 3 days after the second injection of the cycle. The treatment cycle was repeated at

approximately six-week intervals for up to three additional times, for a maximum of 8 total injection procedures and 4 total modeling procedures. In addition, patients were instructed to perform penile modeling at home for six weeks after each treatment cycle.

In Studies 1 and 2, the co-primary endpoints were:

- the percent change from baseline to Week 52 in penile curvature deformity **and**
- the change from baseline to Week 52 in the Bother domain of the Peyronie’s Disease Questionnaire (PDQ)

The Bother domain score is a composite of the following patient-reported items: concern about erection pain, erection appearance, and the impact of Peyronie’s disease on intercourse and on frequency of intercourse.

XIAFLEX treatment significantly improved penile curvature deformity in patients with Peyronie’s disease compared with placebo (Table 7). The percentage improvement in curvature deformity was numerically similar among patients with baseline deformity from 30 to 60 degrees and those with curvature deformity from 61 to 90 degrees.

XIAFLEX significantly reduced patient-reported bother associated with Peyronie’s disease compared with placebo (Table 8). The reduction in the Bother domain score was numerically similar between patient groups stratified by degree of baseline curvature deformity (30 to 60 degrees and 61 to 90 degrees).

Table 6 provides the baseline disease characteristics for the study population and Tables 7-8 provide the results of the co-primary efficacy endpoints measured in the 2 double-blind placebo-controlled studies 1 and 2.

**Table 6: Baseline disease characteristics of patients<sup>a</sup>with Peyronie’s Disease (PD)**

	Study 1		Study 2	
	XIAFLEX N=277	Placebo N=140	XIAFLEX N=274	Placebo N=141
Mean age (years) (Min-Max)	57.9 (28 - 79)	58.2 (30 - 81)	57.3 (23 - 84)	57.6 (33 - 78)
Mean duration of PD (years) (Min-Max)	3.9 (1.0 - 35.9)	4.8 (1.0 - 50.8)	4.2 (1.1 - 30.9)	3.4 (1.1 - 17.1)
Mean Penile Curvature Deformity (degrees) (Min-Max)	48.8 (30-90)	49.0 (30-89)	51.3 (30-90)	49.6 (30-85)
Peyronie’s Disease Questionnaire (PDQ) <sup>b</sup> , – Mean Patient-Reported PD Bother Domain Score (range: 0-16) <sup>c</sup>	7.5	7.4	7.4	8.2
History of Erectile Dysfunction N (%)	128 (46.2)	75 (53.6)	134 (48.9)	76 (53.9)

a Subjects were from ITT population and received at least one dose of study drug in Study 1 or 2

b Each PDQ assessment required subjects to have had vaginal intercourse in the 3 months prior to completion

c Higher scores represent worse symptoms

**Table 7: Mean percent change in penile curvature deformity from baseline to week 52 – Studies 1 and 2**

	Study 1		Study 2	
	XIAFLEX N=199	Placebo N=104	XIAFLEX N=202	Placebo N=107
Baseline Mean (degrees)	48.8°	49.0°	51.3°	49.6°
Mean Percent Change <sup>a</sup>	-35.0%	-17.8%	-33.2%	-21.8%
Treatment Difference (95% CI)	-17.2% <sup>b</sup> (-26.7%, -7.6%)		-11.4% <sup>b</sup> (-19.5%, -3.3%)	

<sup>a</sup> Mean percent change, treatment difference, 95% CI, and p-value were based on an ANOVA model with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. The mITT population was defined as all randomised subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.

<sup>b</sup> p-value < 0.01

**Table 8: Mean Change in Peyronie’s Disease Bother Domain Score from Baseline to Week 52 - Studies 1 and 2**

	Study 1		Study 2	
	XIAFLEX N=199	Placebo N=104	XIAFLEX N=202	Placebo N=107
Baseline Mean	7.5	7.4	7.4	8.2
Mean Change <sup>a</sup>	-2.8	-1.6	-2.6	-1.5
Treatment Difference (95% CI)	-1.2 <sup>b</sup> (-2.4, -0.03)		-1.1 <sup>b</sup> (-2.1, -0.002)	

<sup>a</sup> Mean change, treatment difference, 95% CI, and p-value all based on an ANOVA model with factors for treatment, stratum of baseline penile curvature, and their interaction and using last observation carried forward (LOCF) in the modified intent-to-treat (mITT) population. The mITT population was defined as all randomised subjects who had both a penile curvature deformity measurement and a PDQ assessment at baseline and at one or more subsequent time points.

<sup>b</sup> p-value < 0.05.

There were no clinically meaningful differences in the mean percent improvement in curvature deformity or mean reduction in the Bother domain score following treatment with XIAFLEX based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use.

## INDICATIONS

XIAFLEX is indicated for:

- The treatment of Dupuytren’s contracture in adult patients with a palpable cord.
- 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.

## CONTRAINDICATIONS

Do not use in patients with hypersensitivity to the active substance or to any of the excipients.

Do not use for the treatment of Peyronie’s plaques that involve the penile urethra due to potential risk to this structure.

## PRECAUTIONS

### ***Allergic reactions***

#### Dupuytren's Contracture

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

Because XIAFLEX contains foreign proteins, severe allergic reactions to XIAFLEX can occur. Anaphylaxis was reported in a post-marketing clinical trial 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 titres with successive XIAFLEX injections. Physicians must be appropriately equipped and prepared to address any severe local or systemic allergic reactions including the potential for anaphylaxis that may occur following injection. The patient should therefore be observed for at least 20 minutes following the injection of XIAFLEX for signs of any severe local or systemic allergic reactions including anaphylaxis.

#### Peyronie's Disease

In the double-blind portion of the two phase 3 placebo-controlled clinical trials in Peyronie's disease, a greater proportion of XIAFLEX-treated patients (4%) compared to placebo-treated patients (1%) had localised pruritus after up to 4 treatment cycles (involving up to 8 XIAFLEX injections). The incidence of XIAFLEX-associated pruritus was similar after each injection regardless of the number of injections administered.

Physicians must be appropriately equipped and prepared to address any severe local or systemic allergic reactions including the potential for anaphylaxis that may occur following injection.

### ***Tendon rupture or other serious injury to the finger/hand in the treatment of Dupuytren's Contracture***

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

Patients should be instructed to promptly contact their physician if they have trouble bending the finger after the swelling has subsided as it may be a symptom of tendon rupture.

Patients with Dupuytren's contractures that adhere to the skin may be at higher risk of skin lesions as a result of the pharmacological effect of XIAFLEX and the finger extension procedure on the skin overlying the targeted cord. If this occurs, cover the area with gauze and apply gentle pressure until bleeding stops. Standard wound care with regular dressings should be applied. Skin lacerations requiring skin grafting have been reported.

***Corporal rupture (fracture of penis) or other serious injury to the penis in the treatment of Peyronie's Disease.***

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 must 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.

Corporal rupture was reported as a serious adverse event after XIAFLEX injection in 5 out of 1044 patients (0.5%) 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 haematoma, 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 haematoma was also reported as an adverse reaction in 39 of 1044 patients (3.7%) in the controlled and uncontrolled clinical studies in Peyronie's disease.

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 haematoma, which may require surgical intervention. Physicians should advise patients to wait two weeks after the second injection of a treatment cycle before resuming sexual activity, provided pain and swelling have subsided.

***Special penile conditions/diseases not studied in clinical trials***

There is limited information on the treatment of patients with disease of less than 1 year duration. Patients with penile curvature greater than 90° were not studied in the clinical studies. Xiaflex treatment in patients having a calcified plaque that could have interfered with the injection technique, chordee in the presence or absence of hypospadias, thrombosis of the dorsal penile artery and/or vein, infiltration by a benign or malignant mass resulting in penile curvature, infiltration by an infectious agent, such as in lymphogranuloma venereum, ventral curvature from any cause and isolated hourglass deformity

of the penis has not been studied and treatment in these patients should be avoided.

### ***Use in patients with coagulation disorders***

XIAFLEX must be used with caution in patients with coagulation disorders or those taking anticoagulants. In the clinical studies 70% and 38% of XIAFLEX-treated patients reported ecchymosis/contusion and haemorrhage respectively at the injection site at a significantly higher rate than placebo patients. In the two double-blind, placebo-controlled phase 3 studies in Peyronie's disease, 65.5% of XIAFLEX-treated patients developed penile haematoma and 14.5% developed penile ecchymosis. The efficacy and safety of XIAFLEX in patients receiving anticoagulant medicinal products other than up to 150 mg acetylsalicylic acid per day prior to XIAFLEX administration is not known. Use of XIAFLEX in patients who have received anticoagulants (with the exception of up to 150 mg acetylsalicylic acid daily) within 7 days prior to receiving an injection of XIAFLEX is not recommended.

### ***Immunogenicity and Autoimmune disease***

As with any non-human protein medicinal product, patients may develop antibodies to the therapeutic protein. During clinical studies, blood samples from patients with Dupuytren's contracture were tested at multiple time points for antibodies to the protein components of the medicinal product (AUX-I and AUX-II). In the Dupuytren's contracture clinical trials 30 days after the first injection, 92% of patients had circulating antibodies detected against AUX-I, and 86% of patients against AUX-II. After a third or fourth injection, all subjects developed positive antibodies to both AUX-I and AUX-II. At five years after the initial injection of XIAFLEX, 92.8% and 93.4% of subjects were seropositive for anti-AUX-I and anti-AUX-II respectively.

Among patients in Study AUX-CC-867 who reported no prior exposure to XIAFLEX, the cumulative immunological response of two concurrent doses of XIAFLEX 0.58 mg (total dose of 1.16 mg) in the same hand was approximately one mean log titre unit less than the cumulative immunological response observed after two single sequential injections of XIAFLEX 0.58 mg administered 4 weeks apart (cumulative total dose of 1.16 mg).

There was no apparent correlation of antibody frequency, antibody titres, or neutralising status to clinical response or adverse reactions.

Long-term follow-up of 634 patients who participated in the Phase 3 studies showed that approximately two years after the initial injection of XIAFLEX, 7.7% (49/634) of patients were serum negative for AUX-I antibodies and 5.0% (32/634) were serum negative for AUX-II antibodies. Of the 49 subjects who were serum negative for AUX-I antibodies at the Year 2 follow-up, 44 had been positive for AUX-I antibodies during Phase 3. Of the 32 who were serum negative for AUX-II antibodies at the Year 2 follow-up, 29 had been positive for AUX-II antibodies during Phase 3.

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

No safety concerns related to the inhibition of endogenous MMPs have been observed, in particular no adverse events indicating the development or exacerbation of autoimmune diseases or the development of a musculoskeletal syndrome (MSS). Whilst there is no clinical evidence from the current safety data of a musculoskeletal syndrome developing following the administration of XIAFLEX, the potential for it to occur cannot be excluded. If this syndrome were to develop, it would occur progressively and is characterised by one or more of the following signs and symptoms: arthralgia, myalgia, joint stiffness, stiffness of the shoulders, hand oedema, palmar fibrosis and thickening or nodules forming in the tendons. In the retreatment Study AUX-CC-862 in patients with Dupuytren's contracture, 150 anti-AUX-I antibody positive samples and 149 anti-AUX-II antibody positive samples were assessed for potential cross-reactivity with human MMPs-1, -2, -3, -8, and -13. Results showed no cross-reactivity with any of the five MMPs tested.

In the Peyronie's disease clinical studies, at 6 weeks after the first treatment cycle of XIAFLEX, approximately 75% of patients had antibodies against AUX-I and approximately 55% of patients had antibodies against AUX-II. Six weeks after the eighth injection (fourth treatment cycle) of XIAFLEX >99% of XIAFLEX-treated patients developed high titres of antibodies to both AUX-I and AUX-II.:

In patients treated for these two indications, there was no apparent correlation of antibody frequency, antibody titres, or neutralising status to clinical response or adverse reactions.

### ***Effects on Fertility***

#### **Dupuytren's Contracture**

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).

#### **Peyronie's Disease**

Peyronie's disease occurs exclusively in adult male patients and hence there is no relevant information for use in females.

Low levels of XIAFLEX were quantifiable in the plasma of evaluable male patients for up to 30 minutes following administration of XIAFLEX into the penile plaque of patients with Peyronie's disease (see PHARMACOKINETICS).

### ***Use in Pregnancy (Category B1)***

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. 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. Parturition or postnatal development studies in animals were not conducted since human pharmacokinetic studies show that XIAFLEX levels are not quantifiable in the systemic circulation following injection into a Dupuytren's cord. Almost all patients develop anti-drug antibodies (anti-AUX-I and anti-AUX-II) after treatment with XIAFLEX, the cross-reactivity of which versus endogenous matrix metalloproteinases involved in pregnancy and labour cannot be excluded. The potential risk for humans on parturition and postnatal development is unknown. Therefore the use of XIAFLEX is not recommended in pregnancy and treatment should be postponed until after pregnancy.

### ***Use in Lactation***

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.

### ***Paediatric use***

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

### ***Use in the Elderly (> 65 years of age)***

No overall differences in safety or effectiveness were observed between elderly and younger patients.

### ***Driving/Operating Machinery***

XIAFLEX may have a major influence on the ability to drive and use machines due to the swelling and pain which may impair the use of the treated hand.

Other minor influences on the ability to drive and use machines include dizziness, paresthesia, hypoesthesia, and headache that have also been reported following injection of XIAFLEX. Patients must be instructed to avoid potentially hazardous tasks such as driving or using machines until it is safe to do so or as advised by the physician.

### ***Genotoxicity***

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.

### ***Carcinogenicity***

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

### ***Long-term safety***

Long-term safety of XIAFLEX is not fully characterised. The impact of treatment with XIAFLEX on subsequent surgery, if needed, is not known.

## INTERACTIONS WITH OTHER MEDICINES

Due to the lack of quantifiable systemic exposure of XIAFLEX in patients with Dupuytren's contracture and minimal and short-lived systemic exposure of XIAFLEX in patients with Peyronie's disease, no formal medicinal product interaction studies with XIAFLEX have been performed.

Anticoagulant drugs: XIAFLEX should be used with caution in patients receiving concomitant anticoagulants (except for low-dose acetylsalicylic acid) [see WARNINGS AND PRECAUTIONS].

Tetracycline, anthracycline, and anthraquinone drugs: There is no clinical evidence of an interaction between XIAFLEX and tetracycline, anthracycline, anthraquinone, or their derivatives. However, such drugs have been shown to inhibit matrix metalloproteinase-mediated collagen degradation at suprapharmacological concentrations *in vitro*. Therefore, use of XIAFLEX in patients who have received tetracycline antibiotics (e.g., doxycycline) within 14 days prior to receiving an injection of XIAFLEX is not recommended.

## ADVERSE EFFECTS

### Dupuytren's Contracture

The data described below are based on two pooled randomised, double-blind, placebo-controlled trials through Day 90 in patients with Dupuytren's contracture (CORD-I and CORD-II). The double-blind study population was comprised of 374 subjects of whom 249 received XIAFLEX 0.58 mg and 125 received placebo. The mean age was 62.9 years (range 33 to 89 years), most (80.5%) subjects were men, and all subjects were white except for one subject who was Hispanic. 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.

The number of XIAFLEX- and placebo-treated subjects who experienced at least one adverse event was 243/249 (97.7%) and 64/125 (51.2%), respectively. These events were classed as mild in 35.3% vs 35.2%, moderate in 52.2% vs 14.4%, and severe in 10.0% vs 1.6% of subjects. Serious adverse events were experienced by 8 (3.2%) subjects treated with XIAFLEX and by 1 (0.8%) subject treated with placebo. Some patients developed vasovagal syncope after finger extension procedures.

**Table 9: Adverse Events Occurring in ≥ 1% of XIAFLEX-Treated Subjects and at a Greater Incidence than Placebo – Studies CORD-I and CORD-II**

	XIAFLEX N=249	Placebo N=125
N (%) of subjects with at least one adverse effect	243 (97.6)	64 (51.2)
Blood and Lymphatic System Disorders:		
Lymph node pain	21 (8.4)	0 (0.0)
Lymphadenopathy <sup>a</sup>	33 (13.3)	0 (0.0)
Gastrointestinal disorders:		
Nausea	3 (1.2)	1 (0.8)
General disorders and Administration		

Site Conditions:		
Axillary pain	15 (6.0)	0 (0.0)
Inflammation	8 (3.2)	0 (0.0)
Injection site haemorrhage	95 (38.2)	4 (3.2)
Injection site reaction <sup>b</sup>	87 (34.9)	7 (5.6)
Injection site swelling <sup>c</sup>	61 (24.5)	8 (6.4)
Injection site vesicles	6 (2.4)	1 (0.8)
Peripheral oedema <sup>d</sup>	183 (73.5)	6 (4.8)
Pruritus <sup>e</sup>	37 (14.9)	1 (0.8)
Swelling	6 (2.4)	0 (0.0)
Tenderness	60 (24.1)	0 (0.0)
Infections and Infestations:		
Lower respiratory tract infection	3 (1.2)	0 (0.0)
Injury, Poisoning, and Procedural Complications:		
Contusion	137 ( 55.0)	4 (3.2)
Skin laceration	22 (8.8)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders:		
Arthralgia	11 (4.4)	1 (0.8)
Joint swelling	6 (2.4)	0 (0.0)
Myalgia	3 (1.2)	1 (0.8)
Pain in extremity	87 (34.9)	5 (4.0)
Shoulder pain	3 (1.2)	0
Nervous System Disorders:		
Burning sensation	3 (1.2)	0 (0.0)
Dizziness	4 (1.6)	0 (0.0)
Headache	6 (2.4)	5 (4.0)
Hypoesthesia	6 (2.4)	0 (0.0)
Paraesthesia	7 (2.8)	1 (0.8)
Skin and Subcutaneous Tissue Disorders:		
Blister	11 (4.4)	0 (0.0)
Blood blister	10 (4.0)	0 (0.0)
Ecchymosis	51 ( 20.5)	0 (0.0)
Erythema	14 (5.6)	0 (0.0)
Hyperhidrosis	3 (1.2)	0 (0.0)
Rash	3 (1.2)	1 (0.8)
<p><sup>a</sup> Includes the terms: lymphadenopathy and axillary mass</p> <p><sup>b</sup> Includes the terms: injection site reaction, injection site erythema, injection site inflammation, injection site irritation, injection site pain, and injection site warmth</p> <p><sup>c</sup> Includes the terms: injection site swelling and injection site oedema</p> <p><sup>d</sup> Most involved swelling of the treated extremity.</p> <p><sup>e</sup>Includes the terms: pruritus and injection site pruritus</p> <p>Severe AEs: injection site reaction, pain in extremity (2%); peripheral oedema, contusion (1.6%); injection site haemorrhage (1.2%); and tenderness, injection site cellulitis, ligament injury, skin laceration, tendon rupture, chest wall pain, irritability (&lt;1%).</p>		

Table 10 presents adverse reactions listed by system organ class and frequency category, using the convention: uncommon ( $\geq 1/1,000$  to  $< 1/100$ ). Within each frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions reported from the clinical programme are those that occurred in the Phase 3 double blind placebo controlled studies.

The most frequently reported adverse reactions during the XI AFLEX clinical studies were local injection-site reactions such as oedema peripheral (local to the injection site), contusion (including ecchymosis), injection-site haemorrhage, and injection-site pain. Injection site reactions were very common, occurring in the vast majority of patients, were mostly mild to moderate in severity and generally subsided within 1-2 weeks post injection.

Lymphangitis was reported in 1% of subjects (11/1082) who received at least one injection of XIAFLEX and has been reported post marketing. 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.

Serious adverse reactions of tendon rupture, tendonitis, other ligament injury and complex regional pain syndrome related to the medicinal product were reported

**Table 10: Uncommon Adverse Reactions (≥1/1,000 to <1/100) Listed by System Organ Class – Studies CORD-I and CORD-II**

System organ class	Uncommon ≥1/1,000 to <1/100
Infections and infestations	Injection site cellulitis, Lymphangitis
Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Hypersensitivity
Psychiatric disorders	Disorientation, Agitation, Insomnia, Irritability, Restlessness
Nervous system disorders	Complex regional pain syndrome, Monoplegia, Syncope vasovagal, Tremor
Eye disorders	Eyelid oedema
Vascular disorders	Haematoma, Hypotension
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Hyperventilation
Gastrointestinal disorders	Diarrhoea, Vomiting, Abdominal pain upper
Skin and subcutaneous tissue disorders	Rash erythematous, Rash macular, Eczema, Swelling face, Pain of skin, Skin exfoliation, Skin lesion, Skin disorder, Scab, Skin discolouration, Skin tightness
Musculoskeletal and connective tissue disorders	Axillary mass, Chest wall pain, Groin pain, Joint crepitation, Joint stiffness, Limb discomfort, Muscle spasms, Muscular weakness, Musculoskeletal discomfort, Musculoskeletal stiffness, Neck pain, Shoulder pain
Reproductive system and breast disorders	Breast tenderness, Hypertrophy breast
General disorders and administration site conditions	Pain, Injection site irritation, Injection site reaction, local swelling, Pyrexia, Discomfort, Fatigue, Feeling hot, Influenza like illness, Injection site anaesthesia, Injection site desquamation, Injection site discolouration, Injection site nodule, Malaise
Investigations	Lymph node palpable, Alanine aminotransferase increased, Aspartate aminotransferase increased, Body temperature increased
Injury, poisoning and procedural complications	Tendon rupture, Ligament injury, Limb injury, Open wound, Wound, Dehiscence

**Table 11: Undesirable effects in Post-Marketing Reports (rare <1/1000; very rare <1/10,000)**

Blood and lymphatic system disorders	Rare:	Lymphadenopathy
	Very rare:	Lymphadenitis, Lymph node pain
Nervous system disorders	Very rare:	Burning sensation, Dizziness, Hypoesthesia, Loss of consciousness, Paraesthesia, Presyncope, Sleep disorder
Eye disorders	Very rare:	Vision blurred
Ear and labyrinth disorders	Very rare:	Vertigo

Cardiac disorders	Very rare:	Atrial fibrillation, Cyanosis, Myocardial infarction
Vascular disorders	Rare:	Haematoma
Respiratory, thoracic and mediastinal disorders	Very rare:	Dyspnoea, Throat irritation
Gastrointestinal disorders	Very rare:	Nausea
Skin and subcutaneous tissue disorders	Rare:	Blister, Blood blister, Dry skin, Ecchymosis, Erythema, Pruritus, Rash, Rash pruritic, Scar, Skin discolouration, Skin exfoliation, Skin haemorrhage, Skin lesion, Urticaria
Reproductive system and breast disorders	Very rare	Erectile dysfunction
General disorders and administration site conditions	Rare: Very rare:	Drug ineffective, Injection site haematoma, Injection site swelling, Oedema peripheral, Swelling Administration site pain, Asthenia, Axillary pain, Chest pain, Condition aggravated, Discomfort, Drug effect decreased, Fatigue, Injection site discolouration, Injection site haemorrhage, Injection site pruritus, Injection site reaction, Injection site vesicles, Local reaction, Malaise, Needle issue, No adverse event, No therapeutic response, Oedema, Pain, Product reconstitution issue, Pyrexia, Tenderness, Hypersensitivity, Lymphangitis
Investigations	Rare: Very rare:	Pain in extremity Blood glucose increased, Intra ocular pressure increased, Arthralgia, Dupuytren's contracture, Muscular weakness, Musculoskeletal stiffness, Myalgia, Tenosynovitis
Injury, poisoning and procedural complications	Rare: Very rare:	Contusion, Laceration Accidental exposure, Drug administration error, Fall, Hand fracture, Inappropriate schedule of drug administration, Incorrect dose administered, Injury, Ligament injury, Medication error, Procedural pain, Tendon injury, Tendon rupture, Wound, Wound haemorrhage, Wrong technique in drug usage process.
Surgical and medical procedures	Rare: Very rare:	Skin graft Off label use

The safety of two concurrent injections of XIAFLEX into Dupuytren's cords in the same hand was evaluated in a historically-controlled, open-label multi-centre trial in 715 adult patients with Dupuytren's contracture (Study AUX-CC-867). In Study AUX-CC-867, finger extension procedures were performed approximately 24 to 72 hours after injection.

Out of 715 patients who received two concurrent injections of XIAFLEX in the same hand (1450 XIAFLEX injections) in Study AUX-CC-867, one (0.1%) patient experienced a tendon rupture of the treated finger within 3 days of the injection and one (0.1%) patient who was previously treated with XIAFLEX in another study experienced an anaphylactic reaction.

The incidence of skin laceration (29.1%) was higher for subjects treated with two concurrent injections of XIAFLEX in Study AUX-CC-867 compared with subjects treated with up to three single injections in the studies CORD-I and CORD-II (skin laceration [9%]). There were no other clinically relevant differences between two concurrent injections of XIAFLEX in the same hand and up to three single injections of XIAFLEX in the types of adverse events reported (ie., most adverse events were local to the treated extremity and of mild or moderate intensity).

Table 12 shows the incidence of adverse reactions that were reported in XIAFLEX-treated patients after two concurrent injections of XIAFLEX in the same hand through Day 60 in Study AUX-CC-867.

**Table 12: Adverse Reactions Occurring in Subjects who received Two Concurrent Injections of XIAFLEX in Study AUX-CC-867 (listed by system organ class and frequency categories)**

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100
Blood and lymphatic system disorders	Lymphadenopathy	Lymph node pain	Lymphadenitis
Cardiac disorders			Palpitations
Eye disorders			Eye pruritus Pigment dispersion syndrome
Gastrointestinal disorders		Nausea	Diarrhoea Palatal oedema Vomiting
General disorders and administration site conditions	Injection site pain Oedema peripheral <sup>a</sup>	Axillary pain Injection site haematoma Injection site haemorrhage Injection site laceration Injection site oedema Injection site pruritus Injection site Swelling Injection site vesicles Swelling	Chills Fatigue Feeling cold Feeling hot Inflammation Injection site discomfort Local swelling Malaise Mass Nodule Pain
Immune system disorders			Anaphylactic reaction
Infections and infestations			Fungal infection Gingival infection Infection Influenza Lymphangitis
Injury, poisoning and procedural complications	Contusion Skin laceration	Procedural pain	Post procedural hemorrhage Tendon rupture Wound
Investigations			Aspartate aminotransferase increased Blood cholesterol increased Blood creatinine increased Blood urine present Eosinophil count increased Grip strength decreased Lymph node palpable Monocyte count increased Neutrophil count increased Protein urine present

<b>System organ class</b>	<b>Very common ≥1/10</b>	<b>Common ≥1/100 to &lt;1/10</b>	<b>Uncommon ≥1/1,000 to &lt;1/100</b>
Musculoskeletal and connective tissue disorders	Pain in extremity	Arthralgia Joint swelling Musculoskeletal stiffness	Finger deformity Joint crepitation Joint range of motion decreased Joint stiffness Limb discomfort Muscle spasms Muscular weakness Musculoskeletal chest pain Musculoskeletal pain Tenosynovitis stenosaurs Trigger finger
Neoplasma benign, malignant and unspecified (incl cysts and polyps)			Pyogenic granuloma
Nervous system disorders		Paraesthesia	Burning sensation Carpal tunnel syndrome Complex regional pain syndrome Dizziness Headache Hyperaesthesia Hypoaesthesia Presyncope Sensory loss
Renal and urinary disorders			Polyuria
Reproductive system and breast disorders			Breast swelling
Respiratory, thoracic and mediastinal disorders			Epistaxis Pulmonary embolism
Skin and subcutaneous tissue disorders	Blood Blister Pruritus	Blister Ecchymosis	Dermatitis Dry skin Erythema Hyperhidrosis Pruritus generalized Rash Skin burning sensation Skin exfoliation Skin haemorrhage Skin tightness
Vascular disorders		Haematoma	Deep vein thrombosis Flushing Peripheral coldness Raynaud's phenomenon Superficial vein prominence

<sup>a</sup> “oedema peripheral” includes “injection site oedema” and “oedema”

The overall safety profile was similar regardless of the timing of the post-injection finger extension procedure (ie., 24 hours, 48 hours, and ≥72 hours

after injection) among patients who received two concurrent injections of XIAFLEX in Study AUX-CC-867.

A study was conducted (AUX-CC-860) to evaluate the long-term safety profile of XIAFLEX. No new safety signals were identified among patients who were followed for 5 years after their initial injection of XIAFLEX in a previous clinical study. The majority of adverse events reported during the long-term follow-up period were non-serious, mild or moderate in intensity, and were not related to the local administration of XIAFLEX. These data support the long term safety profile of XIAFLEX confirming that no new safety risks were identified during the 5 year follow-up period.

### Peyronie’s Disease

XIAFLEX was studied in patients with Peyronie’s disease in two randomised, double-blind, placebo controlled studies (Studies 1; AUX-CC-803 and 2; AUX-CC-804). The double-blind study population comprised 832 male patients of whom 551 patients received XIAFLEX and 281 received placebo. The median age was 58 years (range 23 to 84 years).

In the controlled and uncontrolled clinical studies of XIAFLEX in Peyronie’s disease, out of 1044 patients who received a total of 7466 XIAFLEX injections, corporal rupture and other serious penile injury were reported as follows:

- 5 (0.5%) patients had corporal rupture of the penis.
- 9 (0.9%) patients had a combination of penile ecchymoses or haematoma, sudden penile detumescence, and/or a penile “popping” sound or sensation and in these cases, a diagnosis of corporal rupture cannot be excluded.
- 39 (3.7%) patients had severe penile haematoma.

The majority of Peyronie’s patients experienced at least one adverse reaction (92% XIAFLEX-treated patients, 61% placebo-treated). Most adverse reactions were local events of the penis and groin and the majority of these events were of mild or moderate severity, and most (79%) resolved within 14 days of the injection. The adverse reaction profile was similar after each injection, regardless of the number of injections administered.

The most frequently reported adverse drug reactions (> 25%) during the XIAFLEX clinical studies were penile haematoma, penile swelling and penile pain. Table 13 shows the incidence of adverse reactions that were reported in greater than or equal to 1% of XIAFLEX-treated patients and at a frequency greater than placebo-treated patients.

**Table 13: Adverse Events Occurring in ≥ 1% of XIAFLEX-Treated Subjects and at a Greater Incidence than Placebo – Studies 1 and 2.**

	<b>XIAFLEX N=551</b>	<b>Placebo N=281</b>
N (%) of subjects with at least one adverse events	508 (92.2)	172 (61.2)
Gastrointestinal disorders:		
Diarrhoea	11 (2.0)	5 (1.8)
General disorders and Administration Site Conditions:		

Injection site vesicles	8 (1.5)	0 (0.0)
Nodule	8 (1.5)	0 (0.0)
Localised oedema	7 (1.3)	0 (0.0)
Injection site pruritus	6 (1.1)	0 (0.0)
Supra pubic pain	6 (1.1)	0 (0.0)
Infections and Infestations:		
Nasopharyngitis	20 (3.6)	7 (2.5)
Sinusitis	15 (2.7)	4 (1.4)
Influenza	6 (1.1)	3 (1.1)
Injury, Poisoning, and Procedural Complications:		
Procedural pain	12 (2.2)	6 (2.1)
Skin laceration	8 (1.5)	1 (0.4)
Excoriation	6 (1.1)	0 (0.0)
Musculoskeletal and Connective Tissue Disorders:		
Musculoskeletal pain	14 (2.5)	2 (0.7)
Muscle spasms	6 (1.1)	1 (0.4)
Pain in extremity	6 (1.1)	1 (0.4)
Nervous System Disorders:		
Headache	16 (2.9)	6 (2.1)
Reproductive system and breast disorders		
Penile haematoma <sup>a</sup>	388 (70.4)	70 (24.9)
Swelling <sup>b</sup>	319 (57.9)	11 (3.9)
Pain <sup>c</sup>	268 (48.6)	31 (11.0)
Ecchymosis <sup>d</sup>	168 (30.5)	25 (8.9)
Penile blister	18 (3.3)	0 (0.0)
Penile erythema	18 (3.3)	4 (1.4)
Pruritus genital	18 (3.3)	1 (0.4)
Erectile dysfunction	17 (3.1)	3 (1.1)
Painful erection	16 (2.9)	1 (0.4)
Priapism	10 (1.8)	5 (1.8)
Dyspareunia	6 (1.1)	0 (0.0)
Respiratory, thoracic & mediastinal disorders		
Cough	8 (1.5)	4 (1.4)
Skin and Subcutaneous Tissue Disorders:		
Blood blister	26 (4.7)	0 (0.0)
Skin discolouration	10 (1.8)	0 (0.0)
Skin hyperpigmentation	6 (1.1)	0 (0.0)
[a] Includes: injection site haematoma and penile haematoma were reported with the verbatim term of penile bruising or injection site bruising in 87% of patients.		
[b] Includes: injection site swelling, penile oedema, penile swelling, local swelling, scrotal swelling, and injection site oedema.		
[c] Includes: injection site pain, penile pain, and injection site discomfort.		
[d] Includes: contusion, ecchymosis, penile haemorrhage, and injection site haemorrhage.		

Severe penile haematoma or severe injection site haematoma were reported in 33/551 (6.0%) of XIAFLEX-treated patients and 0/281 (0%) of placebo-treated patients, in Studies 1 and 2 combined.

A popping noise or popping sensation in the penis, sometimes described as “snapping” or “cracking”, and sometimes accompanied by detumescence, haematoma and/or pain, were reported in 73/551 (13.2%) XIAFLEX-treated patients and 1/281 (0.3%) placebo-treated patients, in Studies 1 and 2 combined.

Table 14 presents adverse reactions listed by system organ class and frequency categories, using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), and uncommon ( $\geq 1/1,000$  to  $< 1/100$ ). Within each

frequency group, adverse reactions are presented in order of decreasing seriousness. Adverse reactions reported from the clinical programme are those that occurred in the Phase 3 double-blind placebo controlled studies at an incidence greater than placebo.

**Table 14: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), and uncommon ( $\geq 1/1,000$  to  $< 1/100$ ) Adverse Reactions Listed by System Organ Class – Studies 1 and 2.**

System Organ Class	Very Common $\geq 1/10$	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$
Blood and lymphatic system disorders			Lymph node pain Eosinophilia Lymphadenopathy
Cardiac disorders			Tachycardia
Ear and labyrinth disorders			Tinnitus
Gastrointestinal disorders			Abdominal distension Constipation
General disorders and administration site conditions		Injection site vesicles Localised oedema Injection site pruritus Nodule Suprapubic pain	Feeling hot Injection site reaction Injection site discolouration Pyrexia Swelling Asthenia Chills Cyst Induration Influenza like illness Injection site nodule Oedema Secretion discharge Tenderness
Immune system disorders			Drug hypersensitivity
Infections and infestations			Fungal skin infection Infection Upper respiratory infection
Injury, poisoning and procedural complications		Procedural pain	Fracture of penis Skin laceration Open wound Scrotal haematoma Joint injury Penis injury
Investigations			Blood glucose increased Blood pressure systolic increased Body temperature increased Eosinophil count increased
Metabolism and nutrition disorders			Fluid retention
Musculoskeletal and connective tissue disorders			Back pain Pubic pain Groin pain Ligament disorder Ligament pain Musculoskeletal discomfort
Nervous system disorders			Headache Dizziness Dysgeusia Paraesthesia

			Burning sensation Hyperaesthesia Hypoaesthesia
Psychiatric disorders			Abnormal dreams Depression Sexual inhibition
Renal and urinary disorders			Dysuria Pollakiuria
Reproductive system and breast disorders	Penile haematoma <sup>a</sup> Penile swelling <sup>b</sup> Penile pain <sup>c</sup> Penile ecchymosis <sup>d</sup>	Penile blister Pruritus genital Painful erection Erectile dysfunction Dyspareunia Penile erythema	Penile adhesion Penis disorder Peyronie's disease Sexual dysfunction Testicular pain Scrotal erythema Genital discomfort Genital haemorrhage Pelvic pain Penile size reduced Penile vein thrombosis Scrotal oedema Scrotal pain
Respiratory, thoracic and mediastinal disorders			Cough
Skin and subcutaneous tissue disorders		Blood blister Skin discolouration	Skin hyperpigmentation Erythema Pigmentation disorder Skin nodule Blister Granuloma skin Night sweats Penile ulceration Rash erythematous Skin disorder Skin irritation Skin oedema
Vascular disorders			Haematoma Hypertension Haemorrhage Lymphangiopathy Thrombophlebitis superficial

a Includes: injection site haematoma and penile haematoma were reported with the verbatim term of penile bruising or injection site bruising in 87% of patients.

b Includes: injection site swelling, penile oedema, penile swelling, local swelling, scrotal swelling, and injection site oedema.

c Includes: injection site pain, penile pain, and injection site discomfort.

d Includes: contusion, ecchymoses, penile haemorrhage, and injection site haemorrhage.

There were no clinically meaningful differences in the incidence of adverse events following treatment with XIAFLEX based on the severity of baseline erectile dysfunction or concomitant phosphodiesterase type 5 (PDE5) inhibitor use.

XIAFLEX was not associated with shortening of penile length in clinical trials in the treatment of Peyronie's disease.

## **DOSAGE AND ADMINISTRATION**

### Dupuytren's Contracture

XIAFLEX is only to be administered by qualified doctors who are experienced in the diagnosis of Dupuytren's disease and are experienced in injection

procedures of the hand. All qualified doctors must have either experience in the surgical management of Dupuytren's disease or been an investigator in the clinical trial program. Prior to use of XIAFLEX, all qualified doctors must have undergone a prescriber education and training program by Actelion Pharmaceuticals Australia Pty Ltd including training in the appropriate administration of XIAFLEX.

Ensure appropriate equipment, monitoring of vital signs and treatments are available to address any severe local or systemic reactions including the potential for anaphylaxis that may occur following injection of XIAFLEX.

The recommended dose of XIAFLEX is 0.58 mg per injection into a palpable Dupuytren's cord. Each vial of XIAFLEX and sterile diluent for reconstitution should only be used for a single injection. If cords of two affected joints on the same hand are to be treated during a treatment visit, separate vials and syringes should be used for each reconstitution and injection.

The volume of reconstituted XIAFLEX to be administered into the Dupuytren's cord differs depending on the type of joint being treated (see Table 15).

Approximately 24 -72 hours after injection, a finger extension procedure may be performed, as necessary, to facilitate cord disruption.

If a satisfactory response has not been achieved, the injection and finger extension procedures may be repeated after approximately 4 weeks.

Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.

Inject up to two cords or two affected joints in the same hand according to the injection procedure during a treatment visit. Two palpable cords affecting two joints may be injected or one palpable cord affecting two joints in the same finger may be injected at two locations during a treatment visit. Each injection contains a 0.58 mg dose.

If the disease has resulted in multiple contractures, additional cords may be treated at other treatment visits approximately 4 weeks apart, as determined by the physician.

Patients should be instructed to return to see their physician approximately 24 - 72 hours after injection for an examination of the injected hand and a possible finger extension procedure(s) to disrupt the cord(s).

#### Peyronie's Disease

XIAFLEX should be administered by a physician appropriately trained in the correct administration of the product and experienced in the diagnosis and treatment of male urological diseases (e.g., urologists and sexual health physicians).

The recommended 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.

The volume of reconstituted XIAFLEX to be administered into the plaque is 0.25 mL (see Table 15).

A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of two XIAFLEX injections and one penile modeling procedure. The second XIAFLEX injection of each treatment cycle is administered 1 to 3 days after the first injection. The penile modeling procedure is performed 1 to 3 days after the second injection of each treatment cycle. If a satisfactory response has not been achieved after the first treatment cycle, the injection and penile modeling procedures may be repeated after approximately 6 weeks.

If the curvature deformity is less than 15 degrees after the first, second or third treatment cycle, or if the physician 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 for Peyronie's disease is not known.

#### Special population

##### *Elderly*

No overall differences in safety or effectiveness were observed between elderly and younger patients.

##### *Hepatic impairment*

Due to the lack of quantifiable systemic exposure in patients with Dupuytren's contracture and minimal and short-lived systemic exposure of XIAFLEX in patients with Peyronie's disease, no dose adjustment is necessary.

##### *Renal impairment*

Due to the lack of quantifiable systemic exposure in patients with Dupuytren's contracture and minimal and short-lived systemic exposure of XIAFLEX in patients with Peyronie's disease, no dose adjustment is necessary.

##### *Paediatric population*

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

#### Method of administration

Intralesional use.

Product is for single use in one patient only. Not all the reconstituted solution is injected, refer to Volume for Injection for volume to be administered.

Discard any unused reconstituted solution or diluent.

### *Volume for reconstitution*

XIAFLEX must only be reconstituted with the diluent provided and to the appropriate volume prior to use:

- For MP joints use 0.39 mL of diluent
- For PIP joints use 0.31 mL of diluent
- For Penile plaque use 0.39 mL of diluent (see Table 15)

### *Volume for injection*

- For cords affecting MP joints each dose is administered in an injection volume of 0.25 mL
- For cords affecting PIP joints, each dose is administered in an injection volume of 0.20 mL
- For Penile plaque each dose is administered in an injection volume of 0.25 mL (see Table 15)

**Table 15: Volumes needed for reconstitution and administration**

<b>Joint to be treated</b>	<b>Diluent required for reconstitution</b>	<b>Injection volume to deliver XIAFLEX 0.58 mg dose<sup>a</sup></b>
MP joints	0.39 mL	0.25 mL
PIP joints	0.31 mL	0.20 mL
Penile plaque	0.39 mL	0.25 mL

<sup>a</sup>Note that injection volume for delivery of a 0.58 mg dose is less than the total volume of diluent used for reconstitution. The entire reconstituted XIAFLEX solution contains 0.9 mg of XIAFLEX. Reconstituted XIAFLEX solution remaining in the vial after the injection should be discarded.

### **Dupuytren's Contracture**

Patients should be instructed:

- To remove all jewellery from the hand to be treated.
- 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 oedema), sensory changes in the treated finger, or trouble bending the finger after the swelling goes down (symptoms of tendon rupture).

- To return to their physician's office within the 3 days, as instructed, for an examination of the injected hand and for a possible finger extension procedure(s) to disrupt the cord(s).

### Peyronie's Disease

Patients should be instructed that serious complications of XIAFLEX injection include corporal rupture and penile haematoma and may require surgery to correct the complication. Patients should also be instructed:

- 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 severe pain or severe swelling of the penis, severe purple bruising and swelling of the penis, difficulty urinating or blood in the urine, or sudden loss of the ability to maintain an erection. These symptoms may be accompanied by a popping or cracking sound from the penis
- To return to their healthcare provider's office when directed for further injection(s) and/or penile modeling procedure(s)
- To perform the at home penile modeling procedures (3 times daily for the penile stretching procedure and once daily for the penile straightening procedure) for 6 weeks following each treatment cycle
- **To wait two weeks after the second injection of a treatment cycle before resuming sexual activity, provided pain and swelling have subsided**

***Detailed instructions for the physician in the preparation of the medicinal product for injection (reconstitution procedure) and administration are provided in the pack.***

Any unused medicinal product or waste material must be disposed of in accordance with local requirements.

### Instructions for use and handling

#### *Preparation - Reconstitution procedure*

Before use, remove the vial containing the lyophilised 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.

Each vial of XIAFLEX and sterile diluent for reconstitution should only be used for a single injection.

In patients with Dupuytren's contracture, confirm the joint to be treated (MP or PIP) as the volume of diluent required for reconstitution is determined by the type of joint (PIP joint requires a smaller volume for injection). If two cords of affected joints on the same hand are to be treated during a treatment visit, separate vials and syringes should be used for each reconstitution and injection.

Using an aseptic technique, the following procedure for reconstitution must be followed:

1. Remove the flip-off plastic caps from both vials, 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 must be used).
2. Use only the supplied diluent for reconstitution; it contains calcium which is required for the activity of XIAFLEX. Using a sterile syringe calibrated with 0.01 mL graduations, withdraw the appropriate amount of diluent supplied in order to deliver as follows:
  - 0.39 mL for cords affecting a MP joint
  - 0.31 mL for cords affecting a PIP joint
  - 0.39 mL for Penile plaque
3. Inject the diluent slowly onto the sides of the vial containing the lyophilised powder of XIAFLEX. Do not invert the vial or shake the solution. Slowly swirl the solution to ensure that all of the lyophilised powder has gone into solution.

Remove and discard the syringe and needle used for reconstitution.

4. Inspect the solution visually for particulate matter and discolouration prior to administration. The reconstituted solution of XIAFLEX must be clear. If the solution contains particles, is cloudy or discoloured, do not inject it.

Not all the reconstituted solution is to be administered to achieve the recommended dose. See table 15 above for the required injection volume.

5. After injection observe the patient for at least 20 minutes and be prepared to address any severe local or systemic reactions including the potential for anaphylaxis that may occur following injection.

## **OVERDOSAGE**

Administration of XIAFLEX at greater than recommended doses is expected to be associated with increased local reactions at the site of injection. Routine supportive care and symptomatic treatment must be provided in the case of overdose.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

## **PRESENTATION AND STORAGE CONDITIONS**

XIAFLEX powder is supplied in a clear glass vial with rubber stopper, aluminium seal and flip-off cap.

Diluent: 3 mL solution supplied in a clear 5 mL glass vial with rubber stopper, aluminium seal and flip-off cap.

Pack of 1 vial of powder and 1 vial of diluent. AUST R 199854

***Storage Conditions***

*Un-reconstituted powder and diluent:*

Store in a refrigerator (2°C-8°C). Do not freeze.

*Storage condition of the reconstituted medicinal product:*

After reconstitution the solution can be used immediately. Alternatively, reconstituted XIAFLEX can be kept at ambient room temperature (20°C-25°C) for up to one hour or refrigerated 2°C-8°C 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.

**POISON SCHEDULE OF THE MEDICINE**

Prescription Medicine (S4)

**NAME AND ADDRESS OF THE SPONSOR**

Actelion Pharmaceuticals Australia Pty Limited  
Suite 6, 13B Narabang Way  
Belrose NSW 2085

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS: 7 AUGUST 2013**

**Date of most recent amendment: 17 March 2016**