



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Collagenase clostridium histolyticum

Proprietary Product Name: Xiaflex

Sponsor: Actelion Pharmaceuticals Australia Pty
Ltd

August 2016

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright

© Commonwealth of Australia 2016

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

Common abbreviations	5
I. Introduction to product submission	6
Submission details	6
Product background	6
Regulatory status	8
Product information	9
II. Quality findings	9
III. Nonclinical findings	9
Introduction	9
Pharmacology	9
Toxicology	10
Local tolerance	11
Nonclinical summary and conclusions	12
IV. Clinical findings	12
Introduction	12
Pharmacokinetics	14
Pharmacodynamics	14
Dosage selection for the pivotal studies	15
Efficacy	17
Safety	19
First round benefit-risk assessment	21
First round recommendation regarding authorisation	23
Clinical questions	23
Second round evaluation of clinical data submitted in response to questions	25
Second round benefit-risk assessment	25
V. Pharmacovigilance findings	27
Risk management plan	27
VI. Overall conclusion and risk/benefit assessment	39
Quality	40
Nonclinical	40
Clinical	40
Risk management plan	48
Risk-benefit analysis	49
Outcome	56

Attachment 1. Product Information _____ **57**
Attachment 2. Extract from the Clinical Evaluation Report _____ **57**

Common abbreviations

Abbreviation	Meaning
AA4500	Collagenase clostridium histolyticum
ACPM	Advisory Committee on Prescription Medicines
ADA	Antidrug antibody
AE	Adverse event
AUX I	Clostridial type 1 collagenase
AUX II	Clostridial Type II collagenase
BTC	Biologics technology corporation
CI	Confidence interval
CMI	Consumer medicine information
ED	Erectile dysfunction
EU	European union
HED	Human Equivalent Dose
IIEF	International index of erectile function
ITT	Intention to treat
LOCF	Last observation carried forward
mITT	Modified intention to treat
MMPs	Matrix metalloproteinases
NOEL	No observable effect level
PD	Peyronie's disease
PDQ	Peyronie's disease questionnaire
PI	Product information
RMP	Risk management plan
SAE	Serious adverse event
TEAE	Treatment emergent adverse event

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	16 March 2016
<i>Date of entry onto ARTG:</i>	21 March 2016
<i>Active ingredient(s):</i>	Collagenase clostridium histolyticum
<i>Product name(s):</i>	Xiaflex
<i>Sponsor's name and address:</i>	Actelion Pharmaceuticals Australia Pty Ltd 13B Narabang Way, Belrose NSW 2085
<i>Dose form(s):</i>	Injection, Powder (lyophilized) for injection
<i>Strength(s):</i>	0.9 mg [to deliver a 0.58 mg dose]
<i>Container(s):</i>	Composite pack: Powder in Type 1 glass vial and Diluent 3 mL solution supplied in a clear 5 mL glass vial with rubber stopper, aluminium seal and flip-off cap.
<i>Pack size(s):</i>	1s
<i>Approved therapeutic use:</i>	<i>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.</i>
<i>Route(s) of administration:</i>	Intralesional
<i>Dosage:</i>	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. A treatment course consists of a maximum of 4 treatment cycles.
<i>ARTG number (s):</i>	448382

Product background

This AusPAR describes the application by the sponsor Actelion Pharmaceuticals Australia Pty Ltd to extend the indications of Collagenase *Clostridium histolyticum* (Xiaflex is also referred to as AA4500 in this AusPAR) to include the treatment of Peyronie's disease with palpable plaque and curvature deformity of the penis in adult males.

Xiaflex is indicated for the treatment of male adults with Peyronie's disease and a palpable plaque and curvature deformity.

Xiaflex is currently approved for the treatment of Dupuytren's contracture in adult patients with a palpable cord.

The proposed dose is the same as that used for Dupuytren's contracture (0.58 mg; 10,000 Units (U)). The proposed dosing regimen is administration of 0.58 mg in 0.25 mL directly into the Peyronie's plaque. One treatment cycle comprises two injections given 1 to 3 days apart, with up to four cycles six weeks apart being the maximum duration of treatment.

Xiaflex belongs to the pharmacotherapeutic group 'Other drugs for disorders of the musculoskeletal system-enzymes'.

Peyronie's disease is a connective tissue disorder for the penis, characterised by the triad of bent erections, penile pain with erections and palpable penile plaque. It occurs in up to 9% of men, mostly between the ages of 40 and 70 years. The principal finding is scar tissue in the tunica albuginea, in most cases deposited on the outer covering of the erectile bodies. In severe disease the plaque may become calcified. It is postulated that penile trauma may be a contributing factor, although there may be a genetic predisposition. Erectile function may be affected by the deformity and the deformity may prevent vaginal intromission or cause pain for the partner. There is also a large psychological burden, with up to 48% of patients developing depression. The natural history of Peyronie's disease is sudden onset with an acute phase, progression then stabilisation. In patients presenting with active disease the chance of spontaneous improvement is about 20%, progression is approximately 40% and stabilisation is about 40%, although the estimations vary considerably in studies. The management of Peyronie's disease depends on the extent of stabilisation, the severity of the penile defect and erectile function.¹

Collagenase clostridium histolyticum (CCH) consists of two microbial collagenases in an approximate 1:1 mass ratio that are isolated and purified from the fermentation of *Clostridium histolyticum* bacteria: collagenase AUX I (Clostridial Type I collagenase) and collagenase AUX II (Clostridial Type II collagenase). Collagenase is a proteinase that can hydrolyse the triple-helical region of collagen under physiological conditions resulting in collagen breakdown. The sponsor states these two collagenases are not immunologically cross-reactive and have different specificities, such that together they become synergistic.

The clinical rationale is that after local injection at into the Peyronie's plaque there will be selective lysis of collagen at the injection site that will result in disruption of the plaque and reduction of disease symptoms.

The supply of Xiaflex is currently restricted to doctors who have experience with Dupuytren's disease and injection procedures of the hand, specifically doctor's with experience in the surgical management of Dupuytren's contracture or investigators in the clinical trial programme, through a controlled distribution scheme managed by the sponsor.

No new dosage forms or strengths are proposed.

The sponsor proposes that 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.

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.

¹ James Buchanan Brady Institute, Johns Hopkins University

A treatment course consists of a maximum of 4 treatment cycles. Each treatment cycle consists of two Xiaflex injections and one penile modelling procedure. The second Xiaflex injection of each treatment cycle is administered 1 to 3 days after the first injection. The penile modelling 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 modelling procedures may be repeated after approximately 6 weeks.

If the curvature deformity is less than 15 degrees after the first, second or third treatment, 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.

There are no specific TGA adopted European guidelines of direct relevance to this submission.

Regulatory status

CCH for the treatment of Dupuytren's contracture was considered by the TGA's Advisory Committee on Prescription Medicines (ACPM) in June 2013 and Xiaflex was entered on the Australian Register of Therapeutic Goods (ARTG) in August 2013.

CCH has been approved for the treatment of Peyronie's disease in the US (2013), the European Union (EU) (2015). It is under evaluation in Switzerland. The approved indications overseas are as shown in Table 1 below.

Table 1: International regulatory status for CCH 0.9 mg powder/solvent for injection

Country	Trade name	Approved indications	Date of approval
EU and EEA (centralized procedure)	Xiapex	<i>Dupuytren's contracture in adult patients with a palpable cord</i>	28 February 2011
		<i>Adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy</i>	30 January 2015
USA	Xiaflex	<i>Dupuytren's contracture in adult patients with a palpable cord</i>	2 February 2010
		<i>Adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy</i>	6 December 2013
Switzerland	Xiapex	<i>Dupuytren's contracture in adult patients with a palpable cord</i>	13 July 2011

Country	Trade name	Approved indications	Date of approval
Canada	Xiaflex	<i>Dupuytren's contracture in adult patients with a palpable cord</i>	5 July 2012
Australia	Xiaflex	<i>Dupuytren's contracture in adult patients with a palpable cord</i>	30 July 2013

Product information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

To support the new indication, two studies in which beagle dogs received intrapenile injections of collagenase were included in the sponsor's dossier (TRL 507, TRL 510). These studies have previously been evaluated by the TGA. In addition, a previously submitted pivotal study of repeated intrapenile administration in dogs (TRL 520) was summarised. One new primary pharmacology study was also submitted (RU-001) as well as a new pharmacokinetics study (PKPD-005) and a previously evaluated local tolerance (SC injection) study (WIL 696007). The latter two studies were not formally evaluated here due to limited relevance to the proposed extension of indication.

Pharmacology

Primary pharmacology

In vitro treatment of Peyronie's plaque tissue explants demonstrated collagenolytic activity of AA4500 in this tissue. Lysis of Type I and Type III collagen fibres was demonstrated with concentrations of ≥ 750 U and after 1h incubation with 3000 U. In contrast, lysis of Type IV collagen in blood vessel walls was also observed after but only after prolonged exposure (≥ 8 h) following injection of a higher dose into the explant (3000 U, approximately 0.2 mg). This is consistent with the observed necrosis of small veins in repeat dose studies, however it should be noted that lysis was not observed in larger vessels. Based on these findings, it is anticipated that some lysis of Type IV collagen fibres in blood vessels may occur clinically. The activity of AA4500 was similar in explanted Peyronie's plaques to that observed in Dupuytren's cord explants.

Selected literature references from the previous and current submission were evaluated to assess pharmacology statements made in the sponsor's draft PI. Subdermal injection of collagenase or collagen-derived fragments increased vascular permeability in rats. In vitro studies also demonstrated that collagen-derived fragments were chemotactic for neutrophils, monocytes, fibroblasts and keratinocytes, supporting both inflammatory and regenerative activity. These effects are consistent with in vivo observations of oedema, inflammation and neovascular proliferation in repeat dose studies.

Toxicology

Repeat dose toxicity

There was limited systemic exposure following intrapenile, subcutaneous (SC) or intravenous (IV) dosing of AA4500 in dogs and/or rats. Therefore, relative exposures were calculated on dose. Dose comparisons were made based on a 50 kg adult and a body weight of 10 kg for dogs was assumed. Exposure ratios were calculated based on a single local dose in mg and normalised for body weight ($\mu\text{g}/\text{kg}$). The exposure ratios for dogs that received AA4500 as an intrapenile injection were mostly below the anticipated clinical exposure (Table 2). This was in part due to the use of the clinical formulation and dose limiting injection volumes at the injection sites in dogs. The exposure ratios presented below differ modestly from those presented by the sponsor, as the sponsor used 70 kg as the weight for humans in their calculations.

Table 2: Relative exposure in nonclinical studies

Species	Study duration	Dose (intrapenile)		Exposure ratio	
		mg [^] /dose	$\mu\text{g}/\text{kg}$	local (mg)	$\mu\text{g}/\text{kg}$
Dog (beagle) Study TRL-520	Repeat (3 cycles of 3 x q48h)	0.008	0.8	0.01	0.07
		0.025	2.5	0.04	0.2
		0.06	6.1	0.11	0.5
	Single	0.08	8.3	0.14	0.7
		0.15	14.9	0.26	1.3
Human	(Up to 6 cycles of 2x q24 to 72 h)	0.58	12	–	–

[^]In both humans and dogs, 1mg AA4500 gives approximately 17,240 U.

Consistent with limited systemic exposure, no target organs were identified following repeated dosing into the tunica albuginea in dogs. Systemic exposure was assessed following IV dosing in rats. Hepatotoxicity was observed after 16 days of once a day (QD) IV dosing (exposure ratios of ≥ 10 x based on body surface area). Local reactions were observed following IV, SC and intrapenile dosing, with the latter discussed below.

Local tolerance

Single or repeated injection of AA4500 into the tunica albuginea (TA) was relatively well tolerated. The incidence of local swelling and bruising was dose dependent. Discolouration was observed in all groups including those that received vehicle. Microscopic analysis of the injection site showed adventitial haemorrhage and neovascular proliferation at a similar incidence and severity following administration of vehicle and AA4500.

Inflammation was present at the injection site of some treated animals. None of the microscopic findings at the injection site showed a dose response relationship. Sinus erythrocytosis occurred in the inguinal lymph node in control and treated dogs but frequency was treatment and dose related. This effect is likely to be secondary to injection site haemorrhage. Collagen lysis in the TA was also observed in one dog following a single, but not repeated, injection of AA4500 into the TA. The observed effects of injection of AA4500 into the TA were reversible following a 4 week recovery period. As the TA is a dense collagen structure, lysis in this tissue is an expected pharmacological effect. During clinical administration, exposure to AA4500 is intended to be restricted to the Peyronie's plaque. However, diffusion into surrounding tissues has the potential for undesirable pharmacological effects such as lysis in the TA.

Local tolerance studies also assessed the effects of administration of AA4500 into inadvertent penile structures. Dogs received a single injection of AA4500 into the corpus cavernosum (CC), to subcutaneous tissue adjacent to the main vein, artery and nerve complex of the penis (VAN) or to the urethra. Overall, more severe local reactions were observed following injection of AA4500 into these anatomical sites. This is likely related to the "looser" structure of these tissues which allows greater perfusion of AA4500. The severity and incidence of local inflammation and haemorrhage was higher compared to administration into the TA. In addition, necrosis of the stromal, adventitial and/or venous wall was observed following injection into the CC, VAN and urethra (severity range was mild to marked). Mild to moderate haemorrhage was also observed in the arteriolar wall following injection into the VAN and urethra. Lysis of collagen in the TA was also observed in one dog that received AA4500 by injection into the CC. These effects showed evidence of reversal after a 4 week recovery period. However, unlike in the TA, microscopic injury was still present in the CC, VAN and urethra, which may reflect the more extensive histopathological injury in these sites.

While intrapenile injections of AA4500 were tolerated to an extent, there were incidences of dogs requiring euthanasia due to severe local reactions. One dog was euthanised due to marked weight loss secondary to severe bruising, swelling and ulceration (full thickness, involving the prepuce) after receiving two injections of 0.02 mg (2.5 µg/kg) AA4500 into the TA. One dog was euthanised 2 h post dose due to severe haemorrhage following a single 0.13 mg (14.9 µg/kg) injection into the VAN. In addition, dogs that received AA4500 (≥ 0.19 mg/site) into each of the TA, CC and VAN sites, exhibited severe local toxicity requiring euthanasia of 2 of 3 dogs in each group. While the latter examples are of limited clinical relevance, the severe toxicity following repeated injection into the TA may be clinically relevant.

Overall, injection of AA4500 into the TA, which has a similar dense collagen structure to a Peyronie's plaque, was tolerated. The observed reactions were generally either a response to the procedure or expected pharmacological effects. However, the dog studies demonstrated the potential for locally severe reactions in some individuals. The severity of reactions did not show a clear dose response and occurred following injection of lower doses of AA4500 than that proposed clinically (exposure ratio of ≤ 0.1 based on mg per injection).

Nonclinical summary and conclusions

- The nonclinical studies were adequate, with the majority having previously been assessed by the TGA.
- In vitro primary pharmacology studies supported the proposed indication. AA4500 showed similar collagen lysis in tissue explants from Peyronie's disease plaques to that shown in explants from Dupuytren's cord tissue. Lysis was predominantly of collagen Type I and III which are the main collagen fibres in Peyronie's plaques. Some lysis of collagen Type IV occurred in blood vessel walls of explant tissue at higher concentrations after prolonged exposure. Similar effects were observed in smaller veins in vivo.
- There was no systemic toxicity associated with repeated intrapenile (tunica albuginea, TA) dosing in dogs that received $\leq 6 \mu\text{g}/\text{kg}$ (3 cycles of 3 injections every 48 h (q48h), relative exposure 0.5 based on $\mu\text{g}/\text{kg}$). Systemic exposure was generally not quantifiable.
- Repeated administration into the TA was associated with local reactions which included swelling, bruising and discolouration of the penis. The reactions were severe in some animals requiring dose reduction and or euthanasia. These effects were consistent with pharmacological effects and included local haemorrhage, inflammation and neovascular proliferation. Similar effects occurred after a single injection of higher doses, with collagen lysis in the TA observed in one dog. These effects were generally restricted to the injection site and showed evidence of recovery after 4 weeks.
- Local tolerance studies assessed the effects of inadvertent administration of AA4500 to other anatomical regions of the penis, including the corpus cavernosum, subcutaneous tissue adjacent to the main vein, artery and nerve of the penis and/or urethra. Local reactions were generally more severe in these regions compared to administration into the TA but also showed evidence of reversibility.
- The severity of local reactions in some individual dogs indicates a serious safety concern. However, these concerns appear to be captured in the PI and Risk Management Plan (RMP). Therefore, provided there is adequate safety information from clinical data, there are no nonclinical objections to registration.
- Amendments to the draft Product Information document were recommended but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Peyronie's disease

Peyronie's disease is a disease of the localised connective tissue of the tunica albuginea. It typically affects males between the ages of 40 and 70 years. The reported incidence varies greatly (depending on age and other risk factors of the population studied and whether the cases present with symptoms or asymptomatic cases are included), but is estimated to be 1 to 8%. Clinical presentations include penile plaque, palpable indurations along the

penile shaft, penile curvature or deformity, and penile pain. Erectile dysfunction is estimated to occur in around 20% of men with this disease. There is a large psychological burden of the disease, with up to 48% of subjects developing depression. In the early phases of disease, nodule or plaque formation can be confused for malignancy. Penile pain and deformity can impact upon the sexual and emotional health of subjects. Certain sexual positions become difficult and subjects experience concern over their body image. Men with Peyronie's disease sometimes develop a loss of hope, which causes further distancing from sexual activities.

Risk factors for Peyronie's disease include age, penile trauma, diabetes, smoking, family history and the presence of Dupuytren's contracture. Several studies have identified vascular risk factors among men with Peyronie's disease, at rates similar to men with erectile dysfunction.

Histological studies of plaque tissue demonstrate that the normal structure of the tunica albuginea is replaced by collagen fibrils in degenerative bundles. There is accumulation of fibrin, inflammation and aberrant staining of collagen. As the disease progresses there is calcification and ossification.

Two stages of Peyronie's disease are described. The first (acute or inflammatory) phase last 6 to 12 months and is characterised by nodule formation, pain and slight curvature deformity. The second (stable, chronic) phase is characterised by a more stable plaque and more pronounced curvature. The reported rate of spontaneous resolution (of the plaque and deformity) varies considerably in studies, with rates reported of between 13% and 80%. Resolution of these structural changes is more common in the early phases of disease. Resolution of the pain occurs in all patients with time.

Xiaflex

A collagenase is an enzyme that recognises and binds to collagen in its native conformation and cleaves the peptide bonds resulting in collagen breakdown. Clostridial collagenases selectively degrade fibrillar collagen without causing damage to normal tissue components (arteries, nerves and vessels).

It is hypothesised that injection of Xiaflex into a Peyronie's plaque will result in enzymatic disruption of the plaque and a reduction in symptoms due to the disease.

Guidance

There are no TGA adopted guidelines for the evaluation of Peyronie's disease or erectile dysfunction. The evaluator used the information in the sponsor's dossier and a brief literature review for guidance.

Contents of the clinical dossier

Scope of the clinical dossier

The sponsor has submitted a comprehensive dossier containing the following clinical information:

- An open label pharmacokinetic study (AUX-CC-805)
- A Phase IIb study (AUX-CC-801)
- Three Phase III studies
 - Two randomised, double blind placebo controlled studies (AUX-CC-803 and AUX-CC-804)
 - One open labelled study (AUX-CC-802)
- Literature references

Paediatric data

The submission did not include paediatric data. This is appropriate as Peyronie's disease does not occur in children.

Good clinical practice

The studies in the dossier were performed in accordance with good clinical practice (GLP). Local ethics approval was granted for each study site.

Pharmacokinetics

Studies providing pharmacokinetic data

An open label pharmacokinetic study (AUX-CC-805) was submitted.

The sponsor submitted a number of other pharmacology and toxicology studies with the initial application for Dupuytren's contracture. These are not included in this evaluation.

Evaluator's conclusions on pharmacokinetics

The conduct of the Study AUX-CC-805 was adequate. It confirmed that there was minimal systemic exposure after intralesional treatment of Peyronie's disease and no evidence of dose accumulation after 2 doses separated by 48 h.

Pharmacodynamics

Studies providing pharmacodynamic data

There were no human pharmacodynamic studies for clinical evaluation. Nonclinical studies in dogs and guinea pigs have been performed and will be evaluated by the nonclinical section at the TGA.

Evaluator's conclusions on pharmacodynamics

There is a plausible pharmacodynamic mechanism for the use of Xiaflex in Peyronie's disease. Most of the pharmacodynamic studies have been using animal models; the ability to extrapolate these findings to humans is unknown. Xiaflex exerts a local effect on Type I and II collagen. Systemic effects are minimal, despite the increased vascularity of the penile tissue. Local reactions are more likely in Peyronie's disease than in Dupuytren's contracture as the connective tissue is less dense.

Unresolved issues

The pharmacodynamic or histological response to the diluent or placebo was not mentioned but the clinical studies (see *Efficacy* below and in Attachment 2) showed a significant placebo effect.

Dosage selection for the pivotal studies

The sponsor stated that the dosage selected for the clinical trials was based on efficacy and safety data from Phase I and II studies using different dose levels, injection volumes and treatment regimes. The dossier did not contain detailed information from the Phase I and early II clinical trials used to determine the dosage used in the Phase III clinical trials. The clinical evaluator noted two references that described earlier studies using lower doses.

Gelbard et al *The Journal of Urology* (198) the use of collagenase in the treatment of Peyronie's disease

This study took place between 1982 and 1983. It was an open labelled study of several doses of collagenase in 31 men. The mean age was 55.5 years (range 22 to 67), and duration of Peyronie's disease was 22 months (range 2 to 60). Dorsal, lateral and ventral plaques were included, ranging in size from impalpable (< 8 mm) to large (> 15 mm). Pain and deformity were the most common symptoms. Four patients were unable to partake in sexual intercourse. The concentration of collagenase administered was much lower than that used in the more recent studies; 15 subjects received 470 to 620 U/mL and 16 subjects 910 U/mL. The total dose received ranged from 470-2730 units. Oral β aminopropionitrile fumarate was added to improve laxity of the collagen in 25 patients. Overall, 65% of patients had an objective improvement in symptoms. Objective relief of deformity occurred in 50% of those with small plaques, 75% of those with moderate plaques, and 65% of subjects with large plaques. Pain during erection was eliminated in 93% of those with pain at the onset. Three of the 4 men who were unable to have sexual intercourse were able to after the collagenase; the man who failed treatment had a large plaque and 180° curvature. Twenty one of 31 subjects had ecchymosis. One patient had a corporal rupture 2 weeks after therapy. Operations were performed in 2 patients after collagenase treatment. The surgeons noted that the collagenase made the neurovascular bundle harder to mobilise from the tunical tissue, but did not affect the patient's suitability for plaque excision and graft or plaque incision and stent.

Gelbard et al *The Journal of Urology* (1993) Collagenase versus placebo in the treatment of Peyronie's disease: a double blind study

This study took place between 1987 and 1989. It included 49 men with Peyronie's disease. Patients with a coagulation abnormality or significant erectile dysfunction were excluded from the study. The patients were stratified into 3 categories, see Table 3 below, and received 3 injections over 3 consecutive days.

Table 3: Study design and patient response

Category	Treatment	N 49	Response		p
			positive	negative	
Overall	Collagenase: 2000 units per 0.5 mL of diluent	22	8 (36)	14 (64)	< 0.007
	Placebo: Diluent (0.9% NaCl and 2 mM CaCl ₂)	27	1 (4)	26(96)	
1: bend < 30° and/or palpable plaque < 2 cm	3 aliquots of 0.5 mL	3	3 (100)	0	0.14
	0.5 mL placebo	4	1 (25)	3 (75)	
2: 30 to 60° deformity and/or plaque 2 to 4 cm	3 aliquots of 0.8 mL	11	4 (36)	7 (64)	0.03
	0.8 mL placebo	13	0	13 (100)	
3: > 60° deformity and plaque > 4 cm	3 aliquots of 1.15 mL	8	1 (13)	7 (87)	0.4
	1.15 mL placebo	10	0	10 (100)	

Patients with small or moderate plaques and deformity were more likely to respond than those with large plaques and deformity. No adverse events were reported. One patient had penile popping and an ecchymosis during intercourse 3 weeks after the collagenase; this resolved spontaneously.

These studies question whether such a concentrated solution and large injected volume is required and whether using a less concentrated solution may minimise adverse effects.

Study included in the submission

The Phase IIb Study AUX-CC-801 (described in detail in Attachment 2 Section 7.1.1.3) used three treatment cycles of 0.58 mg (10 000 units) AA4500 separated by 42 days. Efficacy and safety was established. The 42 days between treatment cycles was maintained for the Phase III studies as this allowed sufficient time for local reactions to resolve. A further treatment cycle was added to Phase III studies with the aim of improving efficacy.

In Study AUX-CC-801, gentle penile plaque modelling was used to enhance the disruption of collagenous plaques. In this study, there was a significant difference in outcomes between the treatment group and placebo group who received modelling. There was a significant interaction between study drug and modelling indicating both factors were important in the treatment effect. Modelling was included as part of the clinical protocol for subsequent studies based on this study.

More information justifying the dose will be requested from the sponsor, particularly as the submitted clinical trials show a large placebo effect and increased rate of local reactions in the AA4500 group.

Efficacy

Studies providing efficacy data

Peyronie's disease

Table 4 summarises the studies included in the dossier to support the use of Xiaflex for Peyronie's disease.

Table 4: Summary of submitted efficacy studies

	Phase	Description	Intervention	Number of subjects
AUX-CC-805	PK		Two injections of AA4500	20
AUX-CC-801	IIb	Randomised, placebo controlled	AA4500 or placebo, Penile modelling or not	145
AUX-CC-803	III	Randomised, placebo controlled	0.58 mg AA4500 up to 4 treatment cycles with modelling	417
AUX-CC-804	III	Randomised, placebo controlled	0.58 mg AA4500 up to 4 treatment cycles with modelling	415
AUX-CC-802	III	Open labelled	0.58 mg AA4500 up to 3 treatment cycles with modelling 9 months	347

Evaluator's conclusions on efficacy

Peyronie's disease

The sponsor has provided two randomised and controlled trials (RCT) and two supporting trials for the use of Xiaflex in Peyronie's disease. The total number of patients exposed in the RCT was over 800, giving the trials adequate power to assess a difference in primary efficacy outcomes.

The studies showed an improvement in the primary efficacy outcomes of penile curvature and penile bother in both the placebo and treatment groups. These improvements were greater in the group that received Xiaflex. However there was a considerable variability in outcomes within the subjects studied. There was no significant difference between placebo and AA4500 in many of the secondary outcomes in the individual RCTs, however

when the data were pooled there were significant improvements in psychological elements (PDQ² and IIEF³) in the AA4500 group.

The placebo effect was significant and may have had a physiological basis. In a rat model of Peyronie's disease, injections with normal saline resulted in histological changes with decreased staining for collagen and an increased erectile function assessed by injections of saline and cavernous nerve stimulation. However it needs to be noted that in the clinical trials, the subjects had Peyronie's of relatively short duration and no calcifications on ultrasound, which in prospective studies have been the group most likely to regress. A RCT by design should eliminate the effect of variability in outcome factors by defining a large enough sample size. The evaluator notes that the standard deviation (SD) for % improvement chosen for curvature deformity chosen for the power calculations was 20% but the real variability in the clinical trial was in the order of 30%.

The lack of correlation between changes in penile curvature and measures of penile distress and sexual function is noteworthy. This demonstrates the complexity of Peyronie's disease. The patients' experience (suffering) goes beyond the shape of the penis into the psychological domain. The measurement of erectile function as an outcome factor for Peyronie's disease is clouded by this psychological factor as well as the other diseases present in this group of patients which impact erectile function (smoking, diabetes, hypertension, hyperlipidaemia, anxiety and depression).

The use of the PDQ strengthened the studies in that it provided a measure of psychological effect from treatment. However the validity of this is questionable given the low Pearson correlation co-efficient and discrepancy between the PDQ outcomes and patient reported erectile dysfunction as an adverse effect (see under *Safety* in Attachment 2).

The clinical trials have included a select group of patients with Peyronie's disease, which may not be representative of the population that presents to the general practitioner (GP) or urologist with a bend or plaque on the penis or erectile dysfunction. The sponsor's proposed indications and contraindications in the PI do not accurately reflect the patients chosen in the clinical trials.

Peyronie's disease is relatively common. Although not life threatening, it contributes to considerable distress for patients and results in sexual dysfunction, depression and anxiety. The high retention rates in the study demonstrate how motivated these patients were to receive treatment.

The natural history of Peyronie's disease is for regression in a minority, stability in some, deterioration in most. Pain tends to improve over time. There is limited evidence about the safety and efficacy of other non-operative treatments for Peyronie's disease. Clinical trials have demonstrated some efficacy of intralesional verapamil or interferon; topical verapamil; oral potassium para-aminobenzoate and colchicine. Surgical treatment is indicated in patients with stable disease (for at least 3 months) with the aim of correcting

² The Peyronie's Disease Questionnaire (PDQ) is a disease-specific 15-item, self-administered, paper-and-pencil instrument designed to measure the psychosexual consequences of Peyronie's Disease (PD). The PDQ contains three scales: 1) Peyronie's Psychological and Physical Symptoms (6 items), 2) Peyronie's Symptom Bother (6 items), and 3) Penile Pain (3 items).

Patients complete the Peyronie's Psychological and Physical Symptoms and Symptom Bother scales based on their most recent experience. A 5-point Likert-type response scale assesses subjects' level of symptom severity (none, mild, moderate, severe, very severe) with each item on the Peyronie's Psychological and Physical Symptoms scale. A 5-point Likert-type response scale (not at all bothered, a little bit bothered, moderately bothered, very bothered, extremely bothered) assesses patients' level of distress with each item on the *Peyronie's Symptom Bother* scale. Patients complete the items on the Penile Pain scale based on the last 24 hours or their most recent experience. An 11-point numeric rating scale is used to assess the extent of subjects' pain. The PDQ is to be completed by men who have had vaginal intercourse within the last 3 months from the time of questionnaire completion.

³ International index of erectile function

curvature and allowing satisfactory intercourse. The risks of surgery include penile shortening, erectile dysfunction, penile numbness, recurrent curvature, palpation of knots and stitches under the skin and the need for circumcision. Literature reports would suggest a relatively good outcome from surgery but these reports are retrospective and not RCTs.

Safety

Studies providing safety data

In Studies AUX-CC 803, AUX-CC-804, AUX-CC-801 and AUX-CC-802 the following safety data were collected:

- General adverse events (AEs) were assessed by history and examination. They were described using Medical Dictionary for Regulatory Activities (MedDRA) terms.
- AEs of particular interest, including:
 - Erectile function
 - Development of anti AUX I and AUX II antibodies.
- Laboratory tests, including biochemistry and haematology were performed at baseline and before each cycle of therapy.
- Electrocardiogram (ECG) was performed at baseline only.
- Doppler ultrasound was performed at baseline in all studies and at Week 52 in Study AUX-CC-801.

Other studies evaluable for safety

AUX-CC-805

Safety was assessed as part of this pharmacokinetic study. Safety parameters were described as counts and percentages. Comparisons between groups were made using Fishers exact test.

Patient exposure

A summary of subject exposure to AA4500 and placebo in clinical trials is listed below in Table 5.

Table 5: Exposure to AA4500 and comparators in clinical studies

	Total subjects	Number of treatment cycles	Duration of trial	AA4500	Placebo
AUX-CC-801	147	3	36 weeks	111	36
AUX-CC-802	347	4	Up to 36 weeks	347	-
AUX-	417	4	52 weeks	227	140

	Total subjects	Number of treatment cycles	Duration of trial	AA4500	Placebo
CC-803					
AUX-CC-804	415	4	52 weeks	274	141
AUX-CC-805	20	1	29 days	20	-

In Study AUX-CC-803, the majority of AA4500 (77.3%) and placebo (86.4%) subjects received all 8 injections and modelling (70.6 and 76.4%). Sixteen subjects did not receive injections due to an AE (all in the AA4500 group), 28 did not receive an injection as their curve was < 15% (mostly in the active group). Four subjects in the active group were unable to perform modelling due to pain or blistering.

In Study AUX-CC-804, the majority of AA4500 subjects (80.3%) and placebo subjects (89.4%) received all injections. Twelve subjects did not receive all injections due to an adverse event, 19 subjects did not receive an injection as their penile curvature was < 15°. Most of these were in the AA4500 group. Modelling occurred in 73% of the AA4500 group and 83% of the placebo group. Subjects in the placebo group more commonly refused modelling because of bruising or other adverse events.

In AUX –CC-801, 93.2% of the subjects received 6 doses of AA4500.

In AUX-CC-802, 81.3% of subjects received 4 cycles of treatment.

Safety issues with the potential for major regulatory impact

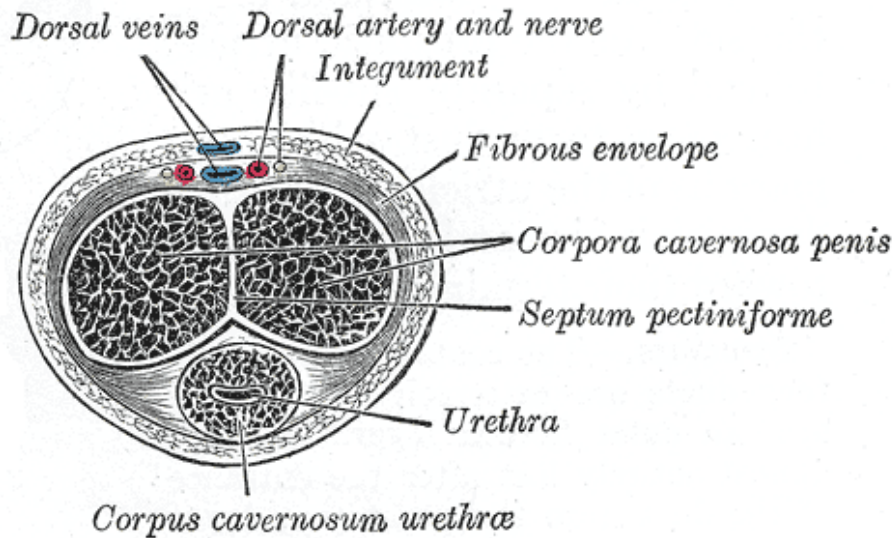
These include treatment-emergent AEs (TEAEs) and are discussed in Attachment 2.

Evaluator's conclusions on safety

Data for over 800 subjects with Peyronie's disease exposed to AA4500 was available from clinical trials. Most patients had received 3 of 4 treatment cycles of AA4500.

There was a high incidence of local reactions to the injection. The most common reactions were bruising, swelling and pain at the injection site or penis. The investigator rated these as mild or moderate. A small number of patients discontinued due to adverse effects or refused modelling. Local reactions generally resolved within 2 to 4 weeks.

A small number of patients experienced serious adverse events. There were 5 cases (0.5%) of corporal rupture described, all during intercourse. Four of these were coded as serious AEs (SAE). Three cases required surgical management, two were managed conservatively. Nine subjects (0.9%) reported a combination of penile ecchymosis or haematoma, sudden penile detumescence and/or penile popping. This was a concern as penile fracture cannot be excluded. All subjects were managed conservatively. No patients experienced urethral injury however such an injury would be more likely to occur with ventral plaques see Figure 1.

Figure 1: Cross sectional image of the penis

It is unknown if the adverse events are due to inadvertent injection of collagenase into other tissue, or extravasation of the collagenase to other tissue, or collagenase exerting a less specific effect for Type I and III collagen in humans than has been demonstrated in vitro and in animal models.

More patients in who received AA4500 (about 3.6%) than placebo (about 0.01%) coded as having erectile dysfunction as a TEAE during the study. It is unclear how many of these had erectile dysfunction at baseline, however overall the prevalence of erectile dysfunction was similar in the treatment groups at baseline and across all studies. The one study that performed Doppler ultrasound at the study endpoint identified abnormalities in those that developed erectile dysfunction. The impact of AA4500 or other factors on these Doppler ultrasound findings is unknown.

One case of acute hypersensitivity in a patient being treated for Dupuytren's contracture has been reported in the post-market setting.

The frequency of adverse effects in clinical trials where investigators would have undergone training and became very familiar with the technique is a concern. In addition, there were a number of dosing and administrative errors despite a comprehensive physician training program in the countries Xiaflex has been registered in.

Unknown safety areas include the use in the elderly, use in the context of coagulation therapy and the impact of Xiaflex on subsequent surgery.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Xiaflex for the treatment of Peyronie's disease are

- Improvement in penile curvature of around 16° (30 to 38%), compared to around 10° (15 to 20%) in the placebo group.
- Improvement in Peyronie's bother scale by 2.4 to 3.3 points (scale 0 to 15) points compared to 1.6 to 2.0 in the placebo group.
- Improvement in erectile function and sexual function

- First round assessment of risks.

The known risks of Xiaflex for the treatment of Peyronie's disease:

- High risk of local reaction; bruising, pain and oedema.
- < 1% risk of corporal rupture

Potential risks include:

- Dosing and administration errors
- Injection into tissues adjacent to the Peyronie's plaque, for example urethra, blood vessels and corpus cavernosa
- Hypersensitivity
- Systemic exposure to collagenase
- Increase rate of adverse events in the elderly as they have looser connective tissue
- Increased rate of complications with subsequent surgery
- Off label use.

First round assessment of benefit-risk balance

Overall, the benefit-risk balance of Xiaflex for Peyronie's disease is favourable. This is based on a positive improvement in Peyronie's symptomatology and clinical need for an efficacious non-invasive treatment option. However a number of changes to the submission are required to minimise the potential risks and ensure patients are adequately informed.

The evidence provided indicates Xiaflex has some benefit in improving penile deformity due to Peyronie's disease and an improvement in psychological symptoms, erectile and sexual function as a result. However there is large variability in individual responses and a significant placebo effect. Peyronie's disease is not life threatening but is disabling to sufferers. There are few other efficacious non-invasive treatment options. Surgery is an option for men with stable disease and a significant curvature deformity and retrospective studies support its efficacy. However, it is also associated with risks and not all men are willing to undergo such an invasive procedure.

The risks of local reactions are high but these are considered mild and resolve with time. Some subjects in the trial have had deterioration in erectile function as a result of treatment. There have been a few cases of corporal rupture. These cases have all been in men who have had vigorous intercourse. There is a potential risk of dosing error and injury to surrounding tissue due to extravasation or incorrect injection technique.

There have been a small number of applications for unregistered use of this medicine. An analysis of data from Special Access Scheme (SAS) applications as of April 2015 showed a total of 20 applications in 2014 and 7 so far in 2015. The requested were from a small number of doctors.

First round recommendation regarding authorisation

At this stage, the clinical evaluator would recommend approval of Xiaflex for the treatment of men with Peyronie's disease, subject to changes to the indications, dosage and administration, the RMP and a satisfactory response to the clinical questions.

The sponsor proposed the following indication:

Xiaflex is indicated for the treatment of male adults with Peyronie's disease and a palpable plaque and curvature deformity.

These indications open the treatment with Xiaflex with a much broader population to that which was studied in the clinical trials.

The evaluator recommends the indication be changed to:

Xiaflex is indicated for the treatment of Peyronie's disease of greater than 12 months duration, penile curvature of greater than 30°, and palpable plaque

The rationale for this is to exclude those who may regress spontaneously and where penile deformity is unlikely to be of clinical significance (penile curvatures up to 30° are within the normal range). This new indication is also more consistent with what has been approved in the USA and Europe.

The sponsor proposes that 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 disease. Although this is appropriate, it has the potential to limit patient access to treatment. It would be anticipated that the majority of doctors administering Xiaflex would be urologists who are experts in the management of male urological disease. However as Australia is a large country with a significant population living in outer metropolitan, rural or remote areas where there may be limited access to an urologist, the need for GPs or surgeons to do procedures such as this is sometimes required. In addition, many procedures in Australia (such as intra-articular injections, renal biopsies and liver biopsies) are now done with imaging guidance by interventionist radiologists.

Other changes suggested to the PI and Consumer Medicine Information (CMI) documents are in relation to making the information more reader friendly and minimising risks. The changes suggested to the RMP relate to the addition of extra groups at potential risk of adverse effects (that is, elderly, those who have subsequent surgical procedures and those who receive off label treatment with Xiaflex).

Clinical questions

Pharmacodynamics

Question 1

If the Xiaflex is administered locally and does not destroy the collagen beyond the plaque, how does the sponsor explain the bleeding and corporal rupture seen?

Question 2

Please provide more information to justify the doses used in the clinical studies. Would a smaller dose have similar efficacy but better safety?

Efficacy**Question 3**

Regarding the PDQ: Please provide a rationale for the cut off for ± 0.3 as the Pearson correlation co-efficient used for convergent and divergent validity

Question 4

Please provide subgroup analyses for penile curvature and Peyronie's bother score for the following subgroups:

- a. Age
- b. Duration of Peyronie's disease
- c. Baseline curvature
- d. Baseline erectile dysfunction
- e. Use of antidepressant medication
- f. Use of Phosphodiesterase-5 (PDE5) inhibitors

Question 5

Study AUX-CC-801: Please provide an analysis of the penile curvature in those treated with AA4500 comparing the groups with and without modelling.

Safety**Question 6**

Could the sponsor please comment on the role of ultrasound or computed tomography (CT) guided injections for administration of Xiaflex. Has this been performed in a clinical trial or is the sponsor aware of any centres in the USA doing this? Has the safety of this form of administration been compared to blind injections?

Question 7

Is there any information about how the use of collagenase impacts upon subsequent surgical outcomes?

Question 8

Please comment on the significance of the Doppler ultrasound findings in those who developed erectile dysfunction in Study AUX-CC-801. Could they be due to Xiaflex?

Question 9

Please explain the rationale for the 2 week period to abstain from sexual intercourse. Several cases of corporal rupture occurred at around 2 weeks. Should this be longer?

Question 10

Please provide the rationale for the packaging of 3 mL diluent and 0.90 mg of Xiaflex when only a fraction of this is used. There is the potential for dosing errors as 3 mL diluent is delivered in the pack (only 0.39 mL is required to make up the powder to the correct concentration for the Peyronie's disease indication). Of 0.39 mL inserted into the vial for reconstitution, only 0.25 mL is to be delivered to the patient. In addition the correct preparation relies upon the physicians having the appropriately small syringes and needles for the procedure. This issue was also raised by the TGA in the sponsor's previous submission for Dupuytren's disease. The sponsor argued that the chance of a dosing error is minimal as the full amount of reconstituted Xiaflex is not able to be extracted from the

vial. This was accepted at that time. However, the risk of local reactions is higher when Xiaflex is injected into the penis.

Has the sponsor considered other ways to minimise the risk of dosing errors. For example, is it possible for the package to contain the exact amount of powdered Xiaflex and diluent and/or small syringes to assist in the preparation? Could pharmacists prepare the Xiaflex for injection in syringes prior to dispensing it?

Question 11

Please explain the proposed mechanism to ensure only physicians trained in the use of Xiaflex are able to access it in Australia. Please outline the process of supply of this medicine through the pharmacist and/or distributor after the doctor writes a prescription.

Second round evaluation of clinical data submitted in response to questions

The details of the sponsor's responses to the *Clinical questions* and the evaluation of these responses are provided in Attachment 2 of this AusPAR.

Second round benefit-risk assessment

Second round assessment of benefits

The benefits of Xiaflex for the proposed indication are unchanged as a result of the second round evaluation.

The benefits of Xiaflex for the treatment of adult men with Peyronie's disease and disease duration of greater than 12 months with a curvature deformity of greater than 30 degrees are:

- Improvement in penile curvature of around 16° (30 to 38%), compared to around 10° (15 to 20%) in the placebo group.
- Improvement in Peyronie's bother scale by 2.4 to 3.3 points (scale 0 to 15) points compared to 1.6 to .0 in the placebo group.
- Improvement in erectile function and sexual function.

Unknown potential benefits:

1. *It is presumed but unknown if Xiaflex prevents the need for surgery for the treatment of Peyronie's disease.*

The evaluator is not convinced of the efficacy of the modelling procedure used with Xiaflex from Study AUX-CC-801. However, as subsequent studies used the modelling procedure and this is standard clinical practice, at this time it is reasonable to include this in the PI.

Second round assessment of risks

The sponsor has addressed a number of concern's the evaluator had around the safety of Xiaflex. There is limited data about the impact of Xiaflex on subsequent surgical procedures, however from the data available there does not appear to be any signals. The sponsor has carefully considered the packaging and reconstitution of Xiaflex.

The known risks of Xiaflex for the treatment of Peyronie's disease are as follows:

- High risk of local reaction; bruising, pain and oedema
- < 1% risk of corporal rupture

Potential risks include:

- Dosing and administration errors
- Injection into tissues adjacent to the Peyronie's plaque such as the urethra, blood vessels and corpus cavernosa
- Hypersensitivity
- Systemic exposure to collagenase
- Increase rate of adverse events in the elderly as they have looser connective tissue
- Off label use

In addition, there are a number of outstanding questions which have not been sufficiently addressed by the sponsor to date:

1. *What is the evidence that abstaining from sexual activity for 2 weeks is effective (or is needed) to mitigate the risk of corporal rupture? Are all forms of sexual activity potentially dangerous or is it only vigorous sexual intercourse or sexual activities in certain positions that are a potential risk?*
2. *Is there sufficient evidence to support a positive risk benefit ratio for the use in patients with duration of Peyronie's disease less than 12 months?*

Second round assessment of benefit-risk balance

The clinical trials submitted have adequately demonstrated the efficacy for Xiaflex for the treatment of penile curvature and symptoms associated with Peyronie's disease. Treatment is associated with acute local adverse effects which are generally mild and resolve with time. There is a small risk of corporal rupture. These risks are well described in the PI, CMI and physician training programme. In addition, the use of Xiaflex will be limited to physicians experienced in the treatment of male urological disease and have undergone the training program.

Thus, the risk-benefit balance for Xiaflex for the proposed indication used by adequately trained health professionals and given to patients who have been fully informed of the potential adverse effects is favourable.

The efficacy for patients with duration of disease less than 12 months is less well defined. The risk benefit ratio in this group of men is unknown as the disease may regress spontaneously in some of these men.

Second round recommendation regarding authorisation

The evaluator would recommend approval of Xiaflex for use in adult men with Peyronie's disease with a palpable plaque and a curvature deformity of at least 30 degrees at the start of therapy with the following conditions:

1. *That a statement in relation to the need to do training to use Xiaflex and how to access this is included in the PI.*
2. *That the results of Study AUX-CC-810 be submitted to the TGA when it is complete.*

3. *Changes are to be made to the summary of safety concerns including Use in the elderly; this was recommended by the clinical evaluator in the first evaluation report. The sponsor has not provided any information as to why this was not included.*
4. *That the RMP team are satisfied that the sponsor has sufficient pharmacovigilance activities for the risks identified in the summary of safety concerns.*
5. *That the changes proposed by this evaluator are made to the PI and CMI are made around protection against and treatment of inadvertent contact between collagenase and the skin or conjunctiva.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 10.0 (dated 9 May 2014, Data Lock Point 16 December 2013) and Australian Specific Annex (ASA) Version 4.0 (dated 28 January 2015)) which was reviewed by the RMP evaluator. A version update was submitted with the sponsor's response.

The EU-RMP considers both Dupuytren's and Peyronie's indications whereas the ASA considers the pharmacovigilance and risk minimisation plan for the Peyronie's indication only.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 6.

Table 6: Sponsor's summary of ongoing safety concerns

Important identified risks	<ul style="list-style-type: none"> • Corporal rupture or other serious injury to the penis • Local reactions • Medication error
Important potential risks	<ul style="list-style-type: none"> • Injection-site bleeding in patients with coagulation disorders, including those on concurrent anti-coagulation therapy • Reactions related to cross-reactivity with endogenous MMPs (including MSS and development/exacerbation of autoimmune disorders) • Severe systemic hypersensitivity/anaphylaxis
Important missing information	<ul style="list-style-type: none"> • Re-treatment with collagenase clostridium histolyticum • Long-term safety

MMPs= Matrix Metalloproteinases; MSS= musculoskeletal syndrome

Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns. Two clinical studies are proposed as additional pharmacovigilance.

Risk minimisation activities

Routine risk minimisation (that is, product labelling) is proposed for all safety concerns. An educational program and distribution plan is proposed however more detail is sought from the sponsor in the context of this evaluation.

Reconciliation of issues outlined in the RMP report

Table 7 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised and the evaluation of the sponsor's responses.

Table 7: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>Safety considerations may be raised by the nonclinical and clinical evaluators and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p><i>The sponsor provides the assurance that any safety concerns raised by the nonclinical, clinical and RMP evaluators will be addressed in this response. Safety considerations, where relevant, will also be addressed in the RMP and/or the Australian Specific Annex.</i></p>	<p>The sponsor's response is noted.</p>
<p>From a risk minimisation perspective it is noted that the proposed indication in Australia is less restrictive than the approved indications in the US and EU which also stipulate a curvature deformity of at least 30 degrees. This disparity could result in CCH treatment of Australian patients with less severe disease.</p>	<p><i>The sponsor acknowledges the recommendations of the evaluator and has amended the AU PI indication accordingly. The Indication proposed is now identical to that approved in the US and EU.</i></p>	<p>The sponsor's response is acceptable from an RMP perspective.</p> <p>PI changes, including indication changes, are subject to final approval by the Delegate.</p>
<p>The Dupuytren's summary of safety concerns includes identified risks 'immune-mediated reactions' and 'skin lesions' whereas the Peyronie's summary does not. The sponsor should</p>	<p><i>In Risk Management Plan (RMP) Version 10, immune mediated reactions and skin lesions are both included as important identified risks for Dupuytren's contracture. At the time that RMP Version 10 was</i></p>	<p>Inclusion of 'immune mediated reactions' and 'skin lesions' as important potential risks in the RMP is considered acceptable at this</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>include 'immune-mediated reactions' and 'skin lesions' as risks associated with the Peyronie's indication or justify these omissions.</p>	<p><i>written, the indication for Peyronie's disease had not been approved anywhere in the world. The section on Peyronie's disease was based on clinical trial experience. For immune-mediated reactions observed during clinical trials, there was a low frequency of events coding to the MedDRA terms associated with immune mediated reactions. For example, there was 1 case of hypersensitivity and 3 cases of erythema. Other immune mediated events such as lymph node pain, lymphadenitis, lymphadenopathy and lymphangitis, were only reported in 4 subjects in the Peyronie's clinical program. These events were mild or moderate in severity and not serious. For skin reactions there was a similarly low frequency of events in the Peyronie's clinical program. For example, penile ulceration was reported for 6 subjects, skin laceration was reported for 6 subjects, wound was reported for 2 subjects, and skin lesion (involving the penis) was reported for only 1 subject. None of these adverse events was severe or serious. Because non-serious, generally mild or moderate intensity immune-mediated reactions and skin lesions had only been observed in a small number of subjects in the clinical trials of subjects with Peyronie's disease, it was determined that this was an important potential risk, that is, there was inadequate evidence to conclude that an association had been established between the events and the drug for this indication. Therefore, both risks are listed as such in RMP Version 10.</i></p> <p><i>RMP Version 11 was written after the indication for Peyronie's disease was approved</i></p>	<p>time.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>in the United States for 14 months and in the EU for approximately 1 month. A total of 8 cases of immune mediated reactions were received from the date of initial approval of Xiaflex for Peyronie's disease through the end of the Periodic Safety Update Report (PSUR) 7 interval (27 February 2015). Four (4) reports were erythema and the other 4 reports were hypersensitivity. All reports were considered non-serious. During the same time period, a total of 4 cases of skin lesions were the subject of post-marketing reports in patients treated for Peyronie's disease. Two (2) cases were lacerations, 1 was a wound and 1 was skin necrosis. Three (3) cases were non-serious and 1 case was serious (skin necrosis).</i></p>	
(continued from previous)	<p><i>The post marketing profile is similar to that of the clinical trial program with infrequent reports of cases of potential immune-mediated reactions and skin lesions that were generally non-serious.</i></p> <p><i>In summary, because of the low number of reports received and the generally mild to moderate and non-serious nature of the majority of the reports, the marketing authorisation holder (MAH) concludes that these reactions are not identified risks at this time as the suspicion to conclude that an association with the drug exists for this indication has not been confirmed. However, the MAH considers both the risk of immune mediated reactions and skin lesions to be important potential risks. The MAH continues to monitor reports of both types of events closely and will re-assess this determination at the time of the next PSUR.</i></p> <p><i>EU RMP Version 11 is provided</i></p>	(see above)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<i>in updated Module 1.8.1. Pharmacovigilance Systems.</i>	
<p>Off-label use should be added as an important potential risk for both Dupuytren's and Peyronie's indications.</p>	<p><i>In both Risk Management Plan (RMP) Version 10 and Version 11, off-label use is an important potential risk for Peyronie's disease in 2 circumstances: use to treat a ventral deformity of the penis and use to treat an isolated hourglass deformity of the penis. In both circumstances, use of Xiaflex could result in injury to the urethra because of the location of the plaque, and, thus, lead to permanent damage.</i></p> <p><i>However, off-label use in Dupuytren's contracture was not considered to be an important potential risk in either Version 10 or Version 11 of the RMP. During the clinical trial program for Dupuytren's contracture, the only restriction for the treatment of Dupuytren's was in the thumb. This restriction was not for safety reasons but because of the difficulty in assessing efficacy in a joint that moves in multiple planes. The prescribing information in the United States and EU does not prohibit use in the thumb and thus, this is not an off-label use.</i></p> <p><i>A search was performed of the global safety database to determine if any off-label use has occurred with Xiaflex for Dupuytren's contracture. No cases have been received representing off-label use for Dupuytren's contracture. Based on this information, the MAH believes there is no basis to include off-label use as an important potential risk for the indication of Dupuytren's contracture as no such circumstance has been identified or reported.</i></p> <p><i>EU RMP Version 11 is provided</i></p>	<p>Off-label use is considered a risk for Xiaflex in general, irrespective of indication.</p> <p>However, taking into account the risk minimisation measures in place for the Dupuytren's indication and proposed for the Peyronie's indication the sponsor's response to this recommendation is acceptable at this time.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<i>in updated Module 1.8.1. Pharmacovigilance Systems.</i>	
<p>According to milestones stated in the pharmacovigilance plan, Study AUX-CC-806 has been completed. The sponsor should provide an update to the TGA regarding the anticipated date of the release of the study report and important safety findings, if available. The status of this study should be reflected in an amendment to the pharmacovigilance plan.</p>	<p><i>Study AUX-CC-806 has been completed and a copy of the full CSR is provided.</i></p> <p><i>The efficacy results of this study demonstrate the therapeutic effectiveness of Xiaflex in the treatment of Peyronie's disease, as shown by statistically significant improvement from baseline in curvature deformity and Peyronie's disease bother score. Improvement in male Peyronie's disease symptoms also showed positive benefit for their female sexual partners.</i></p> <p><i>The safety results of this study indicate that the majority of TEAEs were transient, non-serious, mild or moderate in intensity, and related to the local administration of AA4500. There were no investigator-reported corporal ruptures among the men treated with AA4500 in this study. No clinically meaningful effects on laboratory, vital sign or immunogenicity parameters were observed. There were no reports of local or systemic hypersensitivity reactions related to study drug. The results of this study support the efficacy and safety findings from the placebo-controlled double-blind studies (AUX-CC-803 and AUX-CC-804).</i></p> <p><i>The Pharmacovigilance plan has been amended, as has the ASA, these documents are provided. Pharmacovigilance Systems and updated Module 1.8.2 Risk Management Plan for Australia.</i></p>	<p>This is acceptable.</p>
<p>Protocols of ongoing studies are not reviewed for the purposes of RMP evaluation. Results of ongoing studies should be reported to the</p>	<p><i>The sponsor confirms that results of ongoing studies will be reported to the TGA in an appropriate manner. This will include reporting in PSURs or</i></p>	<p>This is acceptable from an RMP perspective.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
TGA in an appropriate manner. This may include reporting in PSURs or in a safety related application to amend the registration details as appropriate.	<i>safety related application to amend the registration details as appropriate.</i>	
Given overseas approval status, the sponsor should provide an update of post-marketing adverse event reports, especially involving serious injury to the penis.	<p><i>The sponsor has provided the requested update.</i></p> <p><i>For the period 28 February 2015 to 31 July 2015 there were 7 events of corporal rupture with an estimated reporting rate of 2.42 events per 1000 patients. The previous PSUR estimated reporting rate was 3.37 events of corporal rupture per 1000 patients.</i></p> <p><i>In addition there were 36 reported events considered to be serious injury to the penis. 36 serious events were penis injury (2), fracture of penis (7), penile haemorrhage (1), penile haematoma (13), injection site haematoma (3), penile contusion (5), ecchymosis (1), injection site haemorrhage (2), and erectile dysfunction (2).</i></p>	<p>It would appear that reporting rates for the identified risks have been generally stable. There has been no increase in the reporting rate of corporal rupture.</p> <p>As an identified risk this adverse event will continue to be monitored by the sponsor and reported in PSURs.</p>
The sponsor should provide an update of medication error reports in the post-marketing period.	<p><i>During the 5 month period described above a total of 26 medication errors were reported in 22 patients. The events are categorised as follows: inadequate aseptic technique (1); wrong technique in drug usage process (9), prescribed underdose (1); inappropriate schedule of drug administration (7), dose omission (4), drug administration error (2), incorrect dose administration (1), underdose (1). In proportion to the increase in sales during this period, there is no meaningful change in the reporting of medication errors.</i></p>	The incidence of medication errors and the clinical implications of such errors highlight the need for mandatory education and controlled distribution.
The sponsor has provided a copy of the Peyronie's Disease educational program	<i>The Australian education and training materials specific for Peyronie's Disease will generally</i>	The evaluator has no objection to the draft materials provided.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>associated with the US REMS. Whilst the evaluator has no specific objection to these materials, no comment can be made regarding the acceptability of the proposed risk minimisation activities until the Australian educational materials are submitted. The Australian educational materials should be submitted to the TGA preferably before approval. Educational materials for the Dupuytren's indication included hard copy, online and audio-visual material and it is expected that similar materials will be implemented for the Peyronie's indication.</p>	<p><i>follow the format and content of the proposed EU and FDA approved educational materials.</i></p> <p><u><i>Educational Programme and Training Details</i></u></p> <p><i>The sponsor's training programme is designed to comprehensively educate and train all appropriate users of the product. The Educational resources consist of:</i></p> <ol style="list-style-type: none"> <i>1. Physician's Guide</i> <i>2. Audio-visual material</i> <p><i>Training will be delivered in one of two ways:</i></p> <ol style="list-style-type: none"> <i>1. Internet-based</i> <i>2. Peer-to-peer meetings</i> <p><i>Training will be linked to a Prescriber Certification Program described in Clinical Study Report Question 11.</i></p> <p><i>Comprehensive details of each element of the education and training program and certification material are under construction and will be provided as appendices to the amended ASA.</i></p>	<p>The final versions of the materials should be submitted to the TGA when available.</p>
<p>As for the Dupuytren's contracture indication the sponsor should confirm that prescriber certification related to the educational program will be implemented. Details of the certification process should be included in the ASA.</p>	<p><i>The running of the Peyronie's disease training program will closely follow the model already implemented in Australia for Dupuytren's contracture but will be modified so as to be specific for Peyronie's disease. It will be designed to comprehensively educate and train all appropriate users of the product.</i></p> <p><i>The sponsor confirms that the Prescriber Certification Program will be related to the education and training program specific for Peyronie's Disease. Prescribers will be Certified after they have undertaken either a peer-to-peer training session or satisfactorily completed the Web-based</i></p>	<p>This is acceptable from an RMP perspective.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>training program.</i></p> <p><i>Details of the certification process are included in the amended ASA Module 1.8.2 Risk Management Plan for Australia.</i></p>	
<p>The sponsor should confirm that the Peyronie's Disease indication in Australia will be subject to a controlled distribution system as for the Dupuytren's indication. This would be consistent with the current use of CCH in Australia as well as the Risk Evaluation and Mitigation Strategies (REMS) in the US. Details of the controlled distribution system should be included in the ASA.</p>	<p><i>Actelion confirms that the Peyronie's Disease indication in Australia will be subject to a controlled distribution system as for the same set up for the Dupuytren's indication.</i></p> <p><i>Details of the controlled distribution system are included in the amended ASA, Module 1.8.2 Risk Management Plan for Australia.</i></p>	<p>This is acceptable from an RMP perspective.</p>
<p>A condition of registration was imposed on approval of the Dupuytren's indication in Australia that the sponsor was required to regularly report to the TGA about the success of the controlled distribution system. It is recommended that a similar requirement be imposed by the Delegate for this indication.</p>	<p><i>Actelion confirms that in addition to the PSUR, a regular report pertaining to the success of the controlled distribution system will be forwarded to the TGA.</i></p>	<p>This is acceptable from an RMP perspective.</p>
<p>In the Dosage and Administration section of the PI it states that '<i>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 disease</i>'. The sponsor should provide information in the ASA as to how this will be ensured as part of the controlled distribution system.</p>	<p><i>The education and training will be linked to a Prescriber Certification Program. Prescribers will be Certified after they have undertaken either a peer-to-peer training session or satisfactorily completed the Web-based training program.</i></p> <p><i>A controlled distribution system will ensure that only Certified Prescribers will be able to receive product from Actelion's authorised Distributor. The pharmacy ordering process will be tailored to ensure that specific personal information on the prescriber is supplied by the ordering pharmacy at the time</i></p>	<p>This is similar to what is in place for the Dupuytren's contracture indication and is acceptable from an RMP perspective.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	<p><i>product is ordered from the Distributor.</i></p> <p><i>Every order received by the Distributor will be checked against the Certified Prescriber List database prior to shipping product to pharmacy. Product will only be shipped to prescribers whose name appears on the Certified Prescriber List.</i></p> <p><i>Where the prescriber's name is not on the Certified Prescriber List, the Distributor will withhold shipment of product and notify the pharmacy that the prescriber needs to undertake Actelion's education and training program to enable Certification and subsequent receipt of product.</i></p> <p><i>Details of the certification process are included in the amended ASA, Module 1.8.2 Risk Management Plan for Australia.</i></p>	
<p>The sponsor should provide details as to which groups of medical practitioners will be able to access the Peyronie's training.</p>	<p><i>Certification will be restricted to urologists and sexual health physicians.</i></p>	<p>This is acceptable from an RMP perspective.</p>
<p>The Australian PI should contain the following clinically relevant statement which appears in the EU Summary of Product Characteristics (SmPC):</p> <p><i>Patients with penile curvature >90° were not included in the clinical studies. Treatment in this group can therefore not be recommended.</i></p>	<p><i>The sponsor acknowledges the recommendations of the evaluator and has amended the AU PI accordingly.</i></p> <p><i>The new text will appear in the Clinical trials section of the AU PI. The AU PI has been amended so that the clinical trial section contains this additional statement</i></p> <p><i>Patients with penile curvature >90° were not included in the clinical studies. Treatment in this group can therefore not be recommended</i></p> <p><i>The amended AU PI was provided.</i></p>	<p>This is acceptable from an RMP perspective.</p> <p>PI amendments are subject to final approval by the Delegate.</p>
<p>It is noted that the EU SmPC</p>	<p><i>Each pack of Xiaflex will contain</i></p>	<p>The sponsor's</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>contains a detailed description of the penile modelling procedure however the proposed PI does not. The Delegate should consider inclusion of this information in the PI if appropriate.</p>	<p><i>two inserts: one for the treating physician and one (CMI) for the patient.</i></p> <p><i>The physician's insert will contain the PI and an integrated "Physician's Guide". The Physician's Guide will contain detailed information regarding the preparation and reconstitution of Xiaflex, administration of the injection as well as information on the penile modelling procedure.</i></p> <p><i>The CMI insert will contain detailed information on the penile modelling procedure as well as other text normally required in the CMI.</i></p> <p><i>The Physician leaflet was provided.</i></p>	<p>approach is acceptable from an RMP perspective.</p>
<p>The EU SmPC contains the following clinically relevant precaution which should be included in the Australian PI:</p> <p><u><i>Special penile conditions/diseases not studied in clinical trials</i></u></p> <p><i>Xiapex 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.</i></p>	<p><i>The sponsor acknowledges the recommendations of the evaluator and has amended the AU PI accordingly.</i></p> <p><i>The new text will appear in the Precautions section of the AU PI:</i></p> <p><i>Special penile conditions/diseases not studied in clinical trials</i></p> <p><i>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.</i></p> <p><i>The amended AU PI was provided.</i></p>	<p>This is acceptable from an RMP perspective.</p> <p>PI amendments are subject to final approval by the Delegate.</p>

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
<p>In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised as appropriate to reflect changes made to the PI resulting from the evaluation process.</p>	<p><i>The draft consumer medicine information document has been revised as appropriate to reflect changes made to the PI and to include recommendations made by the Clinical and RMP evaluators.</i></p> <p><i>The Physician leaflet was provided.</i></p>	<p>This is acceptable from an RMP perspective.</p> <p>CMI amendments are subject to final approval by the Delegate.</p>
<p>The ASA should be revised to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context. This table should include a comparison of the actual content and wording of the EU SmPC and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences, particularly where it appears the EU SmPC is more restrictive. ASA guidance can be found on the TGA website.</p>	<p><i>The ASA has been amended to include the activities table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context. The table includes a comparison of the actual content and wording of the EU SmPC and the proposed Australian PI and CMI for all of the specified ongoing safety concerns, and missing information and also includes a rationale and justification for any observed differences.</i></p> <p><i>The EU RMP version 11 and the amended ASA were provided.</i></p>	<p>This is acceptable from an RMP perspective.</p>

Summary of recommendations

It is considered that the sponsor's response to the TGA's request for further information has adequately addressed the issues identified in the RMP evaluation report

Additional recommendations are summarised below.

Outstanding issues

Issues in relation to the RMP

The clinical evaluator has recommended that 'Use in the elderly' be added as an item of missing information to the RMP and/or the ASA. The sponsor should add this item of missing information to the RMP and/or the ASA prior to finalisation unless a compelling justification can be provided for its omission. It is considered that routine risk minimisation and pharmacovigilance would be acceptable for this additional item of missing information.

The evaluator has no objection to the draft educational materials. Once finalised, these should be provided to the TGA.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Key changes to the updated RMP

EU-RMP version 10.0 (dated 9 May 2014, DLP 16 December 2013) and Australian Specific Annex version 4.0 (dated 28 January 2015) has been superseded by EU-RMP version 11.0 (dated 29 April 2015, DLP 27 February 2015) and Australian Specific Annex version 5.0 (dated 8 September 2015) and the key changes are summarised below in Table 8.

Table 8: Summary of key changes to the EU-RMP

Summary of key changes noted between EU RMP v10/ASA v4 and EU RMP v11/ASA v5	
Safety specification	New potential risks: 'Immune mediated reactions', 'Skin Lesions', 'Injury of the Urethra', 'Off label use in patients with ventral curvature deformity', 'Off label use in patients with isolated hourglass deformity'.
Pharmacovigilance activities	Pharmacovigilance plan for new potential risks added (NB these safety concerns appear to have been incorporated into existing pharmacovigilance activities – a targeted questionnaire is also proposed for 'Immune mediated reactions').
Risk minimisation activities	Risk minimisation activities are now proposed for the new potential risks A non-interventional post-authorisation safety study (Sobi-Xiapex-PASS01) is now proposed to evaluate the effectiveness of the implemented additional risk minimisation measures in the EU.
ASA	Amended as recommended in RMP evaluation report: More detail regarding educational program and controlled distribution has been added A table comparing risk minimisation activities in the EU and Australia has been added

Suggested conditions of registration*RMP*

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

No wording can be provided this time until the outstanding issue regarding the recommended additional item of missing information is addressed.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new quality data were submitted. The sponsor has not proposed any changes to the formulation of Xiaflex. When reconstituted, Xiaflex is a clear colourless solution of pH 7.5 to 8.5.

Nonclinical

The nonclinical evaluator had no objections to approval of the extension of indications but did note there were safety concerns arising from some of the animal studies. The in vitro pharmacology studies showed similar collagen lysis (Type I and II) in Peyronie's plaque tissue and Dupuytren's cord tissue, although there was some lysis of Type IV collagen in blood vessel walls at higher concentrations after prolonged exposure. Systematic exposure was not generally quantifiable in dogs receiving repeated intrapenile dosing of $\leq 6 \mu\text{g}/\text{kg}$ (3 cycles of 3 injections q48h, relative exposure 0.5 based on $\mu\text{g}/\text{kg}$) into the tunica albuginea. Repeated dosing was associated with local swelling, bruising and discolouration and some reactions were severe. CCH administered to other penile tissues resulted in more severe local reactions (corpus cavernosa/urethra > vein-artery nerve > tunica albuginea). While most of the reactions showed evidence of reversibility some animals experienced severe local toxicity requiring euthanasia, particularly after injection into the main vein, artery and nerve complex. The severity of the reaction did not show a clear dose-response relationship.

Clinical

The clinical evaluator has recommended approval for CCH for the following indication:

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.

The evaluator has accepted the sponsor's proposed dose and dosage regimen.

Pharmacology

The pharmacology study conducted in 20 adult patients with two 0.58 mg doses (a single treatment cycle) of CCH noted the following findings:

- AUX I and AUX II levels were low and detected only up to 30 minutes after injection.
- Peak plasma concentration (C_{max}) and exposure area under the plasma concentration versus time curve from time 0 to the last time point ($\text{AUC}_0 - \text{last}$) were not statistically different on Day 1 and Day 2 suggesting no accumulation.
- Modelling of the plaque (Day 3) did not result in quantifiable levels of AUX I or AUX II.
- No formal elimination studies have been performed because of the short-lived nature of the systemic exposure.

Efficacy

Study AUX-CC-803 was a Phase III, multicentre, double-blind, randomised, placebo controlled study of the safety and efficacy of CCH compared to placebo in 418 adult men with Peyronie's disease for at least 12 months, a curvature deformity of at least 30 degrees and in a stable relationship with a female partner with whom they were willing to have vaginal intercourse, conducted in the US and Australia. Exclusion criteria were numerous but included curvature deformity of < 30 degrees or > 90 degrees, ventral curvature, previous surgery or extracorporeal shock wave therapy, plaque at the base of the penis,

significant erectile dysfunction that failed to respond to oral phosphodiesterase inhibitors, chordee in the presence of hypospadias, thrombosis of the dorsal vein or artery of the penis, neoplastic infiltration of the area, infection including sexually transmitted diseases (STDs), Hepatitis B or C or HIV, and concomitant use of tetracyclines within 5 days of the study drug. The patients were predominantly White (95.2%) with a median age of 59 years (range 28 to 81 years), 11.5% current smokers (35.3% previous smokers), with a median duration of Peyronie's disease of 2.9 years (1 to 50.8 years). Approximately 49% had erectile dysfunction. Most subjects had penile shortening of 1.5 to 5 cm, moderate curvature deformity (52%), no pain in the erect penis (66.4%), no change in penile shape (50.8%), moderate distress in Peyronie's disease (52%) and no history of trauma to the penis (76%). At screening, most subjects had no calcification of their penis (70.3%). The baseline characteristics were similar between the two groups. Common and significant medical histories among the subjects included hypertension (36.7%), hypercholesterolaemia (23.3%), benign prostatic hypertrophy (21.6%), gastroesophageal reflux disease (19.9%), depression (15.8%), hyperlipidaemia (15.1%), anxiety (10.6%), type 2 diabetes (7.7%), hypogonadism 8.2% and hypothyroidism 4.8%. The majority of patients (54.2% and 59.3%) were taking Peyronie's disease medication, most commonly tocopherol (Vitamin E) and verapamil, and for 33.1% were taking medication for erectile dysfunction (sildenafil, tadalafil or vardenafil).

Overall 87% of the CCH arm and 89% of the placebo arm completed all 4 treatment cycles in the study. Premature discontinuations occurred in 12.5% across the study with slightly more in the CCH group (13.0% versus 11.4%), most commonly due to withdrawal of consent (7.2% and 4.3%), loss to follow-up (2.2% and 3.6%) and adverse event (1.4% and 0.7%). The study had 95% power to detect a change in curvature deformity of 19% (SD 30%) and change in Bother score (see ⁴) of 2.2 (SD 4.5).

The study compared 0.58 mg CCH (n=277) injected into the penile plaque at the point of maximum curvature. Two injections were administered 24 to 72 hours apart (one cycle) and two further injections given 42 ± 5 days for up to 4 cycles. After the second injection of each cycle the investigator modelled the plaque with the aim of stretching/elongation of the plaque. The patient repeated the modelling procedure each day of the following six weeks. The placebo (n=140) was a solution of 10 mM tris(hydroxymethyl)aminomethane and 60 mM sucrose reconstituted with the same diluent used for CCH (0.03% calcium chloride dehydrate in 0.9% sodium chloride).

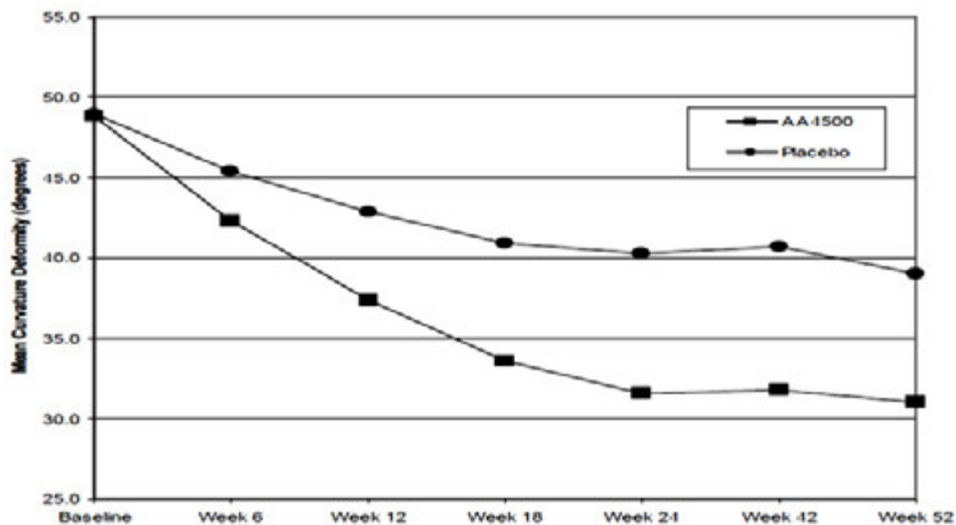
The co-primary efficacy outcomes at 52 weeks were:

- a. Percentage change in curvature deformity from baseline:
 - CCH: 17 degrees improvement or 37.6% (SD 30.29%)
 - Placebo: 10 degrees improvement or 21.3%

In Figure 1, below, depicting the changes in curvature deformity over time, CCH is labelled AA4500.

⁴ Peyronie's Disease Global Assessment: A responder was defined in a subject who had recorded that his Peyronie's disease had improved in a small but important way (score=1), moderately improved (score=2), or much improved (score=3). An improvement of ≥ 1 is considered clinically meaningful.

Figure 1: Study AUX-CC-803: mean penis curvature deformity over time (mITT population). Note Week 52 value is last observation carried forward (LOCF).



b. Change in Peyronie's Bother Score of the Peyronie's Disease Questionnaire (PDQ) from baseline:

- CCH: -3.3 (SD 3.83)
- Placebo: -2.0 (SD 3.53)
- Difference $p=0.045$

The differences of both primary endpoints were greater in patients with lesser curvature at baseline.

The secondary endpoint of the incidence of responders based on the overall global assessment of Peyronie's disease was significantly different for CCH (66.2% versus 29.1%, $p<0.001$).

The remaining secondary endpoints although favourable for CCH did not reach statistical significance when adjusted for multiple comparisons. These endpoints were:

- Change in Peyronie's disease physical and psychological symptom score (-3.2 versus -1.6)
- Change from baseline in IIEF overall satisfaction (1 (SD 2.55) versus 0.5 (SD 2.42)),
- Composite response [change in curvature deformity of $>20\%$, change in Peyronie's bother score of >1 , change in reporting of 'no' to some sexual activity] 50.6% versus 25.4%,
- Change in penile plaque consistency (hard plaques at baseline were the most likely to develop more softness),
- Change in penile length (unchanged)
- Change in penile pain score at 52 weeks (-5.1 (SD5.16) versus -4.0 (SD 4.09))

There were no significant differences between the treatment groups for erectile function, orgasmic function, sexual desire or intercourse satisfaction.

More patients reported spontaneous penile events of penile popping (plaque stretching), improved penile rigidity, penile lengthening and improved penile sensation in the CCH group (15.6%) than in the placebo group (3.8%).

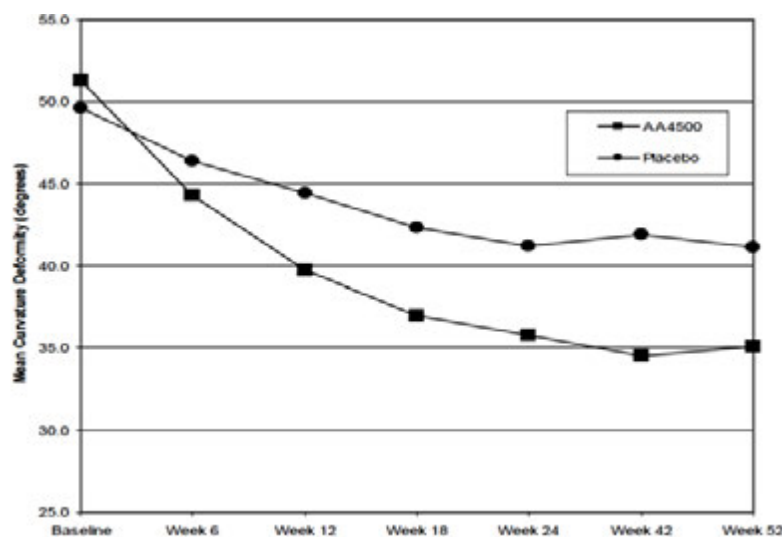
Study AUX-CC-804 had the same study design, treatment protocol and inclusion and exclusion criteria as Study AUX-CC-803. It was a Phase III, multicentre, double-blind study randomised, placebo controlled study in 418 adult men with Peyronie's disease to investigating the safety and efficacy of CCH (n=277) compared to placebo (141). The majority (97.3%) of subjects were White; the median age was 58 years (age 23 to 84). Approximately 11.6% were current smokers, 37.1% previously smoked. Common or significant co-morbidities included hypertension (35.9%), hypercholesterolaemia (25.3%), gastro-oesophageal reflux disease (20.2%), benign prostatic hypertrophy (20.2%), depression (12.8%), anxiety (5.8%), type 2 diabetes (6.7%), hypogonadism (6.5%), and hypothyroidism (4.3%). The majority (56.6% and 59.6%) had taken Peyronie's medication prior to the study, most commonly tocopherol and verapamil. The two groups had similar Peyronie's disease histories, although the Xiaflex group had a longer mean duration of illness than the placebo group (4.24 versus 3.42 years). Approximately 51% had erectile dysfunction. Most subjects had penile shortening of 1.75 to 5 cm moderate curvature deformity (62.1%), no pain in the erect penis (64.1%), no change in penile shape (41.9%), moderate distress in Peyronie's disease (47%). The study was completed by 86.1% of the CCH group and 90.1% of the placebo group, with most of the premature discontinuations due to withdrawal of consent (6.5%). Seventy subjects (45 CCH and 25 placebo) were excluded from the primary efficacy population because they were not sexually active at baseline (required for the PDQ score).

The co-primary efficacy outcomes at 52 weeks were:

- a. Percentage change in curvature deformity from baseline:
 - CCH: 16 degrees or -30.5% (SD 27.7%)
 - Placebo: 8.5 degrees or -15.2% (SD 28.66%)
 - Difference p=0.0059

The time course of the changes in curvature in the CCH (labelled AA4500 in the graph) and placebo groups are depicted in Figure 2, below.

Figure 2: Study AUX-CC-804 Mean curvature deformity over time



- b. Change in Peyronie's Bother Score of the PDQ from baseline
 - CCH -2.4 (SD 3.62)
 - Placebo -1.6 (SD 3.52)
 - Difference p=0.0496

The differences of both primary endpoints were similar regardless of the initial penile curvature.

The secondary endpoint of incidence of responders based on the overall global assessment of Peyronie's disease was significantly different for Xiaflex (55.4% versus 29.9%, $p < 0.0001$).

The remaining secondary endpoints were not statistically significant after adjustment for multiple comparisons.

- Change in Peyronie's disease physical and psychological symptom score change from baseline in IIEF overall satisfaction [-2.6 (SD 4.83) versus -1.0 (SD 4.78)]
- Composite response [change in curvature deformity of >20%, change in Peyronie's bother score of >1, change in reporting of 'no' to some sexual activity] had more responders in the CCH group (42.3% versus 30.6%)
- Change in penile plaque consistency (hard plaques and those described as firm throughout at baseline were the most likely to develop more softness),
- Change in penile length (0.5 cm increase with CCH and 0.2 cm with placebo)
- Change in intercourse satisfaction (1.1 versus -0.1 in a scale of 15)

There were no significant differences between the treatment groups for penile pain, erectile pain, orgasmic function or sexual desire.

More CCH patients reported spontaneous penile events (15.3% versus 5.6%).

Meta- analysis of AUX-CC-803 and AUC-CC-804 showed:

- A mean (SD) % change from baseline in curvature deformity of -34.0% compared to placebo -18.2%, $p < 0.0001$. The improvement was significantly different from placebo starting at Week 24 and continuing to Week 52.
- A mean improvement in PDQ Peyronie's Disease Bother score with a change from baseline of -2.5 in the CCH group and -1.8 in the placebo group, $p = 0.0037$ for the difference
- A statistically significant greater improvement in the CCH group (60.8%) compared to the placebo group (29.5%) for the overall global response to Peyronie's disease.
- A statistically significant greater improvement in the Peyronie's disease physical and psychological symptom score (range 0-24) of -2.9 in the CCH group and -1.3 in the placebo group.
- A statistically significant greater improvement in the IIEF (range 0-10) score of 1.0 in the CCH group and 0.4 in the placebo group.
- Analysis of co-primary endpoints for intrinsic and extrinsic factors:
 - There was a trend to greater improvement in curvature deformity as the duration of Peyronie's disease increased
 - Younger men (< 45 years) had a greater improvement in curvature deformity and bother scale than older men

Study AUX-CC-801 was a Phase IIb, double blind, multicentre, randomised, placebo controlled study of the safety and efficacy of Xiaflex administered to 147 patients with Peyronie's disease with (n=74) and without (n=73) modelling, for up to three treatment cycles in subjects. Randomisation occurred in a 3:1 ratio for CCH to placebo and 1:1 for modelling or no modelling. The same inclusion and exclusion as studies AUX-CC-803 and AUC-CC-804 were applied. The CCH dose was 0.58 mg in a volume of 0.25 mL delivered

into the penile plaque. The diluent used for both treatment groups was 0.9% saline with 2 mM calcium chloride (CaCl₂). Each treatment cycle consisted of 2 injections separated by 24 to 72 hours, followed by modelling. Each cycle was repeated every 6 weeks for a maximum of 3 cycles after which subjects were followed up at weeks 18, 24 and 36. Most of the subjects were White (95.2%). The median age of subjects was 58 years. The duration of Peyronie's disease was longer in the treatment group (2.9 years) than the placebo group (2.1 years). Erectile dysfunction was reported in 44.2% of subjects, penile pain in around 50 to 57%. Most subjects had no calcifications (54%) or non-contiguous stippling of the penis (44.9%). There were no clinically significant abnormalities on Doppler ultrasound. Drugs used to treat erectile dysfunction were taken by 17.7%. The study had 99% power to detect a 35% (SD 25%) change in penile curvature with modelling and a 94% power to detect a 25% (SD 20%) change without modelling.

The primary efficacy outcome at 36 weeks:

- With modelling
 - CCH: 32.4% (SD 30.71%) curvature reduction
 - Placebo: 2.5% (SD 27.56%) curvature worsening, p<0.001
- Without modelling
 - CCH: 27.1% (SD 23.14%) curvature reduction
 - Placebo: 27.9% (SD 26.7%) curvature reduction, p=0.618

Table 9: Study AUX-CC-801: Mean change and mean % change from baseline in penile curvature at Week 36 with and without modelling (mITT), CCH (AA4500) versus placebo

	With Modeling (N=74)		p-value ³	Without Modeling (N=71)		p-value ³
	AA4500 (N=54)	Placebo (N=20)		AA4500 (N=55)	Placebo (N=16)	
Screening (baseline) value						
Mean (SD)	54.7 (15.18)	51.9 (15.88)		54.1 (15.08)	48.9 (14.31)	
Min. Max	33, 89	30, 90		30, 90	30, 80	
Week 36 value (LOCF)						
Mean (SD)	37.2 (18.49)	52.5 (17.78)		39.1 (15.70)	35.9 (16.52)	
Min. Max	5, 85	20, 85		10, 80	5, 60	
Change from baseline						
Mean (SD)	-17.5 (15.28)	0.6 (13.16)	<0.001	-15.0 (14.04)	-13.0 (10.66)	0.618
Min. Max	-60, 40	-20, 40		-50, 7	-30, 0	
Modeling (drug) p-value ^b			0.349			
Overall p-values ^c						
Drug			<0.001			
MDL			0.044			
Drug*MDL			0.004			
% Change from baseline						
Mean (SD)	-32.4 (30.71)	2.5 (27.56)	<0.001	-27.1 (23.14)	-27.9 (26.70)	0.913
Min. Max	-92, 100	-33, 89		-75, 19	-86, 0	
Modeling (drug) p-value ^b			0.306			
Overall p-values ^c						
Drug			0.001			
MDL			0.018			
Drug*MDL			<0.001			

Data source: Table 14.2.2.1

MDL=modeling

^a Drug effect p-value with/without modeling, calculated from factorial ANOVA analysis.

^b Modeling effect p-value with drug, which was calculated from factorial ANOVA analysis.

^c Drug p-value - overall drug effect with/without modeling, MDL p-value - overall modeling effect with/without drug, and Drug*MDL p-value - drug-by-modeling interaction from using ANOVA with factors for drug, modeling and drug-by-modeling interaction.

Overall, there was a 29.7% improvement in penile curvature in the CCH group compared to an 11.0% improvement in the placebo group (p=0.001) but the improvements were only significant in those who received modelling.

Other outcomes:

- PDQ (intercourse discomfort, intercourse constraint, penile pain and Peyronie's Bother Score) showed borderline statistical significance for the Peyronie's Bother Score when comparing CCH and placebo (mean change from baseline (SD) -2.6 (4.63) and -0.8 (3.63), for the CCH and placebo groups, respectively, $p=0.046$) and the result was driven by the modelling group.
- IIEF scores in all domains were not statistically different between CCH and placebo.
- Peyronie's Disease Global Assessment: Response in the CCH groups (56.3%) was greater than placebo groups (29.4%).
- The small mean increases in penile length (0.7 cm SD 1.25 versus 0.5 cm SD 1.24), and decreased plaque area (92.3 (SD 179) versus 102.5 (SD 197.05)) in the CCH compared with the placebo groups, respectively, are reduction of uncertain statistical or clinical significance.
- There was a poor correlation between penile curvature and items of the PDQ.
- Spontaneous penile events were reported for 16 patients in the CCH group, 11 from the modelling group.

Study AUC-CC-802 was a Phase III, multi-centre, multinational, open label study of the safety and efficacy of CCH, with the same treatment regimen as studies AUX-CC-803 and AUX-CC-804 in 348 adult men with a ≥ 12 month history of Peyronie's disease and a curvature deformity of at least 30 degrees (not in a ventral plane), conducted over 36 weeks. Some 96% of patients were White with a median age of 57 years (range 33 to 77) and 51.9% had never smoked. The median duration of Peyronie's disease was 2 years (range 0.6 to 29.4 years). Most patients had < 2.5 cm of penile shortening, moderate-severe plaque, no pain in the erect penis, moderate to severe distress as a result of the Peyronie's disease. Approximately 21% were taking medications for erectile dysfunction. Approximately 88% completed the study with premature discontinuations mostly due to withdrawn consent (5.4%) or loss to follow up (2.9%).

The primary outcomes at Week 36 were:

- Change in penile curvature from baseline: baseline mean of 53° to a value at Week 36 of around 34.7° (-34.4%, $p<0.05$).
- Change in bother score: mean change from baseline -3.3 (max score 16), 95% CI: -2.8 to -3.7.

Other outcomes:

- An improvement in overall global assessment of Peyronie's disease by at least 1 point in 72.3%.
- An improvement in Peyronie's disease physical and psychological symptoms of 4.2 (max score of 24) points, 95% CI 3.6 to 4.9.
- An improvement in IIEF satisfaction of 1.1 points (max score 10), 95% CI: 0.8 to 1.4.
- Softening of penile plaques in most penile plaques that were graded as hard, or firm at baseline.
- Increase in flaccid penile length of 0.4 cm (95% CI: 0.2 to 0.5).
- An improvement in Peyronie's disease pain score.
- A mean improvement in erectile function, orgasmic function, sexual desire, intercourse satisfaction and sexual activity.

Safety

A total of 979 patients received at least one treatment cycle of CCH. Treatment emergent adverse events in studies AUX-CC 803/AUX-CC-804/AUX-CC-801/AUX-CC-802 occurred in 92.4%/92%/90.1%/91.6% of patients. The most common events in Study AUX-CC 803 (CCH versus placebo) included penile haematoma (61.7% versus 13.6%), penile pain (43% versus 7.9%), penile swelling (41.2% versus 0.7%), injection site pain (25.3% versus 3.6%), penile haemorrhage (21.7% versus 10%), injection site haematoma (16.2% versus 10%), penile oedema (16.2% versus 0.7%), injection site swelling (10.8% versus 0%), contusion (10.1% versus 0%), ecchymosis (9.4% versus 0%), and injection site haemorrhage (5.4% versus 7.1%). Most were reported as mild. The most common events in Study AUX-CC-804 were penile haematoma (60.2% versus 15.6%), penile pain (35% versus 5.7%), penile swelling (34.7% versus 1.4%), injection site haematoma (22.3% versus 11.3%), penile haemorrhage (15.7% versus 0.7%), injection site pain (15% versus 2.8%), penile oedema (14.6% versus 0%), injection site swelling (12.8% versus 1.4%), contusion (9.9% versus 0.7%), and blood blister (6.2% versus 0%). Most were reported as mild or moderate. The most common events in Study AUX-CC-801 were injection site bruising (90.1% versus 50%), injection site oedema (49.5 versus 0%), injection site pain (55% versus 13.9%), contusion (22.5% versus 5.6%) and penile pain (12.6% versus 0%). Other common adverse events in the CCH group included painful erection (6.3%) and injection site pruritis (5.4%). There were no differences between the groups that received modelling and those that did not. The most common events in AUX-CC-802 included penile haematoma (51.9%), penile pain (34.6%), injection site pain (26.8%), penile swelling (26.2%), injection site haematoma (24.2%), penile haemorrhage (22.8%), penile oedema (14.1%), injection site swelling (11.5%) and painful erection (5.5%). The majority of the reported adverse events were considered related by investigators.

Deaths occurred in two patients in Study AUX-CC-803 and one in AUX-CC-804. These were considered unrelated to CCH. Across the Studies AUX-CC 803/AUX-CC-804/AUX-CC-801/AUX-CC-802, serious AEs (SAEs) occurred in 3/15/5/13 patients, respectively. Overall, there were 9 patients with SAEs that were related to CCH, including 5 penile haematomas requiring treatment and 4 patients with corporal rupture. Across the studies discontinuations due to adverse events occurred in 19 patients (approximately 2%). The related events included penile haematoma, penile bruising, oedema, and rash, corporal rupture and blood blister.

No safety concerns arose out of the laboratory investigations or vital sign measurements in these studies.

Erectile dysfunction was a common pre-morbid condition but was reported as an adverse event in the four studies AUX-CC 803, AUX-CC-804, and AUX-CC-801. In the pivotal studies 3.1% CCH patients and 0.7% of placebo patients reported the event. For the majority of the patients, minimal change or an improvement in the erectile function score from screening were observed. In Study AUX-CC-801, in which Duplex Doppler ultrasound was routinely performed 5 patients reported erectile dysfunction during the study but clinically significant Doppler ultrasound changes were shown in 2 patients.

Corporal rupture was reported in 5 cases (0.5%). The 4 events considered SAEs occurred during intercourse, 3 events within 2 weeks of a treatment cycle. Another 9 had symptoms suggestive of rupture without a confirmed diagnosis. A popping noise or sensation associated with detumescence, pain or haematoma occurred in about 13% of CCH patients in studies AUX-CC-803 and AUX-CC-804.

Post market events of interest

Corporal rupture was reported in the period 28 February 2015 to 31 July 2015 at a rate of 2.42 events per 1000 patients. In the previous PSUR the event rate was 3.37 per 1000 patients

Immunogenicity

All patients developed AUX I and AUX II antibodies by 24 (AUX-CC-803 and AUX-CC-804) or 36 (AUX-CC-801) weeks, and most appeared in circulation within one or two treatment cycles. In Study AUX-CC-805, antibodies to AUX I and AUX II were identified in 50% and 30% of subjects respectively on Day 29. Neutralising antibodies were most frequently seen at Week 24 (43.8% patients in AUX-CC-803 and 31.3% in AUX-CC-804) but were not generally sustained over more than one time point. There were no systemic immunological events and no clear correlation between antibody titre and local adverse events.

Risk management plan

The TGA has accepted the EU Risk Management Plan (RMP) version 11.0 (dated 29 April 2015, DLP 27 February 2015) and Australian Specific Annex version 5.0 (dated 8 September 2015). Included in the RMP evaluation were aspects of the Education Programme and the Controlled Distribution plan for Xiaflex when used for Peyronie's disease.

Education programme

The sponsor outlined the Educational Programme and Training Details in the responses to the questions of the RMP evaluator. The sponsor's training programme is designed to comprehensively educate and train all appropriate users of the product. The Educational resources consist of a Physician's Guide and audio-visual material. Training will be delivered by either Internet-based training or at Peer-to-peer meetings, after which prescribers will be 'Certified'. Training will be linked to a Prescriber Certification Program that will closely follow the model already implemented in Australia for Dupuytren's contracture but will be specific for Peyronie's disease. Certification will be restricted to urologists and sexual health physicians.

Controlled distribution

Xiaflex has a controlled distribution system for the Dupuytren's indication. A similar distribution system will be put in place for the Peyronie's disease indication. Only Certified Prescribers will be able to receive product from Actelion's authorised Distributor. The ordering pharmacy will supply specific personal information about the prescriber at the time product is ordered from the Distributor and this will be checked against the Certified Prescriber List. Product will only be shipped to prescribers whose name appears on the Certified Prescriber List. The Distributor will not ship the product to uncertified prescribers but will inform the ordering pharmacy that the prescriber needs to undertake Actelion's education and training program to enable Certification and access to the product.

The following were outstanding matters regarding the RMP and should be followed up with the RMP evaluator and in the Pre-ACPM Response:

- There is limited information from patients ≥ 65 years of age, therefore 'Use in the elderly' should be included as an additional missing information item in the RMP and/or Australian Specific Annex.

Risk-benefit analysis

Delegate's considerations

Peyronie's disease can place a significant psychological, as well as physical burden on those with the disease. Non-surgical options to date have been few and there has been limited success with oral therapies. CCH has been investigated as a therapeutic option for patients with Peyronie's disease and dorsal, lateral and dorsal/lateral plaques.

Efficacy

The efficacy of CCH in Peyronie's disease is supported by two well-designed pivotal studies in 936 patients, of whom 551 received CCH, and almost 80% of whom had received the course of four treatment cycles (2 injections in each treatment course, 24 to 72 hours apart, followed by modelling procedures) and additional data from the Phase IIb and open-label Phase III studies. The outcomes for the two co-primary endpoints in the studies were consistent. An improvement in curvature deformity of 31 to 36% was reported for CCH patients compared to placebo (2.5% worse to 28% improvement) after 4 treatment cycles. The meta-analysis of Studies AUX-CC-803 and AUX-CC-804 showed the differences between the two co-primary endpoints to be statistically significantly different in favour of CCH. The changes were sustained over time to 52 weeks or approximately 6 months following the last treatment. Improvements in curvature were also seen with shorter treatment courses. Clinically meaningful improvements in the Bother Score that just reached statistical significance occurred in both treatment groups but the improvements were numerically greater for the CCH group. The sustainability of the improvements for more than 6 months after a full course of 4 treatment cycles is under investigation in Study AUX-CC-810.

Safety and RMP

Adequate numbers of patients were exposed to the proposed treatment course. Although adverse events were common, these were predominantly local reactions. Withdrawal of consent rather than AE was the most common reason for premature discontinuation. Bleeding events were common and may have been due to the rupture of small venules either by direct needle puncture or by the effect of the collagenase on intra or peri plaque vessels. Collagen fragments from clostridial collagenase are known to cause vascular permeability, inflammatory responses and regenerative changes but it is not known if plaque collagenase fragments cause similar responses and contribute to the observed adverse events.

Patients with ventral plaque were excluded from the studies. Ventral plaques may include penile urethral tissue and the treatment of these lesions may pose a risk of urethra injury. The sponsor has proposed a contraindication for the use of Xiaflex in the treatment of Peyronie's plaques that involve the penile urethra.

Corporal rupture was reported in the majority of studies and in the post-market setting. In the studies it was mostly associated with vigorous intercourse early after the completion of a treatment cycle. The sponsor proposes to mitigate the risk with advice to patients to avoid intercourse for 2 weeks after each injection sequence. The ACPM is requested to comment on the adequacy of this risk minimisation strategy. It is noted that in the US a boxed warning about corporal rupture appears in the product information.

Immunogenicity Antibody formation was common but systemic hypersensitivity events were not reported and local reactions such as rash or pruritis were infrequent. Neutralising antibodies appeared transiently and no clear effect on efficacy was demonstrated. The persistence of antibodies beyond 52 weeks will be investigated in the longer-term Study AUX-CC-810.

The sponsor has proposed restriction of the use of Xiaflex for Peyronie's disease to physicians appropriately trained in the correct administration of the product and experienced in the diagnosis and treatment of male urological disease with the intention that use will be by urologists and sexual health physicians. The sponsor plans to require these health professionals undertake the sponsor's training to obtain certification and to restrict the distribution of Xiaflex to certified prescribers. The ACPM is requested to comment on this strategy.

An acceptable RMP has been provided.

Indication

The sponsor has agreed to amend the Indications to include a qualifying statement about the degree of curvature, as follows:

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.

This amendment aligns the Indication with the population in the pivotal trials.

Dose

The data support the proposed dose of 0.58 mg per plaque injection and the treatment regimen of two doses 24 to 72 hours apart with modelling after 48 hours, with repeated treatment cycles 6 weeks after the previous, for a total of 4 treatment cycles.

Data deficiencies

There are a number of data deficiencies:

- There are limited data on the use of Xiaflex in patients aged over 65 years.
- There are limited data on the impact of Xiaflex treatment on future treatment options such as surgery.
- Prescribers may consider repeated treatment courses however there are no data.
- The safety data presented in the submission are limited to 52 weeks from the commencement of therapy, although this may be addressed by the sponsor in the Study AUX-CC-810 which is a long-term safety study in the US and Europe in patients treated in earlier clinical studies.

Conditions of registration

The following are proposed as conditions of registration.

1. *Implement EU Risk Management Plan (RMP) version 11.0 (dated 29 April 2015, DLP 27 February 2015) and Australian Specific Annex version 5.0 (dated 8 September 2015) as agreed with the TGA and any future updates.*
2. *Provide the following studies to the TGA for evaluation:*
 - AUX-CC-806: The Phase III, open-label study in patients that had received placebo in Studies AUX-CC-803 and AUX-CC-804.
 - AUX-CC-810: The long term safety, curvature deformity characterisation and immunogenicity over time in subjects previously treated with AA4500 for Peyronie's disease in Studies AUX-CC-802, AUX-CC-803, AUX-CC-804 and AUX-CC-806.

Questions for the sponsor

The sponsor is requested to address the following issues in their Pre-ACPM Response:

1. Did any patient in the clinical development programme receive more than 4 treatment cycles?
2. Please explain the differences in the reported Mean Percent Change in Table 5 of the draft PI compared with Table 10 page 37 in the Summary of Clinical Efficacy.
3. Similarly, for Table 6 of the draft PI please explain the differences in the Bother Score from those reported in Table 11 of Module 2.7.3.
4. An instruction that the modelling procedure should be performed daily by the patient for 6 weeks after the physician modelling visit is included in the SmPC for Xiapex. Please indicate the reason this instruction does not appear the PI.
5. The clinical evaluator has identified 979 patients in the safety set. The sponsor has included 1044. Please explain the difference in the patient totals.

Summary of issues

The primary issues with the submission are:

- The risk of local bleeding events.
- The risk of corporal rupture and whether the risk mitigation measures are sufficient.

Proposed action

The Delegate had no reason to say, at this time, that the application for Xiaflex should not be approved for registration for the amended indication:

Xiaflex is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. *Has sufficient efficacy and safety information been provided to support the requested indication?*
2. *Does the risk of corporal rupture warrant a boxed warning in the PI?*
3. *Is the controlled distribution proposed by the sponsor including the pre-requisite training programme sufficient to mitigate the risk from inexperienced users?*

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Delegate's summary of issues

The Delegate had the following 2 primary issues with the submission that the sponsor would like to address:

The issues of the risk of local bleeding events

The risk of local bleeding in patients with coagulation disorders is captured in the ASA as a potential risk. The Precaution section of the Australian PI contains detailed information in patients with coagulated disorders where the risk of local bleeding would be higher. This information highlights to the treating physician the associated risks of local bleeding in this patient group. A pre-requisite training program linked to a controlled distribution program, ensures that all treating physicians are properly trained and skilled in

administering and treating patients with Xiaflex. The sponsor believes that although the local bleeding events cannot be eliminated there are adequate measures in place to minimise this risk.

The risk of penile hematoma (including injection site hematoma) in Xiaflex treated patients in placebo controlled trials was 65.5%. The AE section of the PI lists all bleeding events identified from the 2 controlled studies. Severe penile hematoma or severe injection site hematoma were reported in 33/551 (6.0%) of Xiaflex treated patients and 0/281 (0%) of placebo-treated patients. Table 13 of the Australian PI lists penile hematoma, including injection site hematoma, and penile ecchymosis, including contusion, ecchymoses, penile haemorrhage, and injection site haemorrhage, as occurring with a Council of International Organizations of Medical Sciences (CIOMS) frequency of occurrence of 'Very Common' (greater than or equal to 10%). The majority of these local bleeding events are non-serious.

The risk of corporal rupture and whether the risk mitigation measures are sufficient

The sponsor believes that the risk mitigation measures, as outlined in the EU RMP/ASA for corporal rupture are sufficient to mitigate the risk. Corporal rupture is an important identified risk of the use of Xiaflex in the treatment of Peyronie's disease. The current PI and Physicians leaflet provides detailed instructions for the correct administration of the drug. Restriction on the distribution of Xiaflex to only physicians who are experienced in the diagnosis and treatment of male urological diseases (urologists and sexual health physicians) further limits the risk by ensuring that only those physicians properly trained and skilled are administering the medication. Furthermore, patients are counselled about the signs and symptoms of corporal rupture and are instructed to follow directions regarding limitations on sexual activity during the period after medication administration during which healing is occurring and to contact the treating physician should they suspect corporal rupture.

Sponsor comments on ACPM advice sought by the delegate

The Delegate is seeking advice from the ACPM to three specific issues, on which the applicant would like to comment as follows:

Has sufficient efficacy and safety information been provided to support the requested indication?

The co-primary endpoints were achieved in each of the double-blind, randomised, placebo-controlled studies (AUX-CC-803 and AUX-CC-804). Xiaflex was statistically significantly superior to placebo with respect to the mean percent improvement from baseline in curvature deformity ($p \leq 0.0059$) and the mean reduction from baseline in patient-reported Peyronie's disease bother ($p \leq 0.0496$). Among subjects who were treated with Xiaflex in the two placebo controlled studies, improvement in curvature deformity was apparent after the first treatment cycle (Week 6) with continued improvement noted after each of the three subsequent treatment cycles. The improvement in curvature deformity was maintained through the end of the study (Week 52) in both studies. Among subjects who received at least 1 dose of Xiaflex, the most frequently reported TEAEs and treatment-related AEs remained localised to the penis and groin and most commonly included penile ecchymosis (the majority had the verbatim 'penile bruising'), penile swelling and penile pain. Most TEAEs were non-serious, mild or moderate in severity and resolved without intervention before the next scheduled treatment cycle. No clinically meaningful differences in the incidence of TEAEs were observed between subgroups (age, duration of Peyronie's disease, baseline penile curvature deformity, penile trauma history, prior Peyronie's disease treatment, diabetes history, baseline International Index of erectile function, concomitant PDE5 usage or location).

Does the risk of corporal rupture warrant a boxed warning in the PI?

The sponsor believes that the current risk management activities described in the EU RMP/ASA in handling this important identified risk is adequate and the need for a boxed warning is not warranted. The risk of corporal rupture is adequately described in the AU PI under the Precautions and the AE sections. Xiaflex will be restricted to physicians who are experienced in the diagnosis and treatment of male urological diseases (urologists and sexual health physicians). The controlled distribution program will further ensure that only these certified prescribers will be able to access Xiaflex. Furthermore, the CMI contains information specific for the patients about the signs and symptoms of corporal rupture as well as strict directions to be followed regarding limitations on sexual activity during the period after medication administration during which healing is occurring and to contact the treating physician should they suspect corporal rupture. The ACPM committee is advised that the Risk Minimisation Plan to be followed in Australia is the same as that presented in the EU RMP; the EMA has not imposed a box warning regarding corporal rupture in Europe.

Is the controlled distribution proposed by the sponsor including the pre-requisite training programme sufficient to mitigate the risk from inexperienced users?

A controlled distribution system will ensure that only Certified Prescribers will be able to receive product from Actelion's authorised Distributor. The pharmacy ordering process will be tailored to ensure that specific personal information on the prescriber is supplied by the ordering pharmacy at the time product is ordered from the Distributor. Every order received by the Distributor will be checked against the Certified Prescriber List database prior to shipping product. Product will only be shipped to prescribers whose name appears on the Certified Prescriber List. Where the prescriber's name is not on the Certified Prescriber List, the Distributor will withhold shipment of product and notify the pharmacy that the prescriber needs to undertake Actelion's education and training program to enable Certification and subsequent receipt of product. The pre-requisite training program is designed to impart the necessary knowledge and skills to mitigate the risk from inexperienced users and the controlled distribution programme will ensure that only certified prescribers will be able to access Xiaflex.

Responses to the delegate's questions for the sponsor

The Delegate has raised the following five questions requiring the sponsor's clarification.

1. *Did any patient in the clinical development programme receive more than 4 treatment cycles?*

There were no subjects who received more than 4 treatment cycles. There were 8 subjects in an early development study (PEY-1035; posology was 3 treatment cycles of 3 injections per cycle; each cycle separated by 6 weeks) that received 9 injections. Upon review of the clinical development studies, the safety profile of these subjects did not differ from the profile of the 733 subjects that received 4 treatment cycles of 2 injections per cycle.

2. *Please explain the differences in the reported Mean Percent Change in Table 5 of the draft PI compared with Table 10 in the Summary of Clinical Efficacy.*

Table 5 of the draft PI reports the change and/or the percent change based on model-adjusted means that is, Least Squares (LS) Means, whereas Table 10 page 37 reports the change and/or percent change from baseline as the arithmetic mean, the same mean that is reported in the clinical study reports (CSRs) 803 and 804. The reporting of the percent change based on adjusted means was in response to an FDA request during the label negotiations and for consistency the current draft PI retains the percent change based on the LS Means. The model used to calculate the model-adjusted means included factors for treatment, stratum of baseline curvature and their interaction.

3. Similarly, for Table 6 of the draft PI please explain the differences in the Bother Score from those reported in Table 11 of the Summary of Clinical Efficacy.

Similar to the response to Question 2 above, Table 6 of the draft PI reports percent change based on model adjusted means, that is, LS Means, whereas Table 11 the change and/or percent change from baseline as the arithmetic mean, the same mean that is reported in the CSRs 803 and 804. The reporting of the percent change based on model-adjusted means was in response to an FDA request during the label negotiations, and for consistency the current draft PI retains the percent change based on the LS Means.

4. An instruction that the modelling procedure should be performed daily by the patient for 6 weeks after the physician modelling visit is included in the SmPC for Xiapex. Please indicate the reason this instruction does not appear the PI.

The PI and Physician leaflet now includes a statement that the physician is to instruct the patient to perform the at home modelling procedures (3 times daily for the penile stretching procedure and once daily for the penile straightening procedure) for 6 weeks following each treatment cycle.

5. The clinical evaluator has identified 979 patients in the safety set. The sponsor has included 1044. Please explain the difference in the patient totals.

Table 10 below shows the counts from the different studies resulting in the different patient totals.

Table 10: Number of patients from clinical studies

Study	CER	sBLA Safety Update Table
1030	Not reported, not submitted	25
1035	Not reported, not submitted	10
801	111	111
802	347	347
803	227	277
804	274	273
805	20	Reported in Study 802
Total	979	1044

The following reasons contributed to the difference in the CER and the safety population of 1044 subjects:

- There are seven studies included in the integrated safety database (subjects that received at least one injection of AA4500 (0.58 mg) in any of the seven studies) including two Phase II studies PEY-1030 (n=25) and PEY-1035 (n=10), which were not included in the CER.
- Study AUX-CC-803 had 277 enrolled subjects who were treated with AA4500; not 227 as erroneously reported in the CER table.
- The 20 subjects in Study AUX-CC-805 listed in the CER rolled over into Study- CC-802. Study AUX-CC-802 enrolled 347 subjects who were treated with AA4500 and who

either enrolled (N=317) directly into Study AUX-CC-802 or rolled over (N=20) into Study AUX-CC-802 from the pharmacokinetic Study AUX-CC-805, that is, the 347 subjects listed in CER table already includes the 20 subjects from Study AUX-CC-805 so they should not be listed separately that is, recounted, in the CER table.

The following reconciliation of the difference between the CER table (n=979) and the integrated safety population (n=1044) is:

CER = 979 subjects + 50 (Study 803 erroneously listed as n=227 in CER table when the actual n=277) - 20 (Study 805 subjects are already counted in Study 802) = 1009 + 25 (Study 1030) + 10 (Study 1035) = 1044 subjects = sponsor reported integrated safety population.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that; Taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Xiaflex lyophilised powder for injection containing 0.9 mg of collagenase clostridium histolyticum (CCH) to have an overall positive benefit-risk profile for the Delegate's amended indication;

Xiaflex is indicated for the treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy

In making this recommendation the ACPM;

- noted the trial population consisted of patients who had had disease for at least 12 months and a curvature of more than 30° but less than 90°
- noted the small volume of the treatment injection and yet the high rate of reported haematomas

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the Precautions section of the PI and relevant sections of the CMI to against intercourse for at least 2 weeks after each treatment due to the possibility of corporeal rupture

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Has sufficient efficacy and safety information been provided to support the requested indication?*

The ACPM agreed the efficacy of CCH in Peyronie's disease is supported by two well-designed pivotal studies in 936 patients of whom 551 received CCH and additional data from the Phase IIb and open-label Phase III studies. The outcomes for the two co-primary

endpoint in the studies were consistent. An improvement in curvature deformity of 31 to 36% was reported for CCH patients compared to placebo. The changes were sustained to 52 weeks or approximately 6 months following the last treatment.

Adequate numbers of patients were exposed to the proposed treatment course to assess safety. Although adverse events were common, these were predominantly local reactions. Withdrawal of consent rather than AE was the most common reason for premature discontinuation.

2. *Does the risk of corporal rupture warrant a boxed warning in the PI?*

The ACPM noted a total of 979 patients received at least one treatment cycle of CCH.

Overall, there were 9 patients with SAEs that were related to CCH, including 5 penile haematomas requiring treatment and 4 patients with corporal rupture. The latter has been considered for a boxed warning.

The 4 events considered SAEs occurred during intercourse, 3 events occurred within 2 weeks of a treatment cycle. Another 9 reported events had symptoms suggestive of rupture without a confirmed diagnosis.

Post market reporting suggests corporeal rupture occurs at a rate of 2.42 to 3.37 events per 1000 patients.

The ACPM was of the view that a clear precautionary statement in the PI and CMI against intercourse for at least 2 weeks after each treatment would be useful and sufficient in addition to RMP proposals.

3. *Is the controlled distribution proposed by the sponsor including the pre-requisite training programme sufficient to mitigate the risk from inexperienced users?*

The ACPM noted the linked Prescriber Certification Program (based on successful completion of the sponsor's education and training program), controlled distribution plan and pharmacovigilance proposals.

The ACPM also noted the controlled distribution plan in place for Xiaflex in relation to its current indication for Dupuytren's contracture has worked well.

The ACPM agreed administration of this treatment should be restricted to urologists and registered sexual health physicians.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xiaflex containing collagenase clostridium histolyticum 0.9 mg lyophilised powder for injection by local injection, indicated for:

The treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.

Specific conditions of registration applying to these goods

1. The Xiaflex EU Risk Management Plan (EU-RMP), version 11.0, dated 29 April 2015, DLP 27 February 2015) and Australian Specific Annex version 5.0 (dated 8 September 2015), included with submission PM-2014-04262-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

2. The following studies reports must be submitted to the TGA, as soon as possible, for evaluation as a Category I submission:
 - a. AUX-CC-806: The Phase III, open-label study in patients that had received placebo in Studies AUX-CC-803 and AUX-CC-804.
 - b. AUX-CC-810: The long term safety, curvature deformity characterization, and immunogenicity over time in subjects previously treated with AA4500 for Peyronie's disease in Studies AUX-CC-802, AUX-CC-803, AUX-CC-804, AUX-CC-806

Attachment 1. Product Information

The PI approved for Xiaflex with this application is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<https://www.tga.gov.au>