Attachment 1: Product information for AusPAR Xiaflex Collagenase clostridium histolyticum Actelion Pharmaceuticals Australia Pty Ltd PM-2012-01472-3-3. Final 18 November 2013. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

XIAFLEX® (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 0.9mg of collagenase clostridium histolyticum as a sterile, lyophilised powder for reconstitution. Each vial also contains approximately 0.5mg of hydrochloric acid, 18.5mg 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 0.3mg/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.

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.

Pharmacokinetics

Absorption and Distribution

Following administration of a single dose of 0.58 mg of XIAFLEX to patients with Dupuytren's contracture, no quantifiable levels of XIAFLEX were detected in plasma up to 30 days post injection.

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, no formal studies on elimination have been performed.

CLINICAL TRIALS

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

Note: Includes all patients who received at least 1 injection of double-blind study medicinal product (XIAFLEX 0.58 mg or placebo).
[1] 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[d])	N=203[c] 64.0% 57% (47%, 67%)	N=103[c] 6.8% -	N=45 44.4% 40% (14%, 62%)	N=21 4.8% -
	N=133	N=69	N=20	N=11

MP Joints[a] Difference (CI[d])	76.7% 69% (57%, 79%)	7.2% -	65.0% 56% (19%, 83%)	9.1% -
	N=70	N=34	N=25	N=10
PIP Joints[b] Difference (CI[d])	40.0% 34 % (14%, 52%)	5.9% -	28.0% 28% (-10%, 61%)	0.0% -

[a] Metacarpophalangeal joint; [b] Proximal interphalangeal joint; [c] 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) [d] 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
All Joints	N=197[c]	N=102[c]	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)
MP Joints[a]	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)
PIP Joints[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)

[a] Metacarpophalangeal joint; [b] Proximal interphalangeal joint; [c] 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 ($r=0.51$, $p<0.001$).

Recurrence of contracture was evaluated in joints that achieved the primary endpoint, a reduction in contracture to 5° or less. Recurrence was defined as an increase in joint contracture to at least 20° in the presence of a palpable cord, at any time during the double-blind phase or open-label extension phase that persisted at the last available measurement. In a pooled analysis, across the pivotal Phase 3 double-blind placebo controlled and open label studies, there were a total of 838 successfully treated joints. Of these, 28 joints (7 MP

and 21 PIP joints) had a recurrent contracture, giving a recurrence rate of 3.3% at 12 months after subjects had achieved clinical success following treatment with XIAFLEX. Recurrence rates for contractures at 2 years were 19% (34% PIP joint and 14% MP joint) and at 4 years were 42% (62% PIP joint and 35% MP joint).

INDICATIONS

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

CONTRAINDICATIONS

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

PRECAUTIONS

Allergic reactions
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.

XIAFLEX contains foreign proteins and patients developed anti-drug antibodies in greater proportions and higher titres with successive 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 and have been reported in the post-marketing experience. 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 injected extremity
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.

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 hemorrhage respectively at the injection site at a significantly higher rate than placebo patients. 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). At 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. No apparent correlation of antibody development to clinical response or adverse reactions was observed.

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.

Effects on Fertility

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).

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, 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 supratherapeutic 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

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 4: 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[a]	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[b]	87 (34.9)	7 (5.6)
Injection site swelling[c]	61 (24.5)	8 (6.4)
Injection site vesicles	6 (2.4)	1 (0.8)
Peripheral oedema[d]	183 (73.5)	6 (4.8)
Pruritus[e]	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)

[a] Includes the terms: lymphadenopathy and axillary mass
[b] Includes the terms: injection site reaction, injection site erythema, injection site inflammation, injection site irritation, injection site pain, and injection site warmth
[c] Includes the terms: injection site swelling and injection site oedema
[d] Most involved swelling of the treated extremity.
[e] Includes the terms: pruritus and injection site pruritus
Severe AEs: injection site reaction, pain in extremity (2%); peripheral edema, contusion (1.6%); injection site haemorrhage (1.2%); and tenderness, injection site cellulitis, ligament injury, skin laceration, tendon rupture, chest wall pain, irritability (<1%).

Table 5 presents adverse reactions listed by system organ class and frequency category , using the convention: uncommon (≥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 XIAFLEX 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 5: 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 6: Undesirable effects in Post-Marketing Reports (rare <1/1000; very rare <1/10,000)

Blood and lymphatic system disorders	Rare: Very rare:	Lymphadenopathy 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

DOSAGE AND ADMINISTRATION

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. The volume of reconstituted XIAFLEX to be administered into the Dupuytren's cord differs depending on the type of joint being treated (see Table 7).

Approximately 24 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.

Only one cord must be treated at a time.

If the disease has resulted in multiple contractures, treatment of each cord must be undertaken in a sequential order, as determined by the physician.

There are no efficacy or safety data on the simultaneous treatment of more than one cord or on the retreatment of previously treated cords.

Patients should be instructed to return to see their physician the next day for an examination of the injected hand and a possible finger extension procedure to disrupt the cord.

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, no dose adjustment is necessary.

Renal impairment
Due to the lack of quantifiable systemic exposure, 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 (see Table 7).

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.

Table 7: Volumes needed for reconstitution and administration

Joint to be treated	Diluent required for reconstitution	Injection volume to deliver XIAFLEX 0.58 mg dose[a]
MP joints	0.39 mL	0.25 mL
PIP joints	0.31 mL	0.20 mL

[a]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.

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 the next day for an examination of the injected hand and for a possible finger extension procedure to disrupt the cord.

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.

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

1. 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).

2. 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).

3. 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

4. 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.

5. 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.

6. 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: 5 ml solution supplied in a clear 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 (2ºC-8ºC). 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 (20ºC-25ºC) for up to one hour or refrigerated 2ºC-8ºC 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