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

November 2013

TGA Health Safety Regulation

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 <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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.

Contents

List of abbreviations

Abbreviation	Meaning
AA4500	Collagenase clostridium histolyticum
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUX-I	Clostridial type I collagenase
AUX-II	Clostridial type II collagenase
BMI	Body mass index
BTC	Biospecifics Technology Corporation
BUN	Blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CSR	Clinical study report
CRF	Case report form
DB PC	Double-blind placebo-controlled
ECG	Electrocardiogram

Abbreviation	Meaning
ELISA	Enzyme-linked immunosorbent assay
EU	European union
Fixed-flexion deformity/ contracture (degree of flexion)	The angle of the joint when the finger is passively extended (i.e. straightened) as far as possible toward the neutral position of zero degrees (i.e. full extension or normal extension)
Full extension angle	The angle of a joint when the finger is straightened (extended) as far as possible toward the neutral position of zero degrees (expressed in degrees)
Full flexion angle	The maximum angle of a joint when the finger is bent (flexed) as close to the palm as possible (expressed in degrees)
GCP	Good clinical practice
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IRB	Institutional review board
ISE	Integrated Summary of Efficacy
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
LOCF	Last observation carried forward
MAA	Marketing Authorisation Application
MAH	Marketing Authorization Holder
MPP	Mammalian matrix metalloproteinase
mg	Milligram
mL	Milliliter
MP	Metacarpophalangeal
Neutral Zero Method	All motions of a joint are measured from a defined zero starting point position. The degree of motion of a joint are added in the direction the joint moves from the zero starting

Abbreviation	Meaning
	position
PIP	Proximal interphalangeal
ROM	Range of motion
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse events were events with a start
UK	United Kingdom
ULN	Upper limit of normal
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New Biological Entity
Decision:	Approved
Date of decision:	30 July 2013
Active ingredient:	Collagenase clostridium histolyticum
Product name:	Xiaflex
Sponsor's name and address:	Actelion Pharmaceuticals Australia Pty Ltd 13 Narabang Way, Belrose NSW 2085
Dose form:	Lyophilised Powder For Injection
Strength:	0.9 mg
Container:	Type 1 glass vial

Pack size:	Each single-use glass vial of Xiaflex[1] is packaged with a single-use glass vial of sterile diluent[2] for reconstitution.
Approved therapeutic use:	*Xiaflex is indicated for the treatment of Dupuytren's contracture in adult patients with a palpable cord.*
Route of administration:	Intralesional injection into the cord
Dosage:	For cords affecting metacarpophalangeal (MP) joints, each dose is administered in an injection volume of 0.25 mL (0.58 mg). For cords affecting proximal interphalangeal (PIP) joints, each dose is administered in an injection volume of 0.20 mL (0.58 mg). A finger extension procedure can be performed 24 h after the injection. Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.
ARTG Number:	199584

Product background

This AusPAR describes the submission by Actelion Pharmaceuticals Australia Pty Ltd to register a new biological entity, collagenase clostridium histolyticum, for the treatment of Dupuytren's contracture in adult patients with palpable cord.

Dupuytren's contracture is a relatively common disorder in which there is benign, slowly progressive fibrosis of the palmar fascia. Its aetiology and pathogenesis is not well understood but it results in tendon thickening, joint stiffness and a slow loss of full extension over decades. Contractures typically develop that flex one or more fingers at the metacarpophalangeal (MP) joint. There are no approved pharmacological therapies and the main treatment is surgical.

Collagenase clostridium histolyticum (*collagenase*) 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 that these two collagenases are not immunologically cross-reactive and have different specificities such that together they become synergistic, however there are no clinical data regarding the relative contributions of the individual collagenases to the product's efficacy. The clinical rationale is that after local injection at the site of the Dupuytren's cord there will be selective lysis of collagen at this injection site which will result in reduction of the finger contracture.

The sponsor proposed the following indication:

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

There are no TGA adopted European guidelines specific to this indication.

[1] Xiaflex vial containing 0.9 mg sterile lyophilized powder of collagenase *C. histolyticum*
[2] Diluent vial containing 3 mL of 0.3 mg/mL calcium chloride dihydrate in 0.9% sodium chloride of sterile diluent for reconstitution

Regulatory status

Collagenase clostridium histolyticum has not been previously considered by the TGA's Advisory Committee on Prescription Medicines (ACPM).

Collagenase clostridium histolyticum has been approved in the European Union (February 2011), USA (February 2010), Canada (July 2012) and Switzerland (July 2011) for this indication. Its status in New Zealand is unknown. The approved indications overseas are as follows:

Europe

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

USA

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

Canada

Xiaflex (collagenase clostridium histolyticum) is indicated for the treatment of adult patients with Dupuytren's contracture with a palpable cord.

Switzerland

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

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Structure

Drug substance consists of two microbial collagenases: collagenase AUX-I (Clostridial type I collagenase) and collagenase AUX-II (Clostridial type II collagenase). Collagenase AUX-I is a single polypeptide chain containing approximately 1,000 amino acids of known sequence and with a molecular weight of 114 kiloDaltons (kDa). Collagenase AUX-II is also approximately 1,000 amino acids long and has a molecular weight of 113 kDa.

The gene sequences of AUX-I and AUX-II from the production strains have been determined and minor, conservative differences were noticed (AUX-I - D318E, A743T, and S865A; AUX-II - L165I, I172M, V270I, K286E, E402D, E411K, Q413E, and Y552H).

The amino acid sequence for AUX-I (*colG*) and AUX-II (colH) are presented in Figures 1 and 2, respectively. The amino acid residues that are different between the *colG* and colH deposited sequences and the Auxilium production strain sequences are highlighted.

Figure1. Amino acid sequence for AUX-I

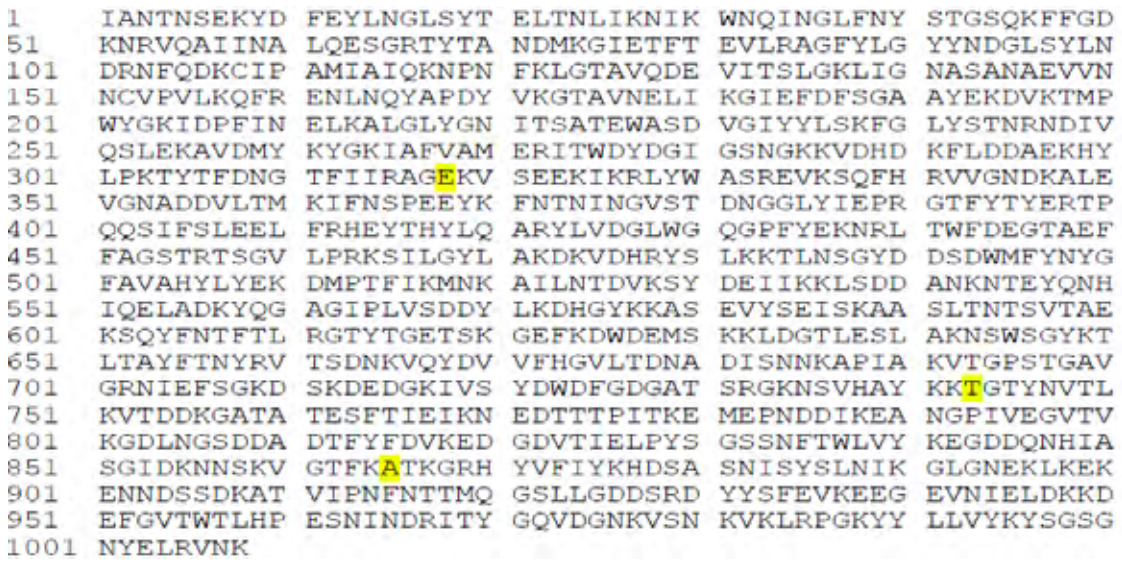
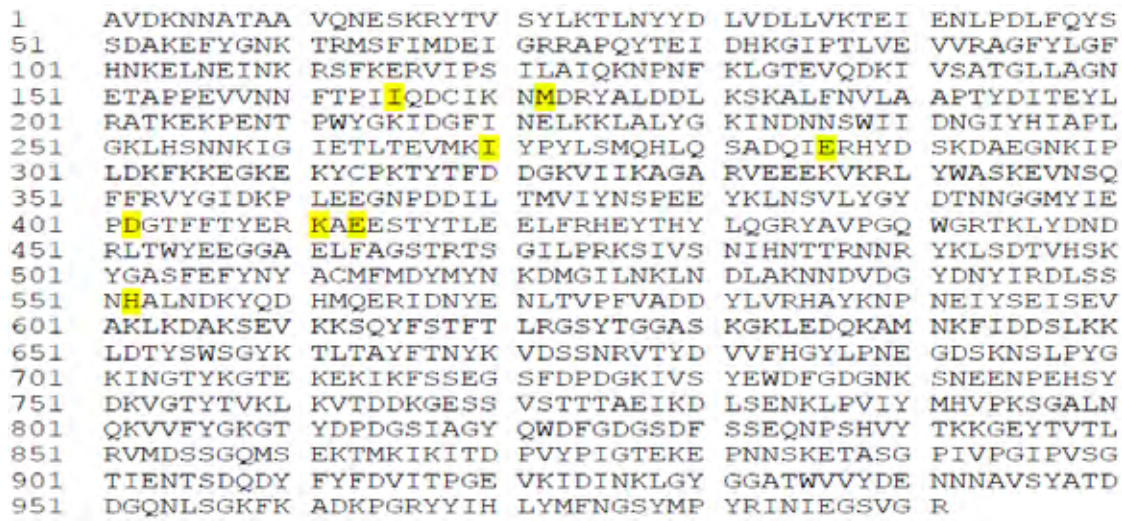


Figure 2. Amino acid sequence for AUX-II



The substitutions maintain the respective hydrophobic or hydrophilic character and relative side chain size of each residue. Substitutions of this nature do not adversely affect the stabilising forces responsible for protein folding. These substitutions are also outside of the active site of the enzyme.

The AUX-I and AUX-II protein sequences have the theoretical masses of 113,915 Daltons (*col*G – NCBI) and 112,979 Daltons (colH – NCBI), respectively. The Auxilium production strains AUX-I and AUX-II protein sequences have the theoretical masses of 113,928 Daltons and 112,972 Daltons, respectively.

Manufacture

AA4500 Bulk Drug Substance (BDS) is produced by the anaerobic fermentation of *Clostridium histolyticum*, a Biosafety Level 2, gram positive bacterium.

Cell banking processes were considered to be satisfactory. All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

The collagenases digest collagen by hydrolysing the triple helical region of collagen under physiological conditions. Collagenase AUX-I functionally belongs to class I collagenase from *Clostridium histolyticum* and Collagenase AUX-II functionally belongs to class II collagenase from *Clostridium histolyticum*. There are substrate specificity differences between the two classes that results in synergistic action when they are present together. Type I collagenases have a narrow substrate specificity, requiring a triple helix structure in the collagen for binding to occur and they also tend to hydrolyse loci near the ends (that is, the amino and carboxy termini) of triple helical domains of collagen. In contrast, the substrate specificity of type II collagenase is much broader and the preferred cleavage sites of the type II collagenases are sites in the interior of the collagen molecule. Collagenases AUX-I and AUX-II are metalloproteases, requiring tightly bound zinc and loosely bound calcium for their activity.

Product-related substances have been identified and characterised. These substances are controlled in the drug substance release specifications.

Process-related impurities have been identified and characterised. These substances are also controlled in the drug substance release specifications.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance were justified and appropriate validation data have been submitted in support of the test procedures.

A trend of decreasing pH with time has been observed in the bulk drug substance (BDS) placed on stability at ≤ -60°C in 5 mL polycarbonate vials filled to 1 mL. This trend was exacerbated by shipping the stability samples on dry ice to contract testing laboratories. The specifications for pH has been widen from 7.5-8.5 at release to 6.5-8.5 at end of shelf-life and appropriate data has been provided to show that no impact of low pH on drug substance quality.

Stability

Stability data have been generated under real time/accelerated/stress conditions to characterise the stability/degradation profile of the substance and to establish a shelf life time.

Drug product

Formulation(s)

AA4500 drug product contains lyophilized AA4500 drug substance at 0.9 mg/vial collagenase *Clostridium histolyticum* as well as sucrose and trometamol. One finished lot of BDS is used to manufacture one finished lot of drug product. There is no further formulation of the drug substance for the preparation of the drug product.

The bulk solution is sterile filtered, aseptically filled at 3.0 mL/vial (+ 0.2 mL) and terminal sterilization completed to yield sterile diluent with a final formulation of 0.9% sodium chloride (NaCl) and 0.03% calcium chloride ($CaCl_2$).

Manufacture

The formulation of the drug product is performed at the drug substance stage. The drug product manufacturing process essentially comprises of thawing of the shipped drug substance, pooling and mixing of the bulk drug product, two sterile filtration steps, filling, lyophilisation, visual inspection and bulk packaging.

Specifications

Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data showed that the product is photostable at the recommended storage condition.

The proposed shelf life of the drug product is 36 months when stored at 5°C (2° to 8°C).

The proposed shelf life of the sterile diluent is 36 months when stored at 2° to 30°C.

In-use stability data have also been submitted. The proposed shelf life and storage conditions for the reconstituted product are one hour when stored at ambient room temperature (20°C - 25°C) or refrigerated 2°C - 8°C for up to 4 hours prior to administration.

To date, Auxilium has not conducted a reconstitution stability studies on the DP batch at the end of shelf-life (36 months). The company states that a 36 month old DP lot will become available soon so that a reconstitution stability study could be completed by the end of 2013.

The company was required to commit for completion of these reconstitution stability studies and notify the TGA any out of specification results.

Biopharmaceutics

Biopharmaceutic data are not required.

Advisory committee considerations

Pharmaceutical sub-committee of ACPM review

The Pharmaceutical Subcommittee reviewed the evaluation report(s) at its 150 meeting on 25 March 2013 and advised the TGA as follows:

Recommendation NO 2306

1. The PSC endorsed all the questions raised by the TGA in relation to the quality and pharmaceutic aspects of the submission by Actelion Pharmaceuticals Australia Pty Ltd to register Xiaflex powder for injection containing 0.9 mg of collagenase clostridium histolyticum.
2. In addition, the PSC advised that the sponsor should be asked to conduct the bioburden testing of the diluent immediately prior to the ultimate terminal steam sterilisation of the filled vials instead of the proposed determination prior to sterile filtration of the final bulk solution.
3. The PSC:
    - Noted the sponsor's justification for not providing information on the relationship between potency specifications and clinical efficacy. The PSC raised concerns that the absence of information makes it difficult to ensure consistency in activity between batches. The Committee agreed that it was difficult to assess how *in vitro* assay relates to clinical activity.
    - Had concerns about the lack of long-term studies in view of the very high rate (about 100%) of seroconversion observed with this product. The impact of this on patients who represents is unknown.

- Noted the significant amount of polymorphism in collagenase AUX-I and collagenase AUX-II sequences and considered the sponsor's response to this issue inadequate.

4. The PSC recommended that the attention of the Clinical Delegate and the Advisory Committee on Prescription Medicines (ACPM) should be drawn to these issues.
5. In the Product Information (PI)
   - This document should be amended to include the pH of the reconstituted drug product.

There is no requirement for this submission to be reviewed again by the PSC before it is presented for consideration by Advisory Committee on Prescription Medicines (ACPM).

Quality evaluator's comment for

Second point

"Ideally, samples for bioburden testing should be taken from filled units. However, given that the product has been aseptically manufactured prior to terminal sterilisation, which included filtration through two 0.22µm filters followed by aseptic filling and that the pre filtration bioburden limit was acceptably low, it is considered that the product is essentially sterile before terminal sterilisation and nothing further would be gained by inclusion of sampling of filled units for bioburden" [a support statement from the sterility evaluator was also made].

Third dot point

The deduced AUX-I (colG) and AUX-II (ColH) amino acid sequences of the production strain contains three and eight conservative amino acid differences, respectively from the model *col*G and *colH* sequences deposited in the National Centre for Biotechnology Information (NCBI) website. The production strain is a non-recombinant cell line derived from a natural *Clostridium histolyticum* isolate, ATCC 21000. The model protein sequence deposited in NCBI is from another *C. histolyticum* isolate, ATCC 19401. The residue differences between the production strain and the model sequence are genetic variations, not spontaneous mutations. All released lots of Collagenase *Clostridium histolyticum* BDS produced by the sponsor have met the potency release tests (activity assays) specifications, confirming the substitutions are not deleterious to enzymatic activity.

Notwithstanding these recommendations/comments, there are no Module 3 objections to registration of Xiaflex Collagenase clostridium histolyticum, AA4500 Powder for Injection vial (0.9 mg/vial) with sterile diluent vial (3 mL/vial).

The Delegate could request further comments from the sponsor regarding the PSC recommendation if warranted.

Batch release conditions of registration for clinical delegate

Should the product be approved, the following conditions of registration should be applied.

Conditions of registration

Batch release testing by OLSS

It is a condition of registration that independent batches of

- Xiaflex Collagenase clostridium histolyticum, AA4500 Powder for Injection vial (0.9 mg/vial) with sterile diluent vial (3 mL/vial) – [AUST R 199584]

imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS).

The sponsor should supply:

1. A Certified Product Details (CPD) document.
2. Certificates of Analysis of all active ingredient (drug substance) and final product.
3. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents.
4. Evidence of the maintenance of registered storage conditions during transport to Australia.
5. Three vials of each batch for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The conditions remain in place until you are notified in writing of any variation.

Certified Product Details (CPD)

An electronic draft of the Certified Product Details (CPD), as described in Appendix 7 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

All quality issues have been satisfactorily resolved. However, the sponsor was required to commit for completion of reconstitution stability studies on the drug product batches at the end of shelf life (36 months), when those batches become available at the end of 2013, and notify the TGA of any out of specification results.

III. Nonclinical findings

Introduction

General comments

The submitted nonclinical data were generally in accordance with the TGA adopted EU guidelines on the (ICH S6) *Preclinical safety evaluation of biotechnology-derived pharmaceuticals*[3] and *Note for Guidance on Non-Clinical Local Tolerance Testing of Medicinal Products*[4]. The nonclinical dossier also contained extensive published literature submitted in support of certain parts of the application [*Primary Pharmacology, Drug Interactions, Secondary Pharmacodynamics, Single Dose Toxicity (dogs) and Local Tolerance*]. However, the majority of these literature reports were utilised as supportive reference material only.

[3] <http://www.tga.gov.au/pdf/euguide/ich030295en.pdf>
[4] CPMP/SWP/2145/00 <http://www.tga.gov.au/pdf/euguide/swp214500en.pdf>

A number of non Good Laboratory practice (GLP) single dose and acute toxicity studies (3 days duration) were conducted in mice (intraperitoneal (IP) and intra muscular (IM) routes) and rats (intravenous route (IV)), respectively. Studies in mice were early screening studies and those in rats were dose-ranging studies for reproductive and developmental toxicity studies to determine the potential systemic toxicity. Notably, the submitted guinea-pig sensitization and dermal irritation studies, as well as a mini-pig subcutaneous (SC) local tolerance were not GLP-compliant. However, the injection site toxicity and potential toxicity following systemic exposure of AA4500 was determined in a range of pivotal GLP compliant local SC toxicity and IV repeat dose toxicity studies, respectively. These studies included single and repeat dose studies using the clinically relevant route (SC injection into the paw) in both rats and dogs and repeat dose IV dosing studies in rats (general toxicity and two reproductive and developmental toxicity studies). Moreover, all pivotal toxicity studies used the AA4500 '*Process 3'* material for final clinical use. The '*early BTC*[5]*'* AA4500 material [or '*AA4500 (Process 1 material)*'; see next section] has been determined to be comparable to the final AA4500 '*Process 3'* material for clinical use, following the conduct of two IV toxicity and toxicokinetic comparability studies (Studies DLB00006 and LAB 1007-1671). All initial studies performed by Biospecifics Technologies Corp. or 'BTC' (GLP single dose local tolerance in rats, *in vitro* and *in vivo* genetic toxicity studies, non-GLP single dose mouse IM and IP toxicity and guinea pig local tolerance and sensitization studies) used the AA4500 '*early BTC process'* material.

Antibody responses were also evaluated and characterised in all sponsor conducted GLP toxicology studies (with the exception of Study DLB00009, an IV embryo-fetal developmental study in rats). Antibody formation against AUX-I and AUX-II was determined to evaluate their potential role in adverse effects, or effects on efficacy resulting from their generation.

Chronic toxicity and carcinogenicity studies were not required due to the lack of chronic use. Pre and postnatal development studies were not submitted due to the lack of systemic exposure. An additional GLP local tolerance study (Study TRL 520) was performed using a route of administration designed to represent a clinically relevant route of administration (local injection into the penis) in support of safety for use in Peyronie's disease.

Comparison of effects of clostridial collagenase (AA4500) from various sources

Purified Clostridial collagenase for injection was developed by Biospecifics Technologies Corp. (BTC) which produced '*early BTC' batches* and this material is referred to as '*early BTC' process batches'* or *'AA4500 (Process 1)'*. Following licensing by Auxilium Pharmaceuticals, Inc., the manufacturing process was optimised (utilizing *Process 3*) and was then referred to as '*AA4500*' which is the product for final clinical use. All pivotal toxicity studies utilized AA4500 '*Process 3'* material and were conducted in accordance with GLP.

In studies using '*early BTC' process batches* of AA4500, concentrations/doses were expressed as units (U) of AA4500 activity. For comparison of findings in all nonclinical studies with *Clostridial Collagenase* (AA4500) manufactured by different processes, all concentrations or doses have been converted to, and are expressed as, their unit equivalent (U) regardless of how the doses were expressed in the original study. This is to allow for a more accurate basis for comparison of results across studies on a pharmacologically relevant basis where AA4500 activity approximately 17,241 U per mg protein [or 10,000 U per 0.58 mg dose; that is, the proposed clinical dosing regimen involves administration of a single dose of AA4500 (0.58 mg, equivalent to 10,000 U) intermittently, approximately every 30 days, by intralesional injection into a Dupuytren's cord].

[5] BTC=Biospecifics Technologies Corp.

Pharmacology

In vitro

Clostridial collagenases are proteinases that can hydrolyse the triple-helical region of collagen under physiological conditions and AA4500 is a parenteral lyophilized product comprised of two collagenases in an approximate 1:1 mass ratio, AUX-I (class I clostridial collagenase) and AUX-II (class II clostridial collagenase). Extensive published literature reports submitted by the sponsor demonstrated that class I and class II clostridial collagenases have different specificities, such that together they become synergistic, providing a broad hydrolyzing reactivity toward collagen. The components of AA4500 (AUX-I and AUX-II) have also been reported to have the appropriate substrate specificities to be considered representative of Class I and Class II collagenases, respectively. A submitted study using a modified fluorogenic rat tail collagen assay which examined the degradation pattern/time course of enzymatic digestion of type I soluble collagen from various sources (rat tail collagen, bovine tendon collagen and recombinant human collagen) demonstrated that synergy of the 1:1 mass ratio mixture of AUX-I and AUX-II in AA4500 was comparable to that described in the literature for similar mixtures of purified class I and class II collagenases.

Ex vivo

As there are no nonclinical animal models for Dupuytren's contracture, examination of *in vivo* activity (normally correlated with systemic exposure) is not possible. The activity of collagen lysis at the site of injection of AA4500 has therefore been investigated in a series of *ex vivo* studies using cultured explants derived from human Dupuytren's cord and Peyronie's plaques (which are similar in structure and collagen composition to a Dupuytren's cord). '*Early BTC' process* material or commercially available clostridium collagenase was used in these studies (and not the final product drug product for clinical use). In both tissues, dose and time dependent effects of collagen lysis at the site of application (independent of dose) were demonstrated, with collagen digestion in injected tissues nearly complete at 24 hours, with the smaller collagen fibers being more readily susceptible to lysis: a dose of 3600 U was adequate to lyse collagen causing significant disruption of isolated Dupuytren's cords.

Collagen lysis in tissues comprised of dense fibrous connective tissue arranged in larger fibrils such as in Dupuytren's cord (as well as in the corpus cavernosum and pericardium) was focal, well circumscribed and mainly localised to tissue directly adjacent to the injection site, suggesting minimal potential for damage to normal tissue structures which are present either within or adjacent to the injected tissue. In contrast, collagen lysis in loosely arrayed fibrous connective tissue comprised of smaller fibrils (such as in Peyronie's plaque) was more diffuse.

Other local effects and secondary/safety pharmacology

Examination of other normal human tissues (pericardium and corpus cavernosum) after clostridium collagenase treatment found that elastic fibers and superficial neurovascular structures were preserved with no damage to adjacent tissue at the collagenase injection site.

Whilst published literature reports have suggested that clostridium collagenase has some activity against type IV (basement membrane) collagen, there were no reported effects on basement membranes examined in the tissue explant studies of Dupuytren's cord and Peyronie's plaques, or in any other studies in the nonclinical program following local injection in animal species at doses of ≥ 10,000 U.

AA4500 is administered locally by injection and systemic exposure is non-quantifiable and/or limited. ICH S7A guidance[6] suggests that safety pharmacology studies are not normally required for compounds with low systemic exposure or where distribution to other organs or tissues is limited. Although no specific studies were undertaken, there appears to be no secondary systemic pharmacodynamic actions of toxicological concern. Similarly, although there were no specific studies, no safety pharmacology concerns have arisen from any of the nonclinical studies. Treatment related adverse effects were confined to the injection site following local dosing (SC injection into rat or dog paw) with no evidence of systemic toxicity (Studies WIL-696001, WIL-696005, WIL-696003, and WIL-696006). Injection site reactions are local secondary pharmacological effects that include alterations in vascular permeability, inflammatory responses and fibroproliferative wound healing responses. These are most likely mediated by the *in situ* generation of smaller collagen fragments, which have pharmacologically active sites that elicit well known and characterized responses.

Pharmacodynamic drug interactions

A number of literature reports were submitted which discussed the potential theoretical interaction of collagenase clostridium with tetracycline derivatives and/or anthracycline and anthroquinolone antibiotics (such as adriamycin, daunarubricin). The interaction with tetracycline derivatives could result from chelation of metal cofactors (calcium (Ca) and zinc (Zn)) essential to the activity of AA4500.[7] However, inhibition of clostridial collagenase by tetracycline derivatives at pharmacologically relevant concentrations has not been demonstrated.

Although there is a published report of inactivation of clostridial collagenase by anthracycline and anthroquinolone antibiotics[8], the sponsor proposes that given the therapeutic use of the latter class of these agents, concomitant treatment with AA4500 is unlikely to occur. Moreover, the limited oral bioavailability of the latter class makes a significant interaction unlikely in the event of concomitant use. The draft Product Information document appropriately cautions the use of Xiaflex in patients who have received these drugs.

Pharmacokinetics

In all repeat-dose GLP toxicology studies, toxicokinetic parameters were determined for the AA4500 components, AUX-I and AUX-II collagenases individually; as well as for anti-AUX-I or anti-AUX-II antibody formation in rat plasma/serum and dog plasma (except in the *IV embryo-fetal developmental study in rats,* that is, study DLB00009). The kinetics of AUX-I and AUX-II were evaluated in either satellite groups (rats) or the study animals (dogs).

IV Studies

The IV (bolus injection) route of administration was used to characterise the systemic effects of AA4500 in rats to ensure adequate systemic exposure, since it does not become systemically available following local injections. Following IV dosing, volume of distribution (Vss) estimates were low due to the nature and size of AUX-I and AUX-II (proteins, circa 115 kDa). For the two IV toxicity/comparability studies (studies DLB00006 and LAB 1007-1671) the IV route was also used for comparison of the toxicokinetics of early 'BTC collagenase' AA4500 and AA4500;

[6] Note for guidance on safety pharmacology studies for human pharmaceuticals. CPMP/ICH/539/00. <http://www.tga.gov.au/pdf/euguide/ich053900en.pdf>
[7] Golub LM *et al.* (1998) Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv Dent Res* **12,** 12-26.
[8] Bols M *et al.* (1992) Inhibition of collagenase by aranciamycin and aranciamycin derivatives. *J Med Chem* **35,** 2768-2771.

that is, early 'BTC Process' batches of AA4500 (Process 1 batches) compared to the final AA4500 batches (Process 3 material) intended for final clinical use.

Systemic exposure to AUX-I and AUX-II generally increased dose-proportionally in single dose IV studies (that is, dosing on Day 1 in repeated dose studies), with no obvious major gender-related differences. Most of the systemic exposure was accounted for by AUX-II (93-100%, based on actual or estimated area under the concentration time profile curve (AUC) values; peak plasma concentration (C_{max}) values, 2 to 25 fold higher) following AA4500 administration; AUX-I exposure levels were generally too low for determination of kinetic parameters. For both AUX-I and AUX-II, half life ($T_{1/2}$ values were very low (about 0.1 h to 0.5 h) and consequently cleared rapidly from the systemic circulation (between 50-5000 U/dose, AUX-I levels were below the limit of quantitation (BLQ) at ≤ 0.5h and AUX-II levels were BLQ at ≤ 2h. Determination of exposure following repeated IV dosing was assessed in studies DLB00006 and LAB 1007-1671 (both were 16 Day rat IV repeat dose toxicity studies), following the last dose (Day 15 and/or 16). AUX-I was not detected in any samples. AUX-II results were generally different in males and females in both studies. In Study DLB00006, there were clear sex differences (particularly at lower doses), no dose proportionality for C_{max} and AUC, there was accumulation of AUX-II and a delay observed in the time to peak plasma concentration (T_{max}). However, for study LAB 1007-1671, there were no gender differences and there were dose-proportional increases in C_{max} still observed; C_{max} and AUC values for AUX-II were less compared to Day 1 values. The different findings in the two studies were proposed to be due to differences in the actual AUX-II detection methods used in the two studies, combined with likely interference by the generated anti-AUX-II antibodies. Interference in the sandwich enzyme-linked immunosorbent assay (ELISA) methods would result in artefactual lowering of plasma levels, whereas interference in the radioimmunoprecipitation assay would result in artefactually increased plasma levels. Except in study DLB00006, exposure to AUX-I or AUX-II (C_{max}, AUC or animals with detectable levels) decreased with time although $T_{1/2,}$ clearance or Vss did not. This indicates that decreases in exposure did not result from changes in distribution or induction of additional clearance pathways. In addition, in Study LAB 1007-1671 there was no major alteration in these parameters ($T_{1/2}$, clearance, Vss), when comparing antibody naive animals (on Day 1) with identically treated antibody positive animals (on Day 7) indicating that antibody formation does not significantly affect systemic exposure to IV administered AA4500. Given the proposed route of dosing (local injections) in the clinical setting and that AA4500 does not require systemic exposure for its pharmacologic activity; these findings are not of clinical relevance.

SC local injection

Determination of exposure following dosing by the clinically relevant route (local injections) was assessed following:

i. single or repeat dose local (SC or intrapenile) injections in dogs [study TRL 520 (intrapenile) and study WIL-6969006 (deep SC injection into the peridigital flexor tendon fascia/connective tissue)] and

ii. repeat local SC injections in rats (study WIL-696003; SC injection into the metatarsal-phalangeal area of the hindlimb).

Following local SC injections there was generally minimal/no systemic exposure to AUX-I and AUX-II, especially following injections into dense fibrous connective tissue structures (tunica albuginea of the penis) or into looser connective tissue (subcutaneous tissue of the rat or dog paw). SC injection into the highly vascular corpus cavernosum (that is, a tissue allowing direct access to the systemic circulation) resulted in limited exposure in the systemic circulation and very low plasma levels (≤40 ng/mL) which disappeared very rapidly (that is, seen at ≤ 0.5 h).

Metabolism

Published reports describing mechanisms of collagenase inactivation and clearance in humans and animal species were provided. The AA4500 clearance mechanism involves an interaction with alpha-2-macroglobulin, a serum protein which acts as a substrate/inhibitor for various proteases including endogenous collagenolytic matrix metalloproteinases (MMPs). Rapid inactivation of AA4500 components by human plasma was confirmed in sponsor submitted studies. Based on literature reports, the sponsor proposes that the inactivation of AA4500 results from complex formation with α-2-macroglobulin (either secreted locally or derived from the serum) followed by rapid removal of the complexes by fixed tissue phagocytes at the injection site, liver and/or spleen.

No metabolism studies have been performed with AA4500. AA4500 is not a substrate for cytochrome P450 or other drug metabolizing enzyme pathways and so active metabolites are not likely to be produced and species differences in metabolism are not expected. No other metabolism, distribution and excretion studies were performed in nonclinical species due to limited systemic exposure in animals and humans following local administration (at the clinical dose in patients with advanced Dupuytren's disease; clinical Studies DUPY 202 and AUX-CC-855). This suggests that AA4500 remains confined to the tissues near the injection site and/or is rapidly degraded before or as it enters the systemic circulation.

Pharmacokinetic drug interactions

No pharmacokinetic drug interaction studies were performed. The sponsor proposes that AA4500 is not a substrate for cytochrome P450 or other drug metabolising enzyme pathways and therefore interactions with other drugs by competition for metabolism, induction or inhibition of cytochrome P450-mediated metabolism is unlikely to occur in the clinical setting. Additionally, since no systemic exposure results from local administration, it is unlikely that there will be competition for protein binding sites and/or clearance of other protein therapeutics by receptor-mediated endocytotic pathways.

Formation of Anti-AUX-I and Anti-AUX-II antibodies

As an exogenous protein given by local injection, anti-drug antibody (ADA) responses to AA4500 were expected to occur in the majority of treated animals. To determine the effects of anti-AA4500 antibody formation on toxicokinetic parameters [antibodies have the potential to alter the pharmacokinetic profiles of AA4500 components (AUX-I and AUX-II)], the time course of onset and/or reversibility and magnitude of antibody responses were evaluated in all GLP toxicology studies in which toxicokinetic assessment was performed [except in Study DLB00009 (IV embryo-fetal developmental study in rats)]. Repeated dose injections to rats or dogs (IV, SC paw or intrapenile injections) produced high and persistent anti-drug antibody (ADA) titres against either AUX-I or AUX-II in nearly all AA4500 treated animals. Significant levels of ADA titres were seen as early as after 7 days after the first dose (Study LAB-1671). Positive responses (measurable antibody titres) were seen after as few as 2-3 doses following either IV or local administration in rats or dogs. Antibody titres persisted or increased in magnitude during the recovery periods in all studies. There was no evidence for any antibody mediated adverse effects or effects on the pharmacodynamic activity in any of the nonclinical studies. Thus, ADAs did not alter the efficacy or collagenolytic activity of AA4500 and did not produce any adverse clinical signs or toxicity in the nonclinical studies of clinical relevance. In particular, there were no events of systemic anaphylaxis, hyperpyrexia, respiratory distress or circulatory failure. Moreover, given that AA4500 acts at the site of injection following local administration, it is likely that circulating neutralizing ADAs might not be able to influence the pharmacodynamic activity/efficacy of AA4500.

ADA titres for AUX-I were slightly higher than those for AUX-II in the rat IV studies, with only a slight dose-response relationship observed at the two lowest doses (50-150 U/dose), with minor sex differences occasionally observed. Following local administration of AA4500 (SC paw or intrapenile injections) to either rats or dogs, there were no marked differences between anti-AUX-I and anti-AUX-II titre levels, or sex differences or time- or dose-related responses in antibody production.

Antibodies in vehicle-treated animals (controls)

In both dog studies (WIL-696006: SC paw injection; TRL 520: intrapenile injection), ADAs for either anti-AUX-I or anti-AUX-II were detected in i) vehicle-treated groups or ii) in animals to be dosed in some pre-dosing samples. However, these ADAs represented only low titres (many orders of magnitude lower than treated animals) and often detected in single animals with the same animal often being positive for both ADAs, and were also often seen with comparable magnitude and incidence in pre-dose samples from the treated animal groups. High anti-AUX-II titres were reported in a few control males in the fertility and early embryonic development study and dosing of these control animals cannot be ruled out. However, after removal of the control animals in question, the findings still support the main conclusion. Overall, the detection ADA titres in some of the controls and some pre-dosing samples are not likely to significantly affect the interpretation of the study findings.

Limitations of nonclinical studies

The nonclinical findings showed AA4500 ADAs may have:

i. limited potential to neutralize the activity of either AA4500 or

ii. its endogenous collagenase homologue [the collagenolytic Ca-Zn dependent matrix metalloproteinases (MMPs)] or

iii. that these possible effects are of no pharmacologic or likely physiological relevance.

The sponsor proposed that the potential of the ADAs to neutralize AUX-I or AUX-II (and possibly contribute to decreased systemic exposure of AA4500 with repeated IV dosing) was not required to be examined since systemic exposure is not a requisite for clinical efficacy and systemic exposure does not occur following local injections in the animal species or after intralesional injection in Dupuytren's patients. The closest structural and functional mammalian homologues to *Clostridium histolyticum* collagenase are a subset of MMPs, those excreted mainly within connective tissues which have activity against collagen and include MMPs - 1, -2, -3, -8, -9, -13.[9] However, there are some differences between the bacterial and the mammalian enzymes that make them both structurally and functionally distinct. Moreover, there were no findings indicative of systemic MMP inhibition (bone and joint changes, decreased fertility, abnormal placentation and/or developmental anomalies) in any of the nonclinical studies. However, unresolved issues of immunogenicity still exist with respect to the neutralising potential of ADAs and the potential cross-reactivity to endogenous homologues such as MMPs. These issues were not specifically examined in the nonclinical studies and should be addressed by the clinical evaluator to determine the relevance (if it exists) and potential relevant clinical effects. This is important as

i. the results of animal studies on ADA induction may not necessarily be predictive for possible effects of toxicological concern in the clinical setting

ii. long-term safety data after repeated administration are lacking and

[9] Somerville RP *et al.* (2003) Matrix metalloproteinases: old dogs with new tricks. *Genome Biology* **4**, 216-216.

iii. potential long-term effects on MMPs due to potential cross-reactivity in humans should be assessed.

Furthermore, bacterial proteins can provoke both immediate (immunoglobulin E (IgE) mediated) and delayed (immunoglobulin G (IgG) mediated) type hypersensitivity responses following parenteral administration and host ADA responses to foreign proteins can be persistent and subjects may be sensitized by previous exposure to microbial organisms.

Toxicology

Acute toxicity

Non-GLP single dose and acute toxicity studies were conducted in mice (IM and IP routes) and rats [IV (slow bolus) dose range finding studies for reproductive and developmental toxicity studies]. The clinical route [that is, SC or intralesional] was not used. Only males were used in the mouse studies and only females were used in the rat IV studies but this is not considered to be a significant deficiency. Adverse clinical signs associated with deaths were piloerection, hyperpnoea and lacrimation with evidence of haemorrhage into body cavities (pleural and/or peritoneal spaces). Mortality was seen at lower doses in mice (IM and IP dosing) suggesting there is a greater effect of collagenase on internal organs and tissues following dosing by IM and IP routes leading to toxicity and lethality (probably due to direct local irritation of visceral organs) compared with the rapid plasma inactivation and degradation of collagenase following IV dosing in rats. The finding of mortality by dosing by the IP route is therefore not considered relevant for the assessment of potential risks associated with either the clinical use or inadvertent mis-dosing of AA4500 in humans. Maximum non-lethal doses were 20 U/dose IP [5 times and 0.4 times the human equivalent dose (HED) on a body weight (U/kg) and surface area (U/m^2) basis, respectively] and 320 U/dose IM [75 times and 6 times the HED on a body weight (U/kg) and surface area (U/m^2) basis, respectively] for mice and 5000 U/dose IV [140 times and 25 times the HED on a body weight (U/kg) and surface area (U/m^2) basis, respectively] for rats, indicating potentially high acute toxicity by the IP route and moderate toxicity by the IM and IV routes. See also Table 2 below: minimal lethal dose was 10,000 U/dose in rats (IV) [180 times and 50 times the HED on a body weight (U/kg) and surface area U/m^2 basis, respectively]. The weight of evidence suggests that the findings from the rat IV studies indicates little concern for safety in the clinical setting, even in the unlikely event of inadvertent IV dosing of a full clinical dose (0.58 mg protein, or 10,000 U) to humans. Systemic toxicity is not anticipated under conditions of clinical use in the event that AA4500 is inadvertently given systemically during treatment of Dupuytren's disease in view of the lack of significant systemic absorption in humans during clinical trials with AA4500 (DUPY 202 and AUX-CC-855), and adequate safety margins of 14 and 2.5 fold the clinical dose on a body mass (U/kg) basis or surface area basis (U/m^2) (see *Repeated-Dose IV Studies In Rats below*).

Repeat-dose toxicity

Pivotal GLP local toxicity and intravenous (IV) studies were performed to characterise the injection site and systemic toxicity of AA4500 (*Clostridium histolyticum* collagenase; Xiaflex®) and included single and repeat-dose studies by a clinically relevant route in rats and dogs (SC injection into the paw; up to 3 months duration) and repeat-dose IV administration in rats (16 days duration). Since systemic exposure to AA4500 was not detected following local dosing (injections) in clinical studies or in animal species, repeat dose toxicity studies were also performed by IV dosing to rats to ensure adequate systemic exposure to assess AA4500's potential for systemic toxicity. Dosing in the repeated-dose studies was intermittent, ranging from every 48 hours in the rat IV studies, every 14 days (seven doses total) in the 13 week rat SC study (WIL-696003) to once monthly in the 13 Week dog SC study (WIL-696006).

The rat and dog are an appropriate nonclinical species for the safety assessment of AA4500 since:

i. AA4500 is a combination of two of bacterial collagenases, both are pharmacologically active as well as immunogenic in humans, rats and dogs

ii. rat and dog are conventional rodent and non-rodent species for toxicity studies and

iii. anatomic structures of the rat and dog paw are analogous to those in the human hand.

All pivotal toxicity studies used AA4500 'Process *3*' material and were conducted in accordance with GLP. The duration of the pivotal studies, the species used and group sizes were consistent with ICH guidelines. These studies demonstrated that Xiaflex has very limited or non-quantifiable systemic exposure and no clinically relevant systemic toxicity following IV (bolus), SC injection (into the paw in rats and dogs) or intrapenile injections in dogs (62 days, dosing 3 times/week, every 4 weeks). The AA4500-induced reactions were confined locally to the injection site and animals recovered partially to completely following a non-dosing recovery period.

Relative exposure

For the purpose of comparing doses across species and to the clinical dose (to determine safety margins), doses expressed on a body surface area (BSA) basis were considered the most appropriate. In most of the toxicology studies (with the exception of TRL 520), animal doses were administered as a fixed quantity of AA4500 per animal as opposed to doses scaled by weight or body surface area. Scaled doses in most cases are thus only approximations. For conversion of doses to U/kg and U/m^2, mice were assumed to weigh 0.025 kg, rats 0.25 kg and dogs 10 kg (note: in Study TRL 520, doses were administered on a U/kg basis, so the U/dose values are approximations). The intended clinical dose of AA4500 is 10,000 U or 0.58 mg protein. For ease of comparison across species, the animal equivalent doses derived from the body surface area-scaled human equivalent dose (HED) for the species used in the toxicology studies are shown below in Table 1. Conversions are based on allometric scaling across species on a body surface area (BSA) basis, with human equivalent doses of 5565 U/m^2 or 0.323 mg protein/m^2 (based on a hypothetical 70 kg human, BSA = 1.797 m^2).

For reference, the doses actually used in each toxicology study are converted to units (U) as mg protein/kg or mg protein/dose and U/m^2 or mg protein/m^2 or U/kg equivalents.

Table 1. Body Surface Area-Scaled Human Equivalent Doses (HED) to Clinical Dose of AA4500 in Toxicology Species

Species	Body Weight (kg)	Body Surface Area (m^2)	Human Equivalent Dose Expressed As			
			Total Dose in:		Dose/kg in:	
			Units	mg protein	Units	mg protein
Human	70.00	1.797	10000	0.580	143	0.0083
Mouse	0.03	0.009	50	0.003	1724	0.1000
Rat	0.25	0.036	200	0.012	759	0.0440
Guinea Pig	1.00	0.089	496	0.029	483	0.0280
Rabbit	2.00	0.159	885	0.051	440	0.0255
Dog	8.00	0.412	2294	0.133	1690	0.0980
Yucatan Minipig	40.00	1.175	6543	0.380	164	0.0095
Göttingen Minipig	8.50	0.416	2304	0.134	272	0.0158

Limited and/or no quantifiable systemic exposure was noted in the repeated dose local toxicity studies by the clinically relevant route of exposure following SC injection in rats or dogs as well as in the repeat-dose intra-penile toxicity study in dogs. Similarly, there was limited systemic exposure in the human clinical studies following local administration (at the clinical dose in patients with advanced Dupuytren's disease; clinical studies DUPY 202 and AUX-CC-855). Therefore relative exposure calculations based on plasma concentration data were not possible.

Major toxicities

AA4500 local SC dosing studies

A number of single dose local toxicity studies with SC injection into the hindlimb of rats or SC and intratendon (IT) injection into the forelimb of dogs revealed local AA4500 adverse treatment related findings at the injection site and the draining lymph node with comparable findings between sexes and the nonclinical species. Findings of mostly swelling and discoloration of the limb (for both the injection site and the draining lymph node) were consistently seen with haemorrhage, oedema, inflammation, collagen lysis and fibroplasia/neovascularization, arterial intramural haemorrhage, and sinus erythrocytosis in lymph nodes on histolopathological assessment. The lymph node findings were secondary to the treatment-related injection site alterations. However, there were no significant findings in adjacent nerve bundles or blood vessels. Following injections at the highest doses into rat or dog paws, some of the clinical findings extended beyond the initial site of application.

At the end of a non-dosing recovery period, there was partial reversal (with evidence of ongoing reversal) to complete reversal of all histolopathological findings. The findings in the single dose studies in rats and dogs were consistent with those reported in the repeat-dose studies.

Rat

In a local single dose SC toxicity study in rats (Study WIL 696001), the effects of AA4500 administration into the paw were examined at 258 U/dose [≥ 7 times the human equivalent dose (HED) on a U/kg basis (1.3 times on U/m^2 basis)], 517 U/dose [at ≥15 times the HED on U/kg basis (2.6 times on U/m^2 basis], 1034 U/dose [at ≥ 29 times the HED on U/kg basis (5 times on a U/m^2 basis)] and 2586 U/dose [at 73 times the HED on U/kg basis (13 times on U/m^2 basis]). Local tissue injection site reactions (including hindlimb swelling and purple discoloration) were seen in both males and females with inflammation at all doses. There were findings of an extension of the injection site inflammation to the periosteum of the metatarsal bones at 1034 U/dose at ≥ 29 times the HED on U/kg basis (5 times on a U/m^2 basis)] and severe skin lacerations (with exposed tendons) resulting in the early sacrifice of three animals at the highest dose level of 2586 U/dose [at 73 times the HED on U/kg basis (13 times on U/m^2 basis)]. All treatment related findings reversed completely or partially with ongoing healing by the end of a 4 week non-dosing recovery period.

Similar local injection site findings and no systemic toxicity were observed following repeated SC injections over a 3 month period (dosing every 14 days; seven doses total) into rat paws (study WIL-696003), with peripheral nerves and arteries unaffected at up to 776 U/dose (22 times and 3.9 times the HED on U/kg and U/m^2 basis). In this repeated-dose study, there was no evidence of an inflammatory response in the periosteum of the metatarsal bones or any severe skin lacerations (with exposed tendons). Moreover, any adverse treatment-related clinical findings usually resolved prior to the next cycle of treatment. Local effects of injected AA4500 did not tend to increase as a function of dose.

Dog

In a local single dose SC toxicity study in dogs (Study WIL-696005) the local injection site findings following either intratendon injection (IT) in the superficial digital flexor tendon of the right forelimb at ≥ 1293 U/dose [≥ 0.9 times HED on U/kg basis (≥ 0.56 times on U/m^2)] or deep

subcutaneous injection in the metacarpal area of the palmar surface of the right forelimb at ≥ 2586 U/dose [≥ 1.8 times HED on U/kg basis (≥ 1.1x on U/m^2)] were comparable with the results observed in the local toxicity studies in rats (see above). Following repeated deep SC injections of AA4500 into the peri-digital flexor tendon fascia/connective tissue area in dogs [once monthly for 3 months (total of 4 doses); Study WIL-696006], the AA4500-induced adverse findings were limited to the site of injection with no evidence of systemic toxicity at doses of up to 6466 U/dose [4.6 times and 2.6 times the HED on a body weight and surface area basis, respectively]. Remarkable clinical signs were swelling, reddening and purplish discoloration of the paw; most were significant after the first dose (starting at 1-2 hours post dose) and less severe and resolved more rapidly following each subsequent dose. Findings at the histopathological assessment at the injection site were comparable to findings in the repeat dose toxicity studies in rats. Interstitial collagen lysis in the deep subcutis was observed affecting loose collagen fibers of the subcutaneous tissue and the walls of small venules composed predominantly of collagen (described as vascular necrosis). Following a dosing free period of recovery, clinical signs or injection site findings reversed completely or partially with ongoing healing process indicative of ongoing recovery.

Overall findings following SC local AA4500 dosing studies

Adverse findings observed following single or repeated doses by the clinical route of injection (SC) into the paw of rats or dogs in the non-clinical studies were restricted to local findings at the site of injection. The findings in the single dose studies in rats and dogs were consistent with those reported in the repeat-dose studies of AA4500 and were consistent with the profile of adverse effects noted in the clinical studies. The clinical observations were usually less severe and resolved more rapidly following repeated administration in dogs compared to rats. All adverse findings were reversible or showed evidence of ongoing resolution and healing following a recovery period without treatment or dosing. Importantly, no systemic toxicity and limited and/or no quantifiable systemic exposure was noted in the repeated dose local administration studies by a clinically relevant route of exposure following SC injection in rats or dogs. There were consistent local toxicity findings in all the nonclinical species (rat and dog) following local SC or intrapenile administration (see below). These included, swelling and discoloration (injection site and the draining lymph node) with haemorrhage, oedema, inflammation, collagen lysis and fibroplasia/neovascularisation, arterial intramural haemorrhage and sinus erythrocytosis in lymph nodes with no effects on adjacent nerve bundles and blood vessels [although in the 13 Week SC study in dogs (study WIL-696006) there was lysis of collagen (described as vascular necrosis) of small venules composed predominantly of collagen]. Local effects of injected AA4500 did not tend to increase as a function of dose. Additionally, there was no damage to elastic tissue elements (elastic fibers) and no significant lysis of the basement membrane of blood vessels or the perineurium and endoneurium of peripheral nerves following repeated SC doses of AA4500, consistent with the mechanism of action. Moreover, there was no evidence of systemic toxicity after local administration including SC, intrapenile, IM, and intratendon (IT) injections. However, there was no clear No Observable Adverse Effect Level (NOAEL) noted in the local toxicology studies as the collagenase enzymes produced the predicted pharmacodynamic effects.

Following direct injection of AA4500 into superficial digital flexor tendon of the paw of dogs or other dense collagenous structures (tunica albuginea; see below), the reported adverse findings were considerably less with more complete recovery compared with the SC injection injections into the rat and dog paw or application into the looser fibrous connective tissue structures (corpus cavernosum, urethra, and VAN complex) of the dog penis (see below).

AA4500 local dosing studies by intrapenile routes - dog penis

Further support for the lack of systemic toxicity and limited systemic exposure was provided by the results of the repeat dose intra-penile toxicity study in dogs (Study TRL 520). This local toxicity study was conducted after injection of AA4500 into the dog penis in support of safety

for use in Peyronie's disease. The purpose was to evaluate the local and systemic toxicity elicited by the injection of AA4500 into various anatomic locations of the dog penis that is representative of both the intended and potential inadvertent sites of administration under clinical use in the treatment of Peyronie's disease. Since the study examined effects on similar tissues to those potentially exposed following treatment of Dupuytren's contracture (that is, subcutaneous connective tissue, blood vessels, nerves and skin) and was performed with the same AA4500 formulation proposed for clinical use, this study is considered relevant to the evaluation of potential adverse local effects of AA4500 for the current proposed indication. The potential systemic toxicity following injection into the tunica albuginea (the most relevant site of clinical administration in Peyronie's disease) was examined, as well as defining the magnitude of collagen lysis that may occur following repeated AA4500 injection to determine if structural weakness resulting in penile fracture could result from treatment.

In addition, other anatomical sites were also studied to determine the effects of single high doses on sites of inadvertent administration including the corpus cavernosum, urethra, and subcutaneous tissue adjacent to the main vein, artery and nerve of the penis (referred to as the VAN complex in the study). This was to determine the potential for AA4500 treatment to result in erectile dysfunction or difficulty in urination as a result of treatment. Similar findings to those following SC injection studies into the paw of rats or dogs (see previous section) were reported following repeat dose intrapenile injection into dogs, with injection site inflammation occurring with single and multiple dosing. As mentioned above, injection of AA4500 into superficial digital flexor tendon of the paw of dogs (see above) or other dense collagenous structures such as the tunica albuginea, the adverse findings were considerably less, with more complete recovery compared with the SC injection injections into the rat and dog paw or application into the looser fibrous connective tissue structures of the dog penis (corpus cavernosum, urethra and VAN complex). Additionally, all adverse findings were reversible or showed evidence of ongoing resolution and healing following a recovery period without treatment or dosing.

Repeated-dose IV studies in rats

In two repeat-dose IV (bolus) studies in rats (Studies DLB00006 and 1007-1671), AA4500 did not induce systemic toxicity at ≤ 500 U/animal (NOAEL: 2.5 times HED, based on U/m^2; 14 times HED, based on U/kg) and only resulted in local injection site findings of clinical signs of blue, red, and/or dark discoloration and/or wounds. At the higher doses, repeat IV administration at ≥ 2240 U/animal (11 times HED, based on U/m^2) resulted in dose-dependent liver findings (serum enzymes, organ weights, gross/histopathology alterations of haematoma, fibrosis, and focal necrosis) with partial reversal and evidence of ongoing healing by the end of the 14 day recovery period. There were also injection site findings of minimal to mild chronic inflammation and perivascular haemorrhage/oedema. Following the recovery period, there was partial reversal and evidence of ongoing healing. At the highest doses (5000 U/animal, 25 times HED, based on U/m^2), mortality was observed, probably related to the adverse findings on hepatic function.

Based on findings in the rat IV studies at ≥ 2240 U/animal (≥ 11 times HED based on U/m^2 or ≥ 63 times based on U/kg) systemic toxicity would likely involve liver findings. On balance, potential systemic toxicity resulting from inadvertent systemic exposure in humans (for example by injection of a partial or full clinical dose into a local vein and/or artery surrounding the Dupuytren's cord, considered worst case) is unlikely to occur in the clinical setting in view of the lack of significant systemic absorption and adequate safety margins of 14 and 2.5 fold the clinical dose on a body mass (U/kg) basis or surface area basis (U/m^2).

Table 2. Summary of Estimated Safety Margins for Inadvertent IV Exposure in Humans Based on Rat Data

Effect	[a] Rat Dose Level/Exposure			[b] HED/ Predicted Human Exposure based on	
	U/dose	U/kg	U/m²	U/kg	U/m²
Minimal lethal dose	10000	40000	280000	180	50
Systemic LOEL *Liver findings*	2240	8960	62720	63	11
Systemic NOEL	500	2000	14000	14	2.5

(a): U/kg and U/m² estimated based on 0.25 kg body weight and 0.036 m².
(b): HED = human equivalent dose, based on a total human dose of 10,000 U (0.58 mg), an average body weight of 70 kg and body surface area of 1.797 m². The respective exposures on a bodyweight and surface area basis were 143 U/kg or 5565 U/m².

Table 3. Systemic Effects of IV-Administered AA4500 and Margins over the Clinical Dose in Rats*

Study Number	Effect	[a] Dose Level/Exposure:			[b] HED/Exposure based on:		
		U/dose	U/kg	U/m²	U/ dose	U/kg	U/m²
DLB00014	Minimum lethal dose	10,000	40,000	280,000	1.0X	280X	50X
DLB00006	NOEL (injection site)	150	600	4167	0.015 X	4.2X	0.7X
	NOEL (systemic toxicity)	500	2000	13,889	0.05X	14.0X	2.5X
LAB 1007-1671	NOEL (systemic)	500	2000	13,889	0.05X	14.0X	2.5X
	NOAEL (injection site)	500	2000	13,889	0.05X	14.0X	2.5X
	Liver findings (histology)	2240	8960	62,222	0.224 X	62.7X	11.2X
	Deaths (associated w. haemorrhage)	5000	20,000	138,889	0.5X	139.9 X	25.0X
	Liver findings (serum enzymes, organ weights, gross/histopathology)	5000	20,000	138,889	0.5X	139.9 X	25.0X

Study Number	Effect	[a] Dose Level/Exposure:			[b] HED/Exposure based on:		
		U/dose	U/kg	U/m²	U/ dose	U/kg	U/m²
	Regenerative anaemia	5000	20,000	138,889	0.5X	139.9 X	25.0X

(*) Source: sponsor's Toxicology Written Summary
(a): U/kg and U/m² estimated based on 0.25 kg body weight.
(b): HED: human equivalent dose, based on human dose of 10,000 U correlating to 143 U/kg or 5565 U/m².

Table 4. Systemic Effects of IV-Administered AA4500 and Margins over the Clinical Dose in Rats *

Study Number	Effect	[a]Dose Level/Exposure:			[b] HED/ Exposure based on:		
		U/dose	U/kg	U/m²	U/dose	U/kg	U/m²
DLB00012	NOEL (male or female fertility, early embryonic development)	2240	8960	62,222	0.224X	62.7X	11.2X
	NOAEL (weight loss)	750	3000	20,833	0.075X	21.0X	3.7X
	NOAEL (injection site)	250	1000	6944	0.025X	7.0X	1.2X
DLB00009	NOEL (developmental toxicity)	2240	8960	62,222	0.224X	62.7X	11.2X
	NOAEL (injection site)	2240	8960	62,222	0.224X	62.7X	11.2X

(*) Source: sponsor's Toxicology Written Summary
(a): U/kg and U/m² estimated based on 0.25 kg body weight.
(b): HED: human equivalent dose, based on human dose of 10,000 U correlating to 143 U/kg or 5565 U/m².

Genotoxicity

A number of genetic toxicology tests were submitted including a bacterial reverse mutation assay, a chromosomal aberration test in human lymphocytes and a micronucleus test in mice. This battery of mutagenicity studies indicated there was no mutagenicity with the '*early BTC Collagenase*' batches of AA4500 manufactured by the BTC process (although results of these tests could reflect process impurities that could be mutagenic). However, the final Collagenase *Clostridium histolyticum* AA4500 drug product for clinical use, produced with the final manufacturing process (AA4500 '*Process 3*' material) has not been examined for genotoxic potential. As large proteins do not cross cell membranes further genetic toxicology tests are not typically required according to the ICH guideline (ICH S6) on the '*Nonclinical safety evaluation of biotechnology-derived pharmaceuticals*'. [3]

Carcinogenicity

No carcinogenicity studies were conducted. This was considered to be acceptable given

i. the nature of the drug according to the ICH guideline (ICH S6) on the '*Nonclinical safety evaluation of biotechnology-derived pharmaceuticals*' (that is, AA4500 does not show any particular biological activity, has no known growth factor activity and does not target any critical receptor type or specific immunological mechanism)

ii. it lacks systemic exposure in humans and animals and

iii. its short term (intermittent) frequency of use (up to 3 injections in any Dupuytren's cord; its clinical use is not considered chronic).

Reproductive toxicity

AA4500 is not for chronic use and there is limited/non-quantifiable systemic exposure in humans and in the nonclinical animal species following dosing by the clinical route (intralesional or SC dosing, respectively). Therefore reproductive toxicity studies would not typically be required on the basis of its intermittent use. However, a non-standard set of GLP compliant reproductive toxicity studies were submitted utilizing the IV dosing route in rats to ensure adequate systemic exposure. These studies examined

i. both male and female fertility and early embryonic development in study DLB00012 and

ii. embryofetal toxicity in study DLB00009 (rat only).

No pre/postnatal development study was undertaken. Adequate animal numbers and dose levels were used during appropriate gestational periods. The final Collagenase *Clostridium histolyticum* AA4500 drug product for clinical use produced with the final manufacturing process (AA4500 '*Process 3*' material) was used. Antibody responses were also evaluated and characterised in all sponsor conducted GLP toxicology studies (with the exception of study DLB00009, an IV embryo-fetal developmental study in rats). Anti-drug antibody (ADA) formation against AUX-I and AUX-II was also determined, to evaluate any potential effects resulting in adverse effects on

i. male and female fertility in rats and

ii. embryofetal development resulting from their generation.

Relative exposure

Toxicokinetic analyses were performed in the pivotal reproductive toxicity studies with systemic exposure to AA4500 also being limited and/or non-quantifiable. Therefore relative exposure calculations were not possible. In Study DLB00012, IV dosing of AA4500 to male and female rats every other day starting before cohabitation, through mating and implantation, resulted in detectable plasma levels of its two components AUX-I (up to 1 h post dosing) and AUX-II (up to 2 h post dose) on the first day of dosing. No samples contained detectable AUX-I and only two samples contained detectable AUX-II levels on either Study Day 55 or Gestational Day (GD) 7. The half-life of AUX-II was short (about 0.5 h) indicating rapid elimination from plasma. C_{max} of AUX-I and AUX-II were lower in female rats compared to male rats. In Study DLB00009, AUX-I and/or AUX-II were only measurable on GD7 (not detected on GD17) with AUX-I levels detected in females receiving 750 and 2240 U/day (mid- and high doses, respectively) at 0.5 h; AUX-II levels on GD7 were detected in rats at 250 U/day (low dose) at 0.5 h only, and up to 2 h in rats at ≥ 750 U/day (mid and high doses). AUX-II represented most (93.6% -100%) of the exposure.

There were no adverse findings in both

i. a fertility/early embryonic development study and

ii. an embryo-fetal development study.

The findings show that AA4500 treatment did not result in any reproductive toxicity with no deleterious effect on fertility in male and female rats, with no effect on the development of rat embryos or fetuses. There was no indication that AA4500 was teratogenic. In the rat studies, the main findings in males and females were clinical signs at the injection site (swelling and/or purple discoloration) at the higher doses.

See Table 5 below for the systemic effects of IV administered AA4500 to rats and margins over the clinical dose. There were no treatment related effects of on mating and fertility indices and no effects on sperm parameters, oestrus cycle or uterine parameters.

Table 5. Systemic Effects of IV-Administered AA4500 and Margins Over the Clinical Dose in Rats *

Study Number	Effect	[a]Dose Level/Exposure:			[b] HED/Exposure based on:		
		U/ dose	U/kg	U/m²	U/dose	U/kg	U/m²
DLB00012	NOEL (male or female fertility, early embryonic development)	2240	8960	62,222	0.224X	62.7X	11.2X
	NOAEL (weight loss)	750	3000	20,833	0.075X	21.0X	3.7X
	NOAEL (injection site)	250	1000	6944	0.025X	7.0X	1.2X
DLB00009	NOEL (developmental toxicity)	2240	8960	62,222	0.224X	62.7X	11.2X
	NOAEL (injection site)	2240	8960	62,222	0.224X	62.7X	11.2X

(*) Source: sponsor's Toxicology Written Summary
(a): U/kg and U/m2 estimated based on 0.25 kg body weight.
(b): HED: human equivalent dose based on human dose of 10,000 U correlating to 143 U/kg or 5565 U/m2.

Parturition or prenatal and postnatal development studies were not performed due to the lack of systemic exposure and limited and/or non-quantifiable systemic exposure in humans in the clinical setting and in the animal species following dosing by the clinical route (intralesional or SC dosing, respectively). No second species was used for the studies on embryofetal development. Since there is no particular regulatory guidance for reproductive toxicity assessment for drug products such as AA4500 having limited and/or non quantifiable systemic exposure and showing no systemic toxicity, this was considered acceptable. Similarly, although antibody responses were not evaluated in Study DLB00009 (an IV embryo-fetal developmental study in rats), this is acceptable, since the majority of rats which were given AA4500 by IV injections developed antibodies and AA4500 antibodies were very likely to have been present in the plasma of rats in the embryo-fetal developmental study. It is reasonable to conclude that embryo-fetal developmental in rats did not appear to have been impaired by the likely presence of anti- AUX-1 and AUX-2 antibodies.

No studies were performed to determine whether placental transfer or excretion in milk of AA4500 occurred in animals.

Pregnancy classification

The sponsor has proposed Pregnancy Category B. This category is appropriate but should be more specifically categorised as B1, that is, "*Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage*."

Local tolerance

Sponsor submitted single dose GLP local tolerability studies used mostly the AA4500 '*Process 3'* material for final clinical use (unless otherwise indicated) and were performed by SC (plantar) injection in Sprague-Dawley rats (Study WIL-696001); deep SC (in the metacarpal area of the palmar surface of the right forelimb) or intratendon injection (IT) in the superficial digital flexor tendon of the right forelimb in dogs (Study WIL-696005); intrapenile injections in dogs (Study TRL 520) and SC (inguinal fat pad) injection in Zucker rats [(Study Pharmaco 95-2384; using *'early BTC Process'* batch (*AA4500)].* In addition, non GLP local tolerance studies were conducted by intracutaneous (intradermal) injection in guinea pigs [Study SS-004; using *'early BTC Process'* batches (*AA4500)]* and SC injection in Göttingen minipigs (Study WIL-696007; using AA4500 '*Process 3'* material for final clinical use). These studies revealed a similar profile of findings to those reported in the pivotal repeated-dose toxicity studies with AA4500 dosing by a clinically relevant route in rats and dogs (with SC injection into the paw, of up to 3 months duration; see *Assessment, Toxicity - Repeat-dose toxicity/Major toxicities*).

Sensitisation

Bacterial proteins may provoke both immediate (IgE-mediated) and delayed (IgG-mediated) type hypersensitivity reactions following parenteral administration. In the nonclinical evaluation of acute anaphylaxis in guinea pig (Studies SS-005 and SS-006), repeated doses of AA4500 derived from the *'early BTC Process'* manufacturing process did not cause antigenic responses. Animals were challenged 14 days after the first immunizing dose by either IP or intracardiac routes of injection. There were no signs of immediate hypersensitivity reactions and there was no relevant treatment-related respiratory distress or systemic toxicity following any given dose. Transient hyperaemia of the ears was noted in all animals dosed with AA4500 as well as transient hyperventilation and hyperactivity noted in one female and three males given AA4500, as well as in one vehicle treated animal (gender unspecified).

Impurities

The genetic toxicology tests undertaken with the '*early BTC process'* material (drug substance that contained impurities) were negative, thereby qualifying the impurities. Additional genotoxicity tests were not warranted for the more pure AA4500 used clinically.

Paediatric use

Dupuytren's contracture is rare in patients under 18 years of age. Therefore studies in juvenile were not undertaken. The Product Information notes that the safety and effectiveness of Xiaflex in paediatric patients less than 18 years old has not been investigated or established.

Nonclinical summary and conclusions

- The nonclinical submission consisted of well designed and documented studies that were conducted in compliance with GLP requirements when required, and generally conformed to the relevant ICH guidelines. All pivotal toxicity studies used the final AA4500 '*Process 3*' material for clinical use. The submission relied in part on published literature reports.
- Local injection site toxicity or the potential toxicity that might result from inadvertent systemic exposure in humans (for example by injection into a vein, considered worst case) was determined in pivotal local SC, intrapenile toxicity or IV repeat dose toxicity studies, respectively. These included single/repeat dose toxicity studies using the clinically relevant route in rats or dogs (SC injection into the paw) and repeat dose IV dosing studies in rats.
- There are no nonclinical animal models for Dupuytren's contracture. Studies conducted in cultured explants derived from human Dupuytren's cord and Peyronie's plaques showed that AA4500 is active in diseased tissues. Doses of 3600 U produced significant collagen lysis causing disruption of isolated Dupuytren's cords. In Peyronie's plaques and other normal human tissues, non-collagenous elements (for example blood vessels and nerves) were preserved, with no damage to adjacent tissue.
- AA4500 is administered locally by injection and systemic exposure is limited and/or non-quantifiable. Although no specific studies were undertaken, no safety pharmacology concerns have arisen from any of the nonclinical studies and there appear to be no systemic secondary pharmacodynamic effects of toxicological concern.
- Following IV bolus doses to rats, AA4500 clearance from the systemic circulation was rapid ($T_{1/2}$ was very low, about 0.1 to 0.5 h for AUX-I and AUX-II). No accumulation of either AUX-I or AUX-II was seen with frequent (every 48 h) repeated dosing. AUX-II accounted for 93-100% of the systemic exposure (based on AUC values). Similarly, local SC injections into non-vascularized tissues (for example, the metatarsal-phalangeal area of the hindlimb, or into the peridigital flexor tendon fascia/connective tissue) resulted in limited/non-quantifiable exposure in plasma of rats or dogs following single or repeated doses. Systemic clearance of involves complexation by the serum protein, alpha-2-macroglobulin followed by rapid removal of the complexes by fixed tissue phagocytes in the injection site, liver and/or spleen.
- AA4500 is a protein of bacterial origin and generation of anti-AA4500 antibodies (ADA) is expected. Repeat dose injections in rats or dogs (IV or SC paw injections) produced high and persistent ADA titres in nearly all animals, as early as after 7 days after the first dose. Following repeated doses there was no evidence for antibody mediated adverse effects or effects on collagenolytic activity, even in the presence of high antibody titres. There were no studies to determine if these antibodies have neutralizing potential or their ability to cross-react with endogenous matrix metalloproteinases (MMPs).
- There were consistent local adverse findings in all the nonclinical species (rat, dog, pig) following repeated (intermittent) local SC or intrapenile administration. These included swelling and discoloration (of the injection site and the draining lymph node) with haemorrhage, oedema, inflammation, collagen lysis and fibroplasia/neovascularization, arterial intramural haemorrhage, and sinus erythrocytosis in lymph nodes with no effects on adjacent nerve bundles and blood vessels (although there was occasional lysis of collagen and necrosis of small venules composed predominantly of collagen). Moreover, there was no evidence of systemic toxicity after local administration [including SC, intrapenile, IM, and intratendon (IT) injections].
- There was no damage to elastic tissue elements (elastic fibers) and no significant lysis of the basement membrane of blood vessels or the perineurium and endoneurium of peripheral nerves, following repeated SC doses of AA4500, consistent with the mechanism of action.

- Based on the maximum doses used in the pivotal studies, findings from rat paw SC injections indicated an exposure margin of 22 times and 3.9 times the human equivalent dose (HED) on a U/kg and U/m^2 basis, respectively. In the toxicity study in dogs, the exposure margin following deep SC local injections was 4.6 times (U/kg) and 2.6 times (U/m^2), respectively.
- In repeated IV dosing studies in rats, the liver was the target organ (with hepatic marker, organ weight and gross/histopathology alterations) with no adverse effects on the cardiovascular, respiratory, or central nervous systems. The NOAEL for systemic administration of AA4500 by the IV route was 500 U/dose, corresponding to 14 times and 2.5 times the clinical dose on a body mass (U/kg) basis or surface area basis (U/m^2), respectively.
- Reproductive and developmental toxicity studies were performed by IV dosing to rats to ensure adequate systemic exposure. Nevertheless, systemic exposure to AA4500 was still limited and/or non-quantifiable. No adverse findings were noted in either the fertility/early embryonic development study or dedicated embryo-fetal development study in rats. AA4500 is not teratogenic.
- Single dose local tolerance studies indicated a similar spectrum of findings to those seen in the pivotal repeated-dose toxicity studies in rats and dogs.
- No immediate hypersensitivity reactions were noted in guinea-pigs after challenge by IP or intracardiac routes of administration in sensitization studies.

Conclusions and recommendation

- Pivotal GLP local toxicity and intravenous (IV) studies were performed to characterise the injection site and systemic toxicity of Xiaflex. These included single and repeat-dose studies by a clinically relevant route (SC injection into the paw) in rats and dogs and repeat dose IV administration (general toxicity, reproductive and developmental toxicity studies) in rats. These studies demonstrated that Xiaflex has very limited or not quantifiable systemic exposure and no clinically relevant systemic toxicity following IV (bolus), SC injection (into the paw in rats and dogs) or intrapenile injections (in dogs). The Xiaflex induced reactions were confined locally to the injection site and animals recovered partially to completely following a non dosing recovery period.
- Hepatic toxicity and injection site perivascular inflammation and fibrosis were observed in the rat repeat IV dosing studies. However, the findings are not relevant to the clinical setting in view of the lack of significant systemic absorption and the exposure margin to the NOEL was 14 times and 2.5 times the clinical dose on a body mass (U/kg) basis or surface area basis (U/m^2).
- Xiaflex is not indicated for chronic use and there is limited systemic exposure in humans and in nonclinical animal species following dosing by the clinical route (intralesional or SC dosing, respectively). Therefore chronic toxicity, reproductive toxicity and carcinogenicity studies are not required. Moreover, as large proteins do not cross cell membranes, genotoxicity tests are also not generally required.
- Rat fertility and early embryonic development and embryo-fetal development studies were performed with IV administration of AA4500 but neither AA4500 nor anti-AUX-I and anti-AUX-II maternal antibodies had any effects on fertility, fetal survival, growth or development. As such, a pre and postnatal study was deemed not warranted as it was proposed that it would not provide meaningful information to human risk assessment. However, the potential effects of maternal anti-drug antibodies [especially on matrix metalloproteinases (MMPs)] on pre and post natal development cannot be completely ruled out due to possible species differences.

- The role of antibodies for future human risks could not be determined in nonclinical studies. Outstanding issues of immunogenicity therefore remain, particularly in regard to the neutralising potential of anti-drug antibodies (ADAs) and potential cross-reactivity to endogenous collagenase homologues such as matrix metalloproteinases (MMPs). This was not examined in the nonclinical studies and still needs to be addressed by the clinical evaluator to determine the relevance (if it exists) and potential relevant clinical effects on efficacy (pharmacodynamic activity) and safety (adverse effects). Presently, this is addressed in the draft Product Information document and the Risk Management Plan.
- There are no nonclinical objections to the registration of Xiaflex® for the proposed indication, provided the identified risks are addressed by the clinical evaluator.
- Amendments the draft Product Information 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

The clinical rationale is that after local injection with Xiaflex at the site of the Dupuyetren's cord there will be selective lysis of collagen at this injection site which will result in reduction of the finger contracture (see also *Product Background*).

Contents of the clinical dossier

The submission contained the following clinical information:

- 45 reports of bioanalytical and analytical methods including determination of anti-drug antibodies and validation reports for the assay methods.
- Two clinical pharmacology studies (AUX-CC-855, and DUPY-202) providing pharmacokinetic data and the latter also providing dose-finding data.
- Three controlled efficacy/safety studies (DUPY-303, AUX-CC-857, AUX-CC-859).
- Four uncontrolled, open label studies (DUPY-404, AUX-CC-854, AUX-CC-856, AUX-CC-858).
- Four other efficacy/safety studies (AUX-CC-851-852, AUX-CC-853, DUPY-101, AUX-CC-860)
- Three Integrated Summaries; Efficacy (tables only), Safety (tables only) and Immunogenicity.
- Four reports of postmarketing experience (February 2010 to February 2011), case report forms and literature references

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The sponsor provided statements in each clinical study report that the studies had been conducted according to Good Clinical Practice guidelines and appropriate ethical and regulatory approval.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 6 below shows the studies relating to each pharmacokinetic topic.

Table 6. Submitted Pharmacokinetic Studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK Single dose	-
	Multi-dose	-
	Bioequivalence† Single dose	-
	Multi-dose	-
	Food effect	-
PK in special populations	Target population§ Single dose	AUX-CC-855
	Multi-dose	DUPY-202
	Hepatic impairment	-
	Renal impairment	-
	Neonates/infants/children/ adolescents	-
	Elderly	-
Genetic/gender-related PK	Males versus females	-
PK interactions	-	-
Population PK analyses	Healthy Subjects	-
	Target Population	-
	Other	-

† Bioequivalence of different formulations.

§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 7 below, lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 7. Pharmacokinetic results excluded from consideration.

Study ID	Subtopic(s)	PK results excluded
DUPY-202	Urinary excretion	Urine PK results

Evaluator's overall conclusions on pharmacokinetics

After a single injection of AA4500 at a dose of 0.58 mg into the Dupuytren's cord on an affected finger and then a subsequent finger extension procedure there was no quantifiable systemic exposure.

No multiple dose pharmacokinetic study was conducted as no exposure was expected with a dosing regimen of up to one injection each four weeks. The sponsor is however conducting a multiple cord treatment study, AUX-CC-861, in which the safety, tolerability and pharmacokinetics will be assessed when two different cords are treated at the same time.

Pharmacodynamics

Studies providing pharmacodynamic data

There is no reported systemic exposure and no specific clinical pharmacodynamic studies were conducted. The sponsor states the primary pharmacodynamic activity data were obtained from *in vitro* studies using exised Dupuytren's cords and Peyronie's plaques.

Evaluator's overall conclusions on pharmacodynamics

As there is no reported systemic exposure no specific clinical pharmacodynamic studies were conducted. The pharmacodynamics of AA4500 has been assessed in the nonclinical program. The activity of AA4500 collagenases is via the hydrolysis of collagen at the injection site. Collagen fragments generated by this lysis are reported to have bradykinin-like effects and are associated with development of local oedema and haemorrhage.

The product, being of bacterial origin, has high intrinsic immunogenicity and while all subjects developed anti-drug antibodies, there was no evidence of cross-reactivity with five representative human collagenases (MMPs (collagenolytic matrix metalloproteinases) 1, 2, 3, 8 and 13) and only low levels of neutralising activity on AUX-I or AUX-II. Further discussions on immunogenicity in relation to efficacy and safety are in *Analysis performed across trials* and *Safety issues with potential for major regulatory impact, Unwanted immunological effects.*

Dosage selection for the pivotal studies

The dosage selection for the Phase III program was based on a single dose-ranging study, DUPY-202. This was a randomised placebo-controlled study in 80 adults with Dupuytren's disease. Doses of 2500 U, 5000 U and 10,000 U were assessed after a single injection. It is noted that this study used the early BTC process study drug.

The clinical success rates[10] were 50.0%, 45.5%, 78.3% in the 3 respective dose groups, compared to 0% in the placebo group. This result was statistically significant for all three doses ($p \leq 0.002$). Response was greatest with the 10,000 U dose when the primary affected

[10] Clinical success was defined as a reduction in contracture (flexion deformity) to ≤5° of normal as measure by finger goniometry 30 days after injection.

joint was the metocarpal phalangeal (MP) or the proximal interphalangeal (PIP) and this was the only dose which had a significantly greater success on the PIP joint than placebo (Table 8).

Table 8. Clinical Success of Primary Joint After a single injection of Study drug, Primary joint Overall and by Joint type. Intent to Treat population. DUPY-202

	AA4500			
	2500 U N=18	5000 U N=22	10,000 U N=23	Placebo N=17
All Primary Joints				
N	18	22	23	17
Number (%) clinical success	9 (50.0)	10 (45.5)	18 (78.3)	0
p-value[a]:				
Compared with 2500 U	NA	1.000	0.097	0.001
Compared with 5000 U	1.000	NA	0.033	0.002
Compared with 10,000 U	0.097	0.033	NA	<0.001
Compared with placebo	0.001	0.002	<0.001	NA
Primary MP Joints				
N	14	15	16	10
Number (%) clinical success	7 (50.0)	6 (40.0)	13 (81.3)	0
p-value[a]:				
Compared with 2500 U	NA	0.715	0.122	0.019
Compared with 5000 U	0.715	NA	0.029	0.051
Compared with 10,000 U	0.122	0.029	NA	<0.001
Compared with placebo	0.019	0.051	<0.001	NA
Primary PIP Joints				
N	4	7	7	7
Number (%) clinical success	2 (50.0)	4 (57.1)	5 (71.4)	0
p-value[a]:				
Compared with 2500 U	NA	1.000	0.576	0.109
Compared with 5000 U	1.000	NA	1.000	0.070
Compared with 10,000 U	0.576	1.000	NA	0.021
Compared with placebo	0.109	0.070	0.021	NA

Data source: Section 14; Tables 10, 10.1, and 10.2
NA=not applicable; MP = metacarpophalangeal; PIP = proximal interphalangeal.
[a] A Fisher's exact test was used for the pairwise comparisons between treatment groups.

For the more severely affected joints (>50° MP and >40° PIP), the response was notably greater with the 10,000 U dose (Table 9). The improvement from baseline in degree of contracture was significantly better with AA4500 than placebo ($p \leq 0.012$), with a mean percentage change of -25.6%, -30.2%, -40.0% and -0.6% for the 2500 U, 5000 U, 10,000 U and placebo groups, respectively. There was, however, no significant difference found between the active dose groups on this parameter (Table 10). Primary joints treated with AA4500 had a significantly greater improvement from baseline in the range of motion compared to those treated with placebo ($p < 0.001$). There were 37 primary joints that did not achieve success after a single injection that had further injections in the open label phase. Of these, 62% (23/37) achieved clinical success after retreatment with up to three 10,000 U injections.

Table 9. DUPY-202. Clinical success by Primary joint type, Baseline joint severity and Dose of AA4500.

Dose Level	MP Joints ≤ 50°	MP Joints >50°
2500 U	6/7 (85.7%)	1/7 (14.3%)
5000 U	4/9 (44.4%)	2/6 (33.3%)
10,000 U	9/10 (90.0%)	4/6 (66.7%)
Dose Level	**PIP Joints ≤ 40°**	**PIP Joints >40°**
2500 U	2/3 (66.7%)	0/1 (0.0%)
5000 U	3/3 (100.0%)	1/4 (25.0%)
10,000 U	2/2 (100.0%)	3/5 (60%)

Data source: Appendix 16.2; Listings 8 and 8.1
MP = metacarpophalangeal; PIP = proximal interphalangeal.

Table 10. DUPY-202. Mean change (%) in Degree of contracture (Flexion deformity) from baseline after a single injection of study drug, Primary joint overall and by Joint type. Intent to Treat Population.

	AA4500			
	2500 U N=18	5000 U N=22	10,000 U N=23	Placebo N=17
All Primary Joints				
Baseline				
N	18	22	23	17
Mean (SD)	46.8 (18.6)	47.1 (21.9)	49.0 (22.3)	55.6 (18.5)
Median	45.0	45.0	43.0	60.0
Min, Max	20.0, 85.0	20.0, 92.0	20.0, 90.0	25.0, 80.0
30 days after the injection				
N	18	22	23	17
Mean percent change (SD)	-25.6 (18.5)	-30.2 (17.0)	-40.0 (22.6)	-0.6 (4.3)
p-value[a]				
Compared with 2500 U	NA	0.405	0.011	<0.001
Compared with 5000 U	0.405	NA	0.065	<0.001
Compared with 10,000 U	0.011	0.065	NA	<0.001
Compared with placebo	<0.001	<0.001	<0.001	NA
Primary MP Joints				
Baseline				
N	14	15	16	10
Mean (SD)	49.8 (18.5)	48.1 (23.9)	44.9 (24.0)	56.5 (16.5)
Median	51.0	45.0	32.5	60.0
Min, Max	20.0, 85.0	20.0, 92.0	20.0, 90.0	25.0, 80.0
30 days after the injection				
N	14	15	16	10
Mean percent change (SD)	-26.4 (20.7)	-28.5 (20.2)	-37.1 (23.3)	0.0 (4.7)
p-value[a]				
Compared with 2500 U	NA	0.774	0.145	0.002
Compared with 5000 U	0.774	NA	0.232	<0.001
Compared with 10,000 U	0.145	0.232	NA	<0.001
Compared with placebo	0.002	<0.001	<0.001	NA
Primary PIP Joints				
Baseline				
N	4	7	7	7
Mean (SD)	36.3 (17.0)	45.0 (18.5)	58.3 (15.2)	54.4 (22.4)
Median	32.5	45.0	65.0	60.0
Min, Max	20.0, 60.0	25.0, 80.0	35.0, 75.0	25.0, 76.0
30 days after the injection				
N	4	7	7	7
Mean percent change (SD)	-22.5 (8.7)	-33.9 (6.1)	-46.9 (20.7)	-1.6 (3.7)
p-value[a]				
Compared with 2500 U	NA	0.151	0.004	0.012
Compared with 5000 U	0.151	NA	0.059	<0.001
Compared with 10,000 U	0.004	0.059	NA	<0.001
Compared with placebo	0.012	<0.001	<0.001	NA

Data source: Section 14; Tables 15, 15.1, and 15.2
NA=not applicable; MP = metacarpophalangeal; PIP = proximal interphalangeal.
[a] p-values are from one-way ANOVA with treatment as a factor.

In this study, the rate of treatment emergent adverse events (AEs) increased with increasing dose of AA4500 (77.8%, 81.8% and 91.3% versus 64.7% in the placebo group), however there was no statistically significant difference found between the active groups. Adverse events were mainly associated with the injection or post-injection finger manipulation (peripheral oedema, tenderness, ecchymosis) and were mild or moderate in severity.

The sponsor also included in the dossier a literature report of an early open label, dose-ranging study of the product in 35 subjects (DUPY-101). This reported that no beneficial effects were found with injections of <10,000 U. [11]

Comment: No clinical study report or data were supplied for this study so evaluation was not possible.

In Study DUPY-202, all AA4500 doses were found to be better than placebo with regard to effects on clinical success rates, improvement in range of motion and reduction in flexion deformity. There was an evident dose response and the highest dose of 10,000 U (equivalent to 0.58 mg) had a response irrespective of joint type (MP or PIP) and was more effective on the more severely contracted joints. Given these efficacy findings and the lack of a significant difference in AE rates between the dose groups, the sponsor selected the 10,000 U dose for the Phase III trials.

Comments: The high efficacy response of the 0.58 mg dose supported not assessing an even higher dose.

The use of study drug from an early manufacturing process mean the efficacy data are only considered supportive as there are no bioequivalence bridging data between this early process and the proposed commercial manufacturing process which was used in the Phase III clinical trials.

Given the proposed dosage of 0.58 mg, it is unclear why the single use product vial is 0.9 mg and a question on this has been included (see *List of Questions*).

Efficacy

Studies providing efficacy data

The following efficacy studies were provided for evaluation:

- Three controlled efficacy/safety studies (DUPY-303, AUX-CC-857, AUX-CC-859).
- Four uncontrolled, open label studies (DUPY-404, AUX-CC-854, AUX-CC-856, AUX-CC-858).
- Four other efficacy/safety studies (AUX-CC-851-852, AUX-CC-853, DUPY-101, AUX-CC-860)

Evaluator's conclusions on clinical efficacy for dupuytren's disease

Dosage selection for the Phase III trials was based on Study DUPY-202 which assessed doses of 2500 U, 5000 U and 10,000U. All doses were found to be significantly better than placebo on clinical success rates, improvement in range of motion and reduction in flexion deformity. There was an evident dose response and the highest dose of 10,000 U (equivalent to 0.58 mg) had a response irrespective of joint type (MP or PIP) and was more effective on the more severely contracted joints. Given these efficacy findings and the lack of a significant difference in AE rates between the dose groups, the 10,000 U dose was selected for the Phase III trials.

Efficacy evaluation was based on two pivotal Phase III trials (AUX-CC-857 and AUX-CC-859). These had the same design with one being conducted in the US and the other in Europe and Australia. Placebo, rather than surgical treatment, was used for the comparator as this allowed blinding and safety assessment as well as not subjecting study participants to the risk of general anaesthesia. Needle fasciotomy was not considered due to high recurrence rates and lack of its routine use in clinical practice. Treatment was stratified by joint type (MP or PIP) and severity

[11] Badalamente MA and Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. *J Hand Surg*. 2000; 25A: 629-636.

of primary joint contracture. In the double-blind phase of the studies up to 3 injections could be given, one a month, over a 90 day period. Subjects underwent a finger extension procedure on the day after the injection in attempt to disrupt the cord. Evaluation was via finger goniometry using a Neutral Zero Method at day 30 post injection. Subjects were required to have Dupuytren's disease with a fixed flexion deformity of at least one finger (other than the thumb) that was ≥20° and ≤100° for MP (≤80° for PIP) caused by a palpable cord and a positive "table top test". The primary endpoint was the proportion of subjects achieving a reduction in contracture of their primary joint to 5° or less at day 30 after the last injection.

In the two pivotal trials, subjects were invariably White (100%), male (80%) and aged between 55 and 74 years. Around 40% had previous surgery for their Dupuytren's disease. After a 90 day double-blind period where up to 3 injections could be given, a statistically superior response in reducing the contracture to 5° or less at the primary joint was found (64.0% versus 6.8%, $p<0.001$ in AUX-CC-857 and 44.4% versus 4.8%, $p<0.001$ in AUX-CC-859). A positive response was seen after the first injection and the mean number of injections required was 1.5 in both studies. Treatment effect was seen at both the MP and PIP joints although response was less at the PIP joint and in joints with more severe contraction. Pooled efficacy data found the clinical success rate at the primary MP joint was 75.2% versus 7.5%, and at the primary PIP joint was 36.8% versus 4.5%. There was improved response on the reduction in contracture degree and the range of motion. It was noted that no confidence intervals were provided for the efficacy endpoints and this should be done.

Results were consistent across subgroups of age, gender, weight and body mass index (BMI) and were associated with improvement in disease severity (as assessed by physicians) and subject satisfaction. Failure to achieve success was associated with not receiving the full injection course (52%) which was typically due to the physician having "no palpable cord to inject".

There were five open label extension periods (DUPY404, AUX-CC-854, 856, 858 and 859) which included efficacy data and allowed non-primary joints to be treated. Subjects could receive up to 5 injections, maximum 3 per joint, in the 9 month period. Study 858 was the extension of 857 and 523 joints were treated. In Study AUX-CC-859, 64 subjects continued with 47 joints treated. Study AUX-CC-854 and 856 included 386 and 201 subjects who had 589 and 293 joints treated, respectively. Overall, efficacy results were consistent with the pivotal trials and confirmed that response was less with the PIP joints and more severely contracted joints.

Study AUX-CC-851, 852, 853 and DUPY-303 and 404 were all affected by premature termination of enrolment; Studies 303 and 404 due to the change in licensing of AA4500 and Studies 851, 852 and 853 due to "manufacturing issues". As a consequence the efficacy data are not sufficiently robust to draw conclusion although they do provide limited evidence which is in line with the major clinical studies.

Pooled data on immunogenicity from the clinical program found that anti-AUX-I or AUX-II antibodies were present in 100% of subjects by the third or fourth injection. Post-hoc analysis of clinical success and improvement versus anti-AUX-I/II titre indicated no relationship between titre level and treatment success or improvement, suggesting that there is likely no antibody-mediated effect on clinical efficacy.

Recurrence of contracture was assessed at 12 months through the pivotal trials and their extensions with longer term data coming from Study AUX-CC-860 which is following 634 subjects (from a possible 950) who were enrolled in open label extension studies. At 12 months the reported recurrence rate was 4.5% of responding joints in Studies 857/858 and 0% in Study 859. At the end of Year 2 (Day 730), of the 618 joints which had been successfully treated, the recurrence rate was 19%. Recurrence was higher in PIP than MP joints (34% versus 14%) and more severely affected joints at baseline. A non-durable response was noted in 32% of joints which had had a measurable response. Progression of disease was found in 29% of joints not

effectively treated. The rate of worsening of disease in untreated joints was 1.9%. The data from the year three follow-up was not included, although should be available and submitted for evaluation.

Safety

Studies providing evaluable safety data

There were 13 clinical studies in the development program of AA4500 in Dupuytren's disease. There were two early clinical studies (DUPY-101 and Badalente and Hurst [2000][12]) which were not included in the safety analyses due to the lack of clinical databases. The dose-ranging Study DUPY-202 and Studies DUPY-303 and DUPY-404 were sponsored by BTC and used an earlier formulation of AA4500. The Studies AUX-CC-851/852, AUC-CC-853 had enrolment terminated early due to a manufacturing issue. There were 20 subjects included in these studies which rolled over into Studies AUX-CC-854 or 856.

In the pivotal efficacy Studies, AUX-CC-857 and AUX-CC-859, the following safety data were collected:

- General AEs as assessed by the investigator at each visit.
- Laboratory tests (haematology, clinical chemistry) and urinalysis.
- Electrocardiograms (ECGs), vital signs, hand grip strength by dynamometry (in kg) in the treated hand.
- Immunogenicity with bloods drawn prior to each injection and 30 days post each injection and at the Day 90 visit. Titres of anti-AUX-I and anti-AUX-II were determined.

The small early Study DUPY-303 provided some additional controlled safety data against placebo in 35 subjects. There were no pivotal safety studies however Study AUX-CC-860 was a non-treatment long-term follow-up which provided data on disease recurrence at two years.

Longer term safety data to 12 months post the first dose was provided by Studies DUPY-202, DUPY-303/404, AUX-CC-851/852, AUX-CC-853, AUX-CC-857/858, AUX-CC-859. These studies collected AEs, vital signs, grip strength, immunogenicity, and clinical laboratory tests (except in DUPY-303/404).

The pooled safety analysis populations are listed below in Table 11 below**.** The *Phase III double-blind placebo-controlled* population was used to compare AE rates to placebo. The *All subjects with at least one dose* was used to identify common events, assess subgroups and assess adverse event rates with increasing injection number. The *All subjects with 12 months post first dose* was used to assess long term safety. There was also the group of *All subjects with at least 1 dose (antibody determination)* which was used for immunogenicity analysis.

Due to the varying follow up time, in the population *All Subjects With At Least 1 Dose of AA4500,* treatment-emergent AEs (TEAEs) were analysed if they occurred from the injection to the 30 day evaluation visit post the last injection.

[12] Badalamente MA and Hurst LC. Enzyme injection as nonsurgical treatment of Dupuytren's disease. *J Hand Surg*. 2000; 25A: 629-636.

Table 11. Analysis Populations

Analysis Population	Studies	Subject Population
Phase 3 Double-Blind, Placebo-Controlled	DUPY-303, AUX-CC-857, AUX-CC-859 (double-blind phase only)	• AA4500 0.58 mg • Placebo
Phase 3 Double-blind, Placebo-Controlled in Support of the Prescribing Information	AUX-CC-857 and AUX-CC-859 (double-blind phase only)	• AA4500 0.58 mg • Placebo
All Subjects With At Least 1 Dose AA4500 0.58 mg	DUPY-202, DUPY-303, DUPY-404, AUX-CC-851, AUX-CC-853, AUX-CC-854, AUX-CC-855, AUX-CC-856, AUX-CC-857, AUX-CC-858, AUX-CC-859	• AA4500 0.58 mg
All Subjects With 12 Months Post First Dose AA4500 0.58 mg	DUPY-202, DUPY-303/404, AUX-CC-851/852, AUX-CC-853, AUX-CC-857/858, AUX-CC-859	• AA4500 0.58 mg
All Subjects With At Least 1 Dose AA4500 0.58 mg (Antibody Determination)	AUX-CC-851/852, AUX-CC-853, AUX-CC-854, AUX-CC-856, AUX-CC-857, AUX-CC-858, AUX-CC-859	• AA4500 0.58 mg

Patient exposure

There were 11 clinical trials providing safety data on 1,112 subjects. In this group, 13 subjects received placebo only, 17 subjects received doses of AA4500 <0.58 mg and 1,082 received at least one injection of AA4500 0.58 mg.

In the '*Phase III double-blind placebo-controlled*' (DB PC) studies there were 272 subjects treated with AA4500 0.58 mg and 137 placebo-treated subjects with 532 cords treated (392 AA4500 and 140 placebo) with 990 injections (597 AA4500 and 393 placebo). The median participation duration was 92 days.

In the '*Subjects with at least one dose*' group, there were 1082 subjects who had 1780 cords treated with 2630 injections and the median study participation duration was 275 days. In the '*All subjects with 12 months post first dose*' group there 268 subjects who had 509 cords treated with 771 injections and 52% received 1 or 2 injections. For these subjects, the median study duration was 366 days.

Demographics have been discussed with the efficacy data. It is noted that there was a substantial proportion of subjects in the trials from Australia; approximately 15% in the double-blind population and 30% of subjects receiving at least one dose.

Postmarketing experience

The sponsor's *Summary of Clinical Safety* contained a review of postmarketing reports to 31 March 2011 and the clinical submission (Module 5) contained four reports covering this period from 2 February 2010 (data of approval in the US) to 31 March 2011. The sponsor reported that in the US between launch in March 2010 to 31 March 2011 more than 7300 vials have been sold. Over this period there were 160 reports of which 146 were non-serious and 14 were serious. The majority of reports were in the System organ Classes (SOCs) of General disorders/administration site conditions (41/146 non serious and 1/14 serious) and Procedural complications (41/146 non-serious and 2/14 serious). The most frequent events were skin laceration (n=48), peripheral oedema (n=41), contusion (n=37), drug ineffective (n=19), pain in extremity (n=14), injection site haematoma (n=12) and lymphadenopathy (n=10). The serious events included: two cardiac events (one atrial fibrillation with possible allergic reaction and the other a fatal (heart attack) 5 days post injection in a 79 year old with cardiac risk factors); one pulmonary embolism one month post injection; one fatal aortic dissection 2 hours post injection; one death from a ruptured abdominal aortic aneurysm one month post injection; 2 tendon ruptures, 1 tendon damage and 5 skin tears requiring skin grafting.

Comment: The sponsor stated that the tendon damage and rupture is possibly due to inadvertent injection into collagen containing structures other than the Dupuytren's cord and the skin tears are likely due to the finger manipulation procedure rather than the product.

Safety issues with the potential for major regulatory impact

Unwanted immunological events

In Studies AUX-CC-851/852, AUX-CC-853, AUX-CC-854, AUX-CC-856, AUX-CC-857, AUX-CC-858, and AUX-CC-859, serum samples were collected at screening and 30 days post injection for determination of anti- AUX-I and anti-AUX-II antibodies. The AA4500 used in these studies were produced by the commercial manufacturing process (Process 3). As discussed in *Secondary pharmacodynamic effect* (Attachment 2) over 85% of subjects had anti drug antibodies (ADAs) after one injection and all did so by the third or fourth injection.

In the clinical program there were eight TEAEs coded as hypersensitivity reactions, three of which were classed as related and these were all local reactions on the treated hand (local allergic reactions of redness itch, heat and swelling of the treated hand). The other five cases were deemed non-related (rash behind knee, nasal allergy, allergic symptoms, allergic cough, and swollen lip from possible bee sting). There were also three cases of urticaria, two of which received a subsequent AA4500 injection without premedication or reappearance of the hives. There were no identified cases of systemic anaphylaxis.

Treatment-related events possibly associated with an immunologic event were examined by injection number and no association was found between increasing number of injections (and by inference an increase in antibody titre) with increasing event rates except for pruritus and to a less extent peripheral oedema (Table 12). In addition, there was no evident increase in the median duration of these TEAEs after receipt of a higher number of injections.

Table 12. Most frequently reported treatment-related AEs and those possibly consistent with an immunologic event by injection number. First Dose AA4500 0.58 mg to 30 days Post Last dose. All subjects with at least 1 dose of AA4500 0.58 mg.

	AA4500 0.58 mg							
Preferred Term[b]	Injection 1 (N=1082)	Injection 2 (N=639)	Injection 3 (N=420)	Injection 4 (N=250)	Injection 5 (N=157)	Injection 6 (N=41)	Injection 7 (N=27)	Injection 8 (N=14)
Number (%) of subjects with ≥ 1 treatment-related AE	1029 (95.1)	605 (94.7)	389 (92.6)	233 (93.2)	140 (89.2)	36 (87.8)	25 (92.6)	14 (100.0)
Peripheral edema[c]	731 (67.6)	413 (64.6)	263 (62.6)	176 (70.4)	116 (73.9)	30 (73.2)	21 (77.8)	11 (78.6)
Contusion[d]	517 (47.8)	240 (37.6)	127 (30.2)	73 (29.2)	49 (31.2)	12 (29.3)	10 (37.0)	4 (28.6)
Injection site pain	344 (31.8)	172 (26.9)	111 (26.4)	54 (21.6)	37 (23.6)	11 (26.8)	7 (25.9)	4 (28.6)
Pain in extremity	282 (26.1)	146 (22.8)	79 (18.8)	42 (16.8)	22 (14.0)	7 (17.1)	6 (22.2)	2 (14.3)
Injection site swelling	176 (16.3)	117 (18.3)	84 (20.0)	41 (16.4)	21 (13.4)	6 (14.6)	2 (7.4)	2 (14.3)
Pruritus	40 (3.7)	50 (7.8)	51 (12.1)	27 (10.8)	26 (16.6)	9 (22.0)	3 (11.1)	2 (14.3)
Lymphadenopathy	92 (8.5)	29 (4.5)	16 (3.8)	7 (2.8)	2 (1.3)	0 (0.0)	1 (3.7)	0 (0.0)
Injection site pruritus	18 (1.7)	15 (2.3)	19 (4.5)	15 (6.0)	8 (5.1)	1 (2.4)	2 (7.4)	0 (0.0)

Data source: ISS Table 14.2.19.1

Note: Includes the four most frequently reported treatment-related TEAEs, and four possibly consistent with an immunologic event and have a relationship to study drug of possible, probable, or missing.

a Includes all subjects who received at least 1 injection of AA4500 0.58 mg.

b Preferred term was coded using MedDRA dictionary (Version 8.0). An AE was counted only once if occurred multiple times for the same injection cycle, but counted multiple times if occurred within different injection cycles.

c Most involved swelling of the treated extremity.

d 1 subject's report of contusion (considered treatment related) was mapped to musculoskeletal and connective tissue disorders SOC (applies to Injection 1) ; all other reports of contusion were mapped to injury, poisoning and procedural complications SOC.

The sponsor undertook an assessment of the relationship between ADA titre and the severity of adverse events of peripheral oedema, contusion, injection site pain, extremity pain, injection site swelling, pruritus, lymphadenopathy and injection site pruritus. This showed that there was no obvious increase in ADA titre in subjects with severe events.

Comment: No formal statistical analysis of this was undertaken.

The sponsor also medically reviewed the TEAEs for events possibly related to inhibition of endogenous collagenases (MMPs) by anti-AUX-I and anti-AUX-II antibodies. There were no musculoskeletal events of polyarthritis, osteolysis or shoulder pain/reduction of range of

motion. Joint stiffness and swelling was noted after the first as well as subsequent doses and Dupuytren's disease was not noted to worsen. The sponsor reported that *in vitro* studies, using 71 samples from AUX-CC-860, found no potential for cross-reactivity of ADAs with the endogenous human MMPs (1, 2, 3, 8 and 13).

Evaluator's overall conclusions on clinical safety

There were 13 clinical studies in the development program of AA4500 in Dupuytren's disease, although two early clinical studies were not included in the safety analyses due to the lack of clinical databases. In the 11 included clinical trials, there were 1,082 subjects who received at least one injection of AA4500 0.58 mg and 1780 cords were treated with 2630 injections.

In the two pivotal efficacy studies, AUX-CC-857 and AUX-CC-859, there were 272 subjects who had 392 cords treated with AA4500 and 137 subjects with 393 cords treated with placebo over a median participation duration of 92 days. There were also 268 subjects with at least 12 months of data post the first dose of AA4500 and half of these subjects received one or two injections.

Adverse events were virtually universal and notably higher than placebo (98% versus 54%). Nearly all TEAEs were classed as treatment-related (97% versus 26%) with most commencing on the injection day (80.6%) or the next day of finger manipulation (67.8%) rather than after Day 1 (33.4%). The duration of the TEAEs was such that, in general, they had resolved prior to the next scheduled injection one month later.

The profile of TEAEs was similar between the pivotal trials and the other safety populations and, as to be expected with a product lacking systemic exposure, the safety risks were mainly associated with the treated hand. The most frequent TEAEs were peripheral oedema (75.7% versus 5.1%), contusion (50.7% versus 2.9%), injection site pain (39.0% versus 9.5%), injection site haemorrhage (34.9% versus 2.9%) and pain in the extremity (33.1% versus 3.6%). Other frequent (>10%) TEAEs were tenderness, ecchymosis, lymphadenopathy and pruritus.

Most events were mild (32%) or moderate (56%) with severe TEAEs being less frequent (10%). All, except three cases, of the severe TEAEs were treatment-related (9% versus 0%) and these included injection site reaction, pain in extremity, peripheral oedema, contusion, injection site haemorrhage, tenderness, injection site cellulitis, ligament injury, skin laceration, tendon rupture, chest wall pain and irritability.

The rate of treatment-related TEAEs was relatively constant when examined by number of injections administered (1 to 8) with the exception of pruritus which increased from 3.7% after injection 1 to 22.0% after injection 6. Peripheral oedema was noted to occur after each injection.

There were 7 (0.6%) deaths in the clinical program with none being considered treatment-related. The rate of non-fatal serious adverse events (SAEs) was 7.7% and there were 9 (0.8%) treatment-related cases: tendon rupture (n=3, 0.3%); ligament injury; tendonitis; finger deformity; Dupuytren's contracture and sensory disturbance of hand; deep vein thrombosis (DVT); and complex regional pain syndrome. Postmarketing data (to March 2011) noted 160 reports with 14 serious cases including 2 tendon ruptures, 1 tendon damage and 5 skin tears requiring grafting. Discontinuation due to adverse events was infrequent (1.3% in the 13 clinical trials overall) and three cases were classed as treatment-related - injection site pain, dizziness and complex regional pain syndrome.

Laboratory assessments and vital signs were unremarkable with no meaningful changes from baseline in mean values and few cases of clinically significant values. There was no reduction in grip strength assessed by hand held dynamometry.

The product was notably immunogenic with over 85% of subjects after one injection and 100% by the third or fourth injection developing anti-drug antibodies. Assessment of unwanted immunologic events found no cases of systemic anaphylaxis although there were three cases of

urticaria and three cases of local allergic type reactions on the hand. The database, however, may be too small to detect anaphylactic reactions. There was no overall association between increasing injection number, and by inference increasing antibody titre, and TEAEs except for pruritus. There was also no obvious association between the severity of events and antibody titre. In addition, there were no musculoskeletal events that may have indicated inhibition of endogenous collagenases.

Analysis of the pivotal trials found a consistent safety profile across subgroups of age, gender, weight, BMI and diabetes. Racial groups could not be assessed due to the development only being conducted in Caucasians. Subjects on anticoagulants (except low dose aspirin) or tetracyclines were excluded from the trials due to possible drug interactions. Safety has not been established in pregnancy or lactation.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Xiaflex 0.58 mg in the proposed usage are:

- A reduction in contracture in advanced Dupuytren's disease that was statistically significant over placebo was confirmed in the two pivotal studies. A reduction of contracture of the primary joint to five degrees or less was achieved in 64% of all treated joints in Study AUX-CC-857 and 44% of all treated joints in Study AUX-CC-859 (compared to 7% and 5% of the placebo joints, respectively).
- Efficacy was also seen in an improvement in the degree of contracture and range of motion and was consistent across subgroups of age, gender, weight and BMI. Efficacy was, however, less in PIP joints than the MP joints, as well as in the more severely contracted joints.
- AA4500 offers a novel, non-surgical treatment for Dupuytren's disease and therefore avoids anaesthetic risks and possible surgical risks such as nerve or vessel injury and wound infections.

First round assessment of risks

The risks of Xiaflex 0.58 mg in the proposed usage are:

- Localised reactions at the treatment site and in the treated limb including peripheral oedema, contusion, injection site pain, injection site haemorrhage and pain in the extremity. These events were generally mild or moderate in severity and resolved prior to the next injection.
- Tendon rupture and ligament damage, particularly in the fifth finger PIP joint (perhaps due to injection into other structures than the Dupuytren's cord). The rate of tendon rupture in the clinical program was 0.3%.
- Poor injection technique and inadvertent injection into surrounding structures and overdosing from drawing up too much reconstituted product.
- Skin tears, including rarer cases requiring skin grafting, possibly due to adherent skin and the finger manipulation post injection.
- Localised haemorrhage and the need to avoid treatment in patients on anticoagulants.
- High immunogenicity and the potential for immunogenicity-related risks. Urticaria was reported but there were no cases of systemic anaphylaxis, nor was there evidence of reduced efficacy or increasing adverse events (apart from pruritus) with increasing injection numbers or antibody titre.

- The potential cross-reactivity of anti drug antibodies with endogenous collagenases leading to musculoskeletal syndrome. There were, however, no reported cases in the safety database of musculoskeletal events of polyarthritis, osteolysis or shoulder pain/reduction of range of motion.
- The impact on subsequent surgery is unknown and there are no data on simultaneous injection of multiple cords.
- There are no studies in pregnancy or lactation and the clinical risks from anti-drug antibodies in these groups are not known.
- A reported recurrence rate of 4% at 9-12 months and 19% at two years as well as a lack of data on retreatment.

First round assessment of benefit-risk balance

Dupuytren's disease is a relatively common, slowly progressive fibroproliferative disease of the palmar fascia in which the resultant flexion contracture can cause significant disability of the hand and interference with normal daily tasks. When hand function is impaired, surgery is the mainstay of treatment and is usually a transection of cords (fasciotomy) or excision of the fascial bands (fasciectomy). Flexion deformity of >30-40° at the MP and >20° at the PIP joint had been suggested as indication for surgery. Surgery is associated with good initial response but recurrence rates are reported to be high. There are currently no pharmacological therapies for the treatment of Dupuytren's disease and as such there is an evident unmet medical need.

Xiaflex is a 1:1 ratio mix of collagenase enzymes produced by Clostridium histolyticum. It is proposed at a dose of 0.58 mg injected into the affected cord at one month intervals to a maximum of three doses. Patients undergo a finger extension procedure on the day after injection if necessary to disrupt the cord. The treatment can be given in the practice rooms. The sponsor has proposed the following indication; *Xiaflex is indicated for the treatment of Dupuytren's contracture in adult patients with palpable cord.* The development of AA4500 commenced with Biospecifics Technologies Corporation, which conducted five trials using an early formulation. Auxilium Pharmaceuticals acquired the global development rights in 2004 and the dossier included eight trials Auxilium sponsored using the proposed formulation for marketing.

Studies have been conducted in patients with Dupuytren's disease and sufficient efficacy data were provided including from the two pivotal randomised placebo-controlled double-blind studies in 374 subjects. These pivotal trials were conducted in a population representative of the target population. In addition, the smaller of the two pivotal trials, in which 45 subjects were treated with AA4500, was conducted in Australian subjects.

The primary endpoint was proportion of subjects achieving a reduction in flexion contracture to 5 degrees or less 30 days post last injection assessed at both MP and PIP joints. This endpoint is rigorous and being close to full extension represents a clinically meaningful outcome. The primary outcome was achieved in the two pivotal trials with a statistically significant success rate at the primary joint of 64% and 44%, compared to 7% and 5% with placebo, in the two pivotal trials. Up to 3 injections were given and benefit was seen with 1 or 2 additional injections in those not achieving response after the first injection. Lower efficacy was seen at the PIP joints and the more severely contracted joints, nevertheless there was still meaningful clinical improvement seen in these types of joints which are known to be more resilient to treatment. Results of the primary efficacy endpoint were supported by significant improvements in secondary endpoints including improved range of motion, physician rating of improvement, subject satisfaction as well as subgroup analysis of age, gender, weight and BMI. Overall, the evaluator believed the efficacy data were sufficient to support the proposed wide range of severity implied by the indication.

The clinical development program did not include any trials against currently available treatment options such as surgery or percutaneous needle fasciotomy. Consequently, any comparison of outcomes between interventions can only be approximated from the literature. This was undertaken by the sponsor and a series with surgical outcomes in 1150 patients reported full correction (0°) of contracture at the MP joint in 70-89% of cases and at the PIP joint in 13-29%.[13] The rate of clinical success in the pivotal trials was 65-77% at the MP joint and 28-40% at the PIP joint and these data provide an indication that AA4500 efficacy may be in line with surgical therapy.

The natural history of the disease for many patients is progression and in the pivotal trials a recurrence rate of 4% was reported which increased to 19% after 2 years. The post-surgery recurrence rates from the literature, as quoted by the sponsor, range from 2% to 60% with an average of 33% (Table 13). An alternative therapy of percutaneous needle fasciotomy has been reported to have even higher recurrence rates of 65%.[14] This implies that, on available data, recurrence is no higher with AA4500 treatment than with the main treatment alternatives. Currently, there has been insufficient follow up time to truly assess the persistence of efficacy and rates of recurrence. Therefore, the additional follow-up data from Study AUX-CC-860 should be submitted to the TGA for evaluation.

Table 13. Extension and recurrence by surgical procedure.

	Reference (Patient Number)	Follow-up	Recurrence [Time to Recurrence]
Limited Fasciectomy	Foucher G, 1995 (n=54)	6.6 yrs	38.9%
	Foucher G, 1992 (n=107)	5.6 yrs	41%; [average: 3.3 yrs]
	Citron ND, 2005 (n=79)	2+ yrs	18% (modified Bruner 33% (Z-plasty) group)
	Tonkin MA, 1984 (n=163)	3.1 yrs	54% (males) and 25% (females)
	Wilbrand S, 2003 (n=103)	4.4 yrs	47% (20% before 6 months and 27% after) [~4.4 yrs]
	Nieminen S, 1986 (n=70)	3.9 yrs	45% [~3.9 yrs]
	Bulstrode NW, 2005 (n=253)	3.6 yrs	33.3%
	Foucher G, 1985 (n=139)	1.5 yrs	2%
	Gonzalez VJ, 1998 (n=583)	0.3+ yrs	22% and 14% (2 treatment arms)
	Norotte G, 1988 (n=58)	10+ yrs	51% in first 2 yrs, 28% between 2–5 yrs and 5% after 5 yrs (primary patients) [~2 yrs]
	Ullah AS, 2009 (n=40)	3 yrs	12.5% (primary patients) [average 0.5 yrs]
Dermo-fasciectomy	Armstrong JR, 2000 (n=103)	5.8 yrs	11.6%
	Hogemann A, 2009 (n=61)	3.45 yrs	10.8%
	Tonkin MA, 1984 (n=163)	2.6 yrs	33% of primary males; 42% of recurrent males
	Roy N, 2006 (n=79)	4.4 yrs	8.9% (primary)
	Ullah AS, 2009 (n=39)	3 yrs	15.4% primary [average of 0.7 yrs]
Total Fasciectomy	Hogemann A, 2009 (n=61)	3.45 yrs	10.5% (primary); 12.5% (recurrent)
Needle Fasciotomy	Foucher G, 2003 (n=211)	3.2 yrs	58.3%
	Van Rijssen, 2006a (n=52)	2.75 yrs	65%
	Van Rijssen, 2010 (n=54)[a]	5 yrs	85%

[a] http://www.dupuytrensymposium.com/Abstracts/Van_Rijssen.pdf

The safety population consisted of 1082 subjects who received at least one dose of 0.58 mg Xiaflex and 1780 cords were treated with 2630 injections. The most frequent reactions were peripheral oedema, contusion, injection site pain, haemorrhage and tenderness. These effects may be a reaction to the actual product or a response to the collagen breakdown. These adverse events were frequent and nearly entirely related to treatment. They were, on the whole, confined to the treated extremity, the intensity generally mild to moderate and the duration such that they had resolved prior subsequent treatment if required one month later. The severe,

[13] McFarlane R and Botz, JS. The results of treatment. In: McFarlane RM, McGrouther DA, and Flint MH, eds. *Dupuytren's Disease Biology and Treatment.* Volume 5. Edinburgh, London, Melbourne, and New York: Churchill Livingstone; 1990:387-412

[14] van Rijssen AL, Werker PM. Percutaneous needle fasciotomy in dupuytren's disease.*J Hand Surg Br*. 2006; 31(5):498

albeit low frequency, safety risks were tendon rupture, ligament injury and skin tears requiring grafting. These risks may have in part been associated inadvertent injection into structures other than the Dupuytren's cord.

In order to address these severe risks, as well as to ensure the clinical success rates are maintained in patients with potentially varying levels of baseline severity, treating physicians must receive thorough training in the use of the product. This should include product reconstitution, dosage, injection technique and post treatment manipulation as well as adverse event information and monitoring. The evaluator assumes that in a clinical trial setting the training of physicians would have been extensive. The sponsor will need to ensure that the same level of expertise is imparted in the 'real world' to ensure maintenance of the benefit-risk balance and this should be a specific condition of registration. The evaluator also recommended that a further condition of registration be that the product is only distributed to prescribers who have undergone such training.

The high immunogenicity of AA4500 poses the other main safety risk. Although there was no evidence of systemic absorption, all patients developed anti-drug antibodies. These antibodies did not appear to affect the efficacy (clinical success or improvement) or safety (adverse event profile, severity or duration) of AA4500. There were no severe hypersensitivity reactions or anaphylaxis reported, although there was a small number of cases of urticaria and the increasing rate of pruritus with a greater number of injections could have immunologic basis. There is also the potential for cross-reactivity of anti-drug antibodies with endogenous human matrix metalloproteinases. This was not found on assessment with five MMPs *in vitro* and the safety data did not indicate any signals for musculoskeletal syndrome.

Despite these findings, the safety database may not have been large enough to detect rarer reactions. For this reason, ongoing postmarketing surveillance of immune-mediated reactions including possible case of musculoskeletal syndrome will be critical to monitor the product risks. The evaluator also recommended that this includes monitoring of auto-immune disorders in existing patients as well as new onset of cases and this needs to be addressed satisfactorily with the context of the Risk Management Plan.

The immunogenicity risks have been covered in the draft PI and it was also recommended by the evaluator that treatment should only be used in a setting able to treat anaphylaxis. This setting may be the physician's practice rooms but the ability to monitor vital signs and administer adrenalin, oxygen and intravenous fluids would need to be present. These setting requirements should also be covered in the context of the proposed Risk Management Plan.

The risk of drug interactions (anticoagulants and tetracyclines) has been adequately covered in the draft PI. Pregnancy and lactation risks have also been covered, although the evaluator recommended that as there are no studies in pregnancy or lactation and the clinical risk from anti-drug antibodies is unknown, that treatment should be deferred until after pregnancy.

The clinical development program has not addressed the administration of concurrent injections. While this was not proposed in the indication, the evaluator recommended wording the dosage section to specify this fact. The evaluator has noted that further clinical development is being conducted in this area (Studies AUX-CC-861 and AUX-CC-864), although no data were included in the current dossier.

Retreatment with A4500 of previously treated cords has not been addressed in this dossier. The sponsor stated that a new Study AUX-CC-862, together with further data from AUX-CC-860, will cover this issue. Until such time as these data are evaluated, the evaluator recommended that this lack of efficacy and safety data in retreatment should be included in the product information.

In summary, Xiaflex injection has a moderate level of efficacy which appears in line with current surgical options together with a safety profile of predominantly mild to moderate adverse events which are confined to treated limb and generally resolved in under a month. While the

immunogenicity-related risks have to date not been concerning, there is an evident need for these to be closely monitored. The product's safety is in part determined by the skill and knowledge of the administering physician and so it will be imperative that physicians using the product are adequately trained. Xiaflex offers a non-surgical treatment which can be administered in the clinical practice and so may offer a viable alternative to surgery which is currently the mainstay of treatment for advanced Dupuytren's disease. As such, the benefit-risk balance of Xiaflex 0.58 mg, given the proposed usage of treatment of Dupuytren's contracture in adult patients with palpable cord, was considered to be favourable. This finding is subject to no change in the benefit-risk balance after evaluation of satisfactory responses to the comments and *Clinical Questions* below.

First round recommendation regarding authorisation

The evaluator recommended approval of Xiaflex 0.58 mg injection for the treatment of Dupuytren's contracture in adult patients with palpable cord. This is subject to no change in the benefit-risk balance after review of responses to the comments and *Clinical Questions* below.

In addition to the pharmacovigilance requirements as set out in the Risk Management Plan, it was recommended that authorisation be subject to:

- the sponsor ensuring that all doctors prescribing and using Xiaflex are experienced in the management of Dupuytren's disease and are appropriately trained in the product's administration. Training must cover the areas of reconstitution of the product, volumes to inject, dosing interval, injection technique, post injection finger manipulation and management, as well as information on immune-mediated reactions including anaphylaxis and its management, matrix metalloproteinase cross-reactivity and musculoskeletal syndrome, and other potential adverse events and the requirement for reporting.
- the product is only distributed to doctors who have been appropriately trained as outlined above.

Clinical questions

Pharmacokinetics

Nil.

Pharmacodynamics

Nil.

Efficacy

1. In the pivotal efficacy Studies AUX-CC-857 and AUX-CC-859 there were no confidence interval provided on any of the efficacy outcomes, in particular clinical success rate, clinical improvement rate, change in degree of contracture and change in range of motion. These should be provided.
2. The dossier included an interim report for Study AUX-CC-860 which summarised data for Year 2. This included data up to April 2010. Given it is now the end of 2012, data should now be available for the Year 3, and even Year 4, of the follow up. This data should be submitted to the TGA for evaluation so that further assessment of long term recurrence rates can be made. Include a discussion on these recurrence rates compared to reported rates in the literature from other treatment options.

3. The dossier included the protocol of Study B1531002 sponsored by Pfizer. It was stated to be a prospective open label Phase III study in 250 European subjects. What is the status of this study? Describe the study and comment on whether there any relevant efficacy data that are available and should be disclosed. If the study is completed, comment on why the data were not included in the dossier.
4. Provide a summary of the clinical trials in progress or planned worldwide with all sponsors and what additional data (efficacy, safety and pharmacokinetics) they are aiming to provide. Include timing for the trials and data availability.

Safety

1. The dossier included an interim report for Study AUX-CC-860 which summarised data for Year 2. This included data up to April 2010. Given it is now the end of 2012, data should now be available for the Year 3, and even Year 4, of the follow up. This data should be submitted for evaluation so that further assessment of long term safety can be made. Discuss any data and associated risks in subjects who may have had surgery on previously treated cords.
2. The dossier included the protocol of Study B1531002 sponsored by Pfizer. It was stated to be a prospective open label Phase III study in 250 European subjects. What is the status of this study? Are there any relevant safety data that are available and should be disclosed? Comment on these data in relation to the safety profile reported in this dossier.
3. The dossier also made reference to a post-approval study in the US, AUX-CC-861. The study was stated to be an open label study assessing the safety, tolerability and pharmacokinetics of two concurrent doses of AA4500 0.58 mg in the same hand of subjects with Dupuytren's contractures and a palpable cord. What is the status of this study? Are there data which should be submitted for evaluation? Again, comment on these data in relation to the safety profile reported in this dossier.
4. Why is the reconstituted dose so much greater than needed (0.9 mg for a dose of 0.58 mg)? This would appear to lead to possibility for overdosing if too much volume is drawn up and injected. Discuss the rationale behind this decision.
5. Discuss what training the investigators in the clinical development program undertook to ensure they were adequately skilled to administer the study injections. How is the sponsor proposing to ensure comparable skill levels of physicians who may use the product in Australia if registered?

Second round evaluation of clinical data submitted in response to questions

Efficacy

1. In the pivotal efficacy studies AUX-CC-857 and AUX-CC-859 there were no confidence intervals provided on any of the efficacy outcomes, in particular clinical success rate, clinical improvement rate, change in degree of contracture and change in range of motion. These should be provided.

Sponsor's response:

For the combined MP and PIP primary joint from Studies AUX-CC-857 and AUX-CC-859, the sponsor provided 95% confidence intervals for clinical success, clinical improvement, percentage change from baseline in contracture and change from baseline in ROM.

In the AA4500 and placebo groups, respectively, the clinical success rates were 64.0% versus 6.8% in AUX-CC-857 and 44.4% versus 4.8% in AUX-CC-859. The 95% CI for the difference in

clinical success rates between AA4500 and placebo were 46.8-66.8 in Study 857 and 13.7-62.3 in Study 859.

The 95% CI for the difference in the rate of clinical improvement between the AA4500 and placebo groups were 63.7-81.7 and 40.1-81.9 for Studies AUX-CC-857 and 859, respectively. The 95% CI for the adjusted mean difference in the percentage change from baseline in contracture was 62.1-74.3 and 46.4-70.8, respectively. The 95% CI for the adjusted mean difference in the change from baseline in range of motion was 27.8-34.9 and 18.3-32.5, respectively.

Evaluator's response:

The data demonstrate satisfactory response ranges. The broader intervals seen in AUX-CC-859 would be a factor of the smaller sample size.

2. ***The dossier included an interim report for Study AUX-CC-860 which summarised data for Year 2. This included data up to April 2010. Given it is now the end of 2012, data should be available for the Year 3, and even Year 4, of the follow up. This data should be submitted for evaluation so that further assessment of long term recurrence rates can be made. Include a discussion on these recurrence rates compared to reported rates in the literature from other treatment options.***

Sponsor's response:

The sponsor provided the interim clinical study report for Year 4. The final report (Year 5) will be available at the end of 2013.

At July 2012, there were 645 subjects enrolled, 644 had at least one post enrolment evaluation and 539 (83.7%) completed the Year 4 visit. The mean study duration was 682.6 days and the mean days since first injection of AA4500 was 1440.8 days (range 618 to 1185 days).

In joints that had been successfully treated, the cumulative recurrence rate through to 1460 days of follow up was 42.1% (262/623) (Table 14). The recurrence rate at the PIP joint was higher than at the MP joint (61.6% versus 34.6%) (Table 15). Of the 623 joints that were successfully treated in the primary study, 12.8% had received medical or surgical intervention by the Year 4 visit.

The sponsor also reported that the recurrence definitions and rates in the literature are variable and range from 12-73% for fasciectomy/aponeurectomy and 33-100% for fasciotomy/apoenurotomy.

Evaluator's response:

Recurrence was shown to continue to increase over time, from 19% after 2 years to 42% after 4 years and remained higher at the PIP joint than the MP joint. These data indicate that for many patients treatment of this progressive condition with AA4500, as with other currently available options, is not permanent.

Table 14. Recurrence and Days of Follow-up for successfully treated joints. 860 Study Population.

Follow-Up Interval (Days)	n (%) of Joints in Each Interval[a]	n (%) of Recurrent Joints in Each Interval[b]	Number of Joints at Risk in Each Interval	Cumulative Nominal Rate (%) of Recurrence[c]	Kaplan-Meier Estimate (%) of Recurrence[d]
0-365	20 (3.2)	19 (7.0)	623	3.0	3.1
366-730	114 (18.3)	103 (37.7)	603	19.6	19.7
731-1095	128 (20.5)	96 (35.2)	489	35.0	35.8
1096-1460	216 (34.7)	44 (16.1)	361	42.1	44.9
>1460	145 (23.3)	11 (4.0)	145	43.8	--

Average follow-up after success:	1133 days
Average follow-up for recurrent joints:	836 days
Total follow-up time after success:	1932 years
Event rate per 100 joint-years of follow-up:	14.13

Data source: Table 14.2.2.1

[a] A joint is considered in an interval if the duration of assessment falls in the interval. The duration of assessment starts at the day of success (visit after the last injection where the 0° to 5° measurement was first recorded). The duration of assessment ends at the last available measurement or at the day of medical intervention for joints that do not recur and the recurrence day for recurrent joints.

[b] A recurrent joint is a joint evaluated by the investigator as having a worsening Dupuytren's contracture due to a palpable cord. The recurrence day is the visit where the recurrence was reported or the day of intervention if a joint was treated for a worsening Dupuytren's contracture. For joints reported as recurring in a previous study, the day of recurrence is the first visit with a fixed flexion contracture measurement of 20° or greater following the report of recurrence.

[c] The nominal rate of recurrence is the total number of recurrences occurring prior to the last day of the interval divided by the total number of joints (×100).

[d] The Kaplan-Meier estimate is the rate of recurrence at the final day of the interval estimated by a survival analysis with joints not recurring censored at their last measurement day or their day of medical intervention.

Table 15. Recurrence and Days of Follow-up for successfully treated joints by joint type. 860 Study Population.

Follow-Up Interval (Days)	n (%) of Joints in Each Interval[a]		n (%) of Recurrent Joints in Each Interval[b]		Number of Joints at Risk in Each Interval		Cumulative Nominal Rate (%) of Recurrence[c]		Kaplan-Meier Estimate (%) of Recurrence[d]	
	Joint Type		Joint Type		Joint Type		Joint Type		Joint Type	
	MP	PIP	MP	PIP	MP	PIP	MP	PIP	MP	PIP
0-365	8 (1.8)	12 (7.0)	8 (4.9)	11 (10.1)	451	172	1.8	6.4	1.8	6.4
366-730	64 (14.2)	50 (29.1)	56 (34.1)	47 (43.1)	443	160	14.2	33.7	14.3	34.0
731-1095	85 (18.8)	43 (25.0)	57 (34.8)	39 (35.8)	379	110	26.8	56.4	27.6	57.6
1096-1460	176 (39.0)	40 (23.3)	35 (21.3)	9 (8.3)	294	67	34.6	61.6	37.7	63.7
>1460	118 (26.2)	27 (15.7)	8 (4.9)	3 (2.8)	118	27	36.4	63.4	--	--

Joint Type	MP	PIP
Average follow-up after success:	1195 days	970 days
Average follow-up for recurrent joints:	896 days	746 days
Total follow-up time after success:	1475 years	457 years
Event rate per 100 joint-years of follow-up:	11.12	23.86

Data source: Tables 14.2.2.2 and 14.2.2.3

[a] A joint is considered in an interval if the duration of assessment falls in the interval. The duration of assessment starts at the day of success (visit after the last injection where the 0° to 5° measurement was first recorded). The duration of assessment ends at the last available measurement or at the day of medical intervention for joints that do not recur and the recurrence day for recurrent joints.

[b] A recurrent joint is a joint evaluated by the investigator as having a worsening Dupuytren's contracture due to a palpable cord. The recurrence day is the visit where the recurrence was reported or the day of intervention if a joint was treated for a worsening Dupuytren's contracture. For joint reported as recurring in a previous study, the day of recurrence is the first visit with a fixed flexion contracture measurement of 20° or greater following the report of recurrence.

[c] The nominal rate of recurrence is the total number of recurrences occurring prior to the last day of the interval divided by the total number of joints (×100).

[d] The Kaplan-Meier estimate is the rate of recurrence at the final day of the interval estimated by a survival analysis with joints not recurring censored at their last measurement day or their day of medical intervention.

3. ***The dossier included the protocol of study B1531002 sponsored by Pfizer. It was stated to be a prospective open label Phase III study in 250 European subjects. What is the status of this study? Describe the study and comment on whether there any relevant efficacy data that are available and should be disclosed. If the study is completed, comment on why the data were not included in the dossier.***

Sponsor's response:

This Phase IIIb study remains ongoing. This multi-centre study has 2 phases: The first is an open-label treatment phase (up to 5 months in duration) and the second is a 6 month follow-up phase. To date, a total of 254 subjects have been treated. No clinically important information has emerged from this ongoing study.

Evaluator's response:

Data should be provided when available.

4. ***Provide a summary of the clinical trials in progress or planned worldwide with all Sponsors and what additional data (efficacy, safety and pharmacokinetics) they are aiming to provide. Include timing for the trials and data availability.***

Sponsor's response:

Table 16. Ongoing studies-Xiaflex in the treatment of Dupuytren's contracture

Study Number	Design	Sponsor	Expected Completion[a]
AUX-CC-860	Phase 3, non-treatment long-term follow-up	Auxilium	Q3, 2013
AUX-CC-862	Phase 3 retreatment of recurrent contractures	Auxilium	Q1, 2014
AUX-CC-867	Phase 3b open-label concurrent treatment	Auxilium	Q1, 2014
AUX-CC-901	Non-treatment study	Auxilium	Q4, 2016
B1531002	Phase 3 open-label treatment study	Pfizer	2Q 2013
B1531005	Non-interventional study	Pfizer	2018
AK160-III-1	Phase 3 treatment study	Asahi	4Q 2013

[a] Final CSR

Q=quarter

Evaluator's response:

The information provided was considered to be limited. Data should be provided to the TGA for evaluation when available.

Safety

1. ***The dossier included an interim report for Study AUX-CC-860 which summarised data for Year 2. This included data up to April 2010. Given it is now the end of 2012, data should be available for the Year 3, and even Year 4, of the follow up. This data should be submitted to the TGA for evaluation so that further assessment of long term safety can be made. Discuss any data and associated risks in subjects who may have had surgery on previously treated cords.***

Sponsor's response:

The sponsor quoted three abstracts presented at conferences which reported that post Xiaflex injection there was "*no significant distortion of anatomy*", "*a reduction in cord volume*" and cords were "*histologically similar*" and "*surgery was not found to be difficult during fascietomy performed after collagenase injections*".

The safety data from Study AUX-CC-860 at Year 4 did not report on any issues relating to surgery of previously treated cords. Of the 644 subjects enrolled in this study, 48 received at least one injection of commercially available Xiaflex. In these subjects the rate of injection site haematoma and injection site oedema was 12.5% and 10.4%, respectively. In the overall study

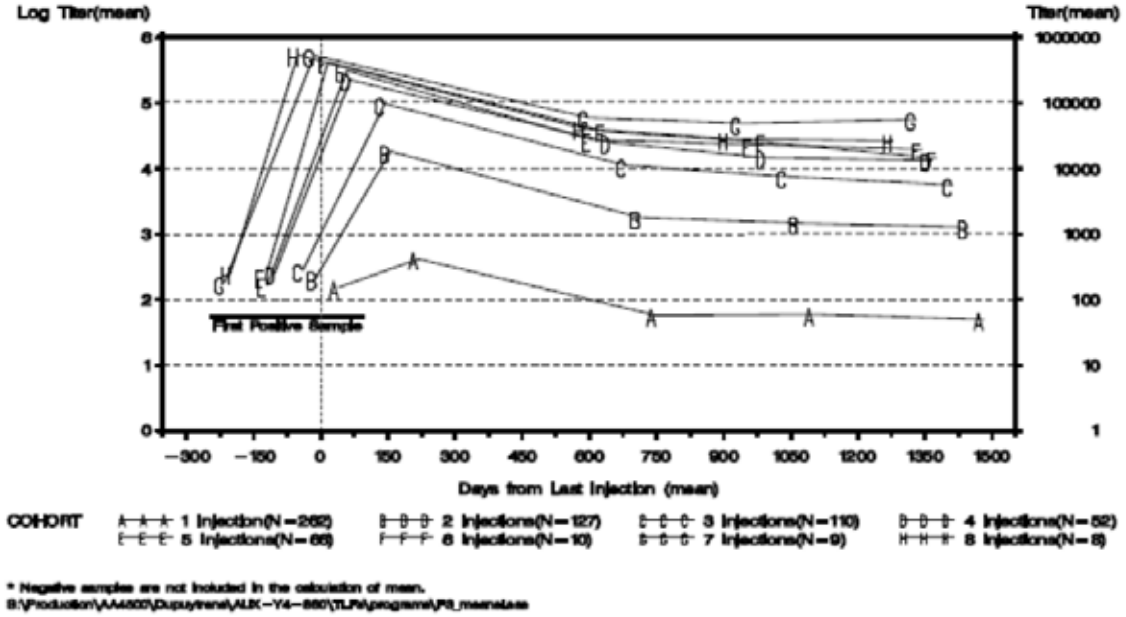
population, there were eight deaths and 81 subjects with at least one non-fatal SAE, none of which were attributed to study drug.

Anti-drug antibodies were measured at Year 4 follow up and while the mean log titres for AUX-I and AUX-II had decreased somewhat by Year 3 the levels at Year 4 were similar to Year 3 (Figures 3 and 4). By Year 4, 14.6% of subjects who had received one injection were seronegative (for AUX-I and for AUX-II) while for those who had received 2 injections only 1.9% and 1.0% were seronegative for AUX-I and AUX-II, respectively. In those who received 3 or more injections, all except one subject remained seropositive.

Evaluator's response:

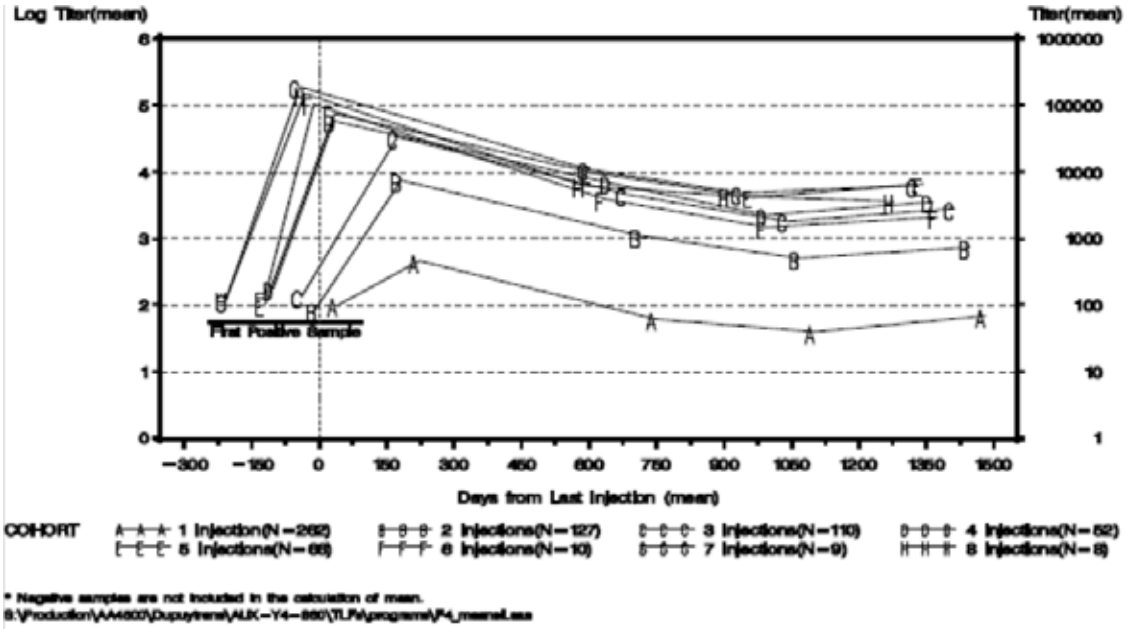
Potential risks in subjects who have surgery on previously treated cords have not been defined. Anti-drug antibodies remain present 4 years after treatment in the vast majority of subjects irrespective of the number of injections received.

Figure 3. Mean log Anti-AUX-I titers at the First positive sample, the Maximum sample, and Year 4 sample relative to the Last injection (Day 0) by Injection cohort.



Note: First positive sample was the time of first serum positive titer relative to the last injection (Day 0). The maximum sample was the time of maximum titer relative to the last injection (Day 0). The Year 4 sample was the time of the Year 4 sample relative to the last injection (Day 0).

Figure 4. Mean log Anti-AUX-II titers at the First positive sample, the Maximum sample, and Year 4 sample relative to the Last injection (Day 0) by Injection cohort.



Note: First positive sample was the time of first serum positive titer relative to the last injection (Day 0). The maximum sample was the time of maximum titer relative to the last injection (Day 0). The Year 4 sample was the time of the Year 4 sample relative to the last injection (Day 0).

2. ***The dossier included the protocol of Study B1531002 sponsored by Pfizer. It was stated to be a prospective open label Phase III study in 250 European subjects. What is the status of this study? Are there any relevant safety data that are available and should be disclosed? Comment on these data in relation to the safety profile reported in this dossier.***

Sponsor's response:

This Phase IIIb study remains ongoing. This multi-center study has 2 phases: The first is an open-label treatment phase (up to 5 months in duration) and the second is a 6 month follow-up phase. To date, a total of 254 subjects have been treated. No new safety risks have been identified from this ongoing study.

Evaluator's response:

Data should be provided to the TGA when available.

3. ***The dossier also made reference to a post-approval study in the US, AUX-CC-861. The study was stated to be an open label study assessing the safety, tolerability and pharmacokinetics of two concurrent doses of AA4500 0.58 mg in the same hand of subjects with Dupuytren's contractures and a palpable cord. What is the status of this study? Are there data which should be submitted for evaluation? Again, comment on these data in relation to the safety profile reported in this dossier.***

Sponsor's response:

The sponsor provided a synopsis of this study and stated that the *study was conducted as part of an ongoing development program to evaluate the safety and efficacy of two concurrent injections of Xiaflex into multiple cords in the same hand. The safety data from this study indicate that the safety profile of Xiaflex after two concurrent injections is similar to that reported after a single injection and no new safety issues were found.*

The study enrolled 12 subjects with at least 3 Dupuytren's contractures and one cord was treated in the first period and 2 cords concurrently treated in the second period. There were no discontinuations due to AEs and no SAEs related to study drug reported.

Evaluator's response:

Without the full clinical study report, conclusions on the relative safety of concurrent treatment of two cords cannot be made.

4. ***Why is the reconstituted dose so much greater than needed (0.9 mg for a dose of 0.58 mg)? This would appear to lead to possibility for overdosing if too much volume is drawn up and injected. Discuss the rationale behind this decision.***

Sponsor's response:

The sponsor conducted a study (reported as 50-1-0004 and 50-1-0005) which evaluated the volume of reconstituted Xiaflex drug product that could be withdrawn from the vial by a healthcare provider (HCP) after removal of the required dosing volume. The average remaining volume withdrawn from the vial after removal of the dosage volume for an MP joint was 0.08 mL (95% CI: 0.07 to 0.1 mL). The average remaining volume withdrawn from the vial after removal of the dosage volume for a PIP joint was 0.05 mL (95% CI: 0.04 to 0.06 mL). The worst case scenarios were 0.03 mL for MP and 0 mL for PIP joints.

The sponsor stated that *these results demonstrate that the overage in the vial is necessary to allow an HCP to comfortably remove a dose from the vial and establish that 0.9 mg is the minimal amount of collagenase clostridium histolyticum per vial required to permit withdrawal of the appropriate dosage volume*.

Evaluator's response:

While the evaluator agreed with the findings, the study does not take into account the risk of healthcare providers drawing up too much reconstituted product initially. Labelling must be very clear that the entire contents of the vial should not be drawn up and that the vials are single use only and the remaining contents should not be used for treating another joint. A sentence has been included in the PI that the *entire reconstituted Xiaflex solution contains 0.9 mg of Xiaflex. Reconstituted Xiaflex solution remaining in the vial after the injection should be discarded.* These issues must be covered in the doctor's training.

5. ***Discuss what training the investigators in the clinical development program undertook to ensure they were adequately skilled to administer the study injections. How is the sponsor proposing to ensure comparable skill levels of physicians who may use the product in Australia if registered?***

Sponsor's response:

With initiation of the Auxilium clinical trial program, investigators were offered injection training in the form of a PowerPoint presentation with a video component and written material in the Investigator's Brochure. The training material covered reconstitution of the lyophilised drug powder with sterile diluent, injection of the reconstituted drug into a Dupuytren's cord and the finger extension procedure, which is carried out the day after each injection.

The sponsor outlined the Training Plan for Australia in response to a question posed in the TGA Risk Management Plan (RMP) evaluation.

The applicant's training programme is designed to comprehensively train all appropriate users of the product. Training materials, therefore, will be delivered to specialist physicians through a variety of mechanisms and media. Physicians are provided access to 3 main elements of the training programme:

1. Training brochure and training video
2. Internet-based training
3. Peer-to-peer training meeting

Training will be linked to a Prescriber Certification Program.

Evaluator's response:

The proposed training appears suitable. The product should only be distributed to doctors who have undergone the training.

PI and CMI

The sponsor satisfactorily responded to all comments on the PI and Consumer Medicine Information (CMI) documents with a couple of exceptions as follows;

- Further data on contracture recurrence from Study AUX-CC-680 should be included in the PI (including recurrence rates at 2 and 4 years);
- Adverse effect data should be presented according to the referenced TGA guidelines and include a tabulation of the more frequent (≥1%) adverse events as well as data on postmarketing adverse reactions.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Xiaflex 0.58 mg in the proposed usage are unchanged from those identified in the *First Round Assessment of benefits*.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Xiaflex 0.58 mg in the proposed usage are unchanged from those identified in *First Round Assessment of Risks* apart from the following:

- The risk of recurrence was noted to continue to increase, from 4% at 9-12 months, to 19% at two years and to 42% at 4 years.
- The nonclinical evaluation found that the role of anti-drug antibodies in potential risks had not been examined in the nonclinical studies.

Second round assessment of benefit-risk balance

After review of information provided by the sponsor, the benefit-risk balance at the end of the second round evaluation remains the same as discussed in *First Round Assessment of Benefit-Risk Balance*.

It was noted that the nonclinical evaluation found the risk of anti-drug antibodies had not been addressed in the nonclinical study program. This adds further weight to the importance of active monitoring of potential immunogenicity risks. The draft PI has adequately covered such risks and the draft Risk management Plan has been updated to ensure relevant immunogenicity-related risks are being monitored.

As previously discussed in the first round evaluation, the training of doctors using the product will be critical in ensuring maintenance of the benefit-risk balance. The sponsor provided a copy of the Training Brochure used in the US and confirms that a similar document will be used in Australia. This will need to be part of the Risk management Plan together with ensuring distribution of the product is only to doctors who have satisfactorily completed the training.

It is known that the contractures may recur following available treatments and this was also the case with Xiaflex where the recurrence rate was 42% at 4 years. The sponsor stated that the PI will be updated with the final 5 year data from the follow-up study. Nevertheless, such data are

available and prescribers should be provided with the most relevant information on which to base prescribing decisions. Therefore, the evaluator maintains that recurrence data beyond one year should be included in the current draft PI.

The recommended changes to the PI and CMI have been adopted apart from the comments relating to the presentation of data in the *Adverse Effects* section. These still need to be addressed as outlined by the evaluator.

Overall, the benefit-risk balance of Xiaflex 0.58 mg, given the proposed usage of treatment of Dupuytren's contracture in adult patients with palpable cord, was considered to be favourable. This finding was subject to satisfactory responses to the remaining comments on the PI.

Second round recommendation regarding authorisation

The evaluator recommends approval of Xiaflex 0.58 mg injection for the treatment of Dupuytren's contracture in adult patients with palpable cord.

The product must only be distributed to doctors who have been appropriately trained. Training must cover the areas of reconstitution of the product, volumes to inject, dosing interval, injection technique, post injection finger manipulation and management, as well as information on immune-mediated reactions including anaphylaxis and its management, matrix metalloproteinase cross-reactivity and musculoskeletal syndrome and other potential adverse events and the requirements for reporting.

This recommendation was subject to satisfactory responses to the remaining comments on the draft PI.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

The original submission included an Australian specific RMP. In response to a number of outstanding issues outlined in the RMP evaluation report the sponsor proposed to replace the Australian RMP with the European Union (EU) RMP and an Australian specific Annex (ASA).

These documents were provided to the TGA on 26 April 2013.

The sections below considers the new EU RMP and ASA in the context of the evaluator's First round RMP evaluation report recommendations. The RMP evaluator stated that the sponsor's response to the TGA consolidated request for information following the first round evaluation report had not adequately addressed all of the issues identified in the first round RMP evaluation report.

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 17.

Table 17. Summary of Ongoing Safety Concerns as specified by the sponsor in the EU RMP

Type of Risk	Safety Concern
Important identified risks	Local reactions
	Immune-mediated reactions
	Skin lesions
	Tendon/Ligament rupture or injury
	Medication errors
Important potential risks	Injection-site bleeding in patients with coagulation disorders, including those on concurrent anti-coagulation therapy
	Severe systemic hypersensitivity/Anaphylaxis
	Reactions related to cross-reactivity with endogenous MMPs (including MSS and development/exacerbation of autoimmune disorders)
Important missing information	Re-treatment with collagenase *Clostridium histolyticum*
	Use during pregnancy
MMPs= matrix metalloproteinases; MSS=musculoskeletal syndrome.	

Evaluator comment

Importantly, this summary now includes the safety concerns recommended for inclusion by the RMP evaluator in the first round report. This was considered to be acceptable.

Pharmacovigilance plan

The pharmacovigilance plan as specified in the EU RMP and the ASA are summarised in Table 18.

Evaluator comment

The proposed use of targeted questionnaires as enhanced routine pharmacovigilance was considered to be appropriate. Draft questionnaires were provided with an assurance that the same questionnaires used in the EU are proposed for Australia. This was considered to be acceptable.

The pharmacovigilance plan describes a Risk Management Committee (RMC) which will meet quarterly to review nonclinical and clinical study data as well as spontaneous reports and pertinent medical literature. *Table 28 Summary of Safety Concern and Planned Pharmacovigilance Actions* describes the RMC as a routine pharmacovigilance activity whereas *Table 53 Overall Summary of the Risk Management Plan* lists it as additional pharmacovigilance. The evaluator considers the RMC enhanced routine pharmacovigilance. Nevertheless this was considered to be acceptable and considered an important activity despite this administrative discrepancy.

According to the RMP the following studies are ongoing as part of the pharmacovigilance plan:

- AUX-CC-860; Phase IIIb long-term follow up study of subjects treated with collagenase *Clostridium histolyticum* in previous studies.
- AUX-CC-862; Phase IV study of retreatment of recurrent contractures in joints effectively treated with collagenase *Clostridium histolyticum.*
- AUX-CC-864; Open-label study to assess the safety and efficacy of concurrent administration of 2 injections of collagenase *Clostridium histolyticum* into the same hand of subjects with multiple Dupuytren's contractures.
- B1531002; Prospective open-label investigation of the non-surgical treatment with collagenase *Clostridium histolyticum* .

The rationale for these studies as additional pharmacovigilance activities for the specified safety concerns is acceptable. As these studies are ongoing their protocols have not been evaluated in detail in this report. It was expected that results of these studies will be directly communicated to the TGA when available and detailed appropriately in PSURs.

According to the RMP there is one planned study, namely B1531005 which is a non-interventional post-approval commitment study to evaluate the outcomes of the various treatment options for Dupuytren's contracture. Although the evaluator has no particular objection to this study, limited detail was given and the protocol should be provided to the TGA for evaluation.

Section 2.2 of the ASA describes the pivotal and supportive studies relating to the application. This section should also describe an overview of the studies proposed as part of the pharmacovigilance plan including their applicability to Australia.

Notwithstanding the issues raised above, the evaluator considered that the pharmacovigilance plan was appropriate to monitor the safety concerns associated with Xiaflex.

Table 18. Pharmacovigilance Plan. Table continued across 3 pages.

Important Identified Risks	Pharmacovigilance Activities
Local reactions	Routine pharmacovigilance Risk Management Committee Additional Pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Re-treatment study (AUX-CC864) Open-label concurrent administration study (AUX-CC864) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)
Immune-mediated reactions	Routine pharmacovigilance Targeted questionnaire Risk Management Committee Additional pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)
Skin lesions	Routine pharmacovigilance Targeted questionnaire Risk Management Committee Additional pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)
Tendon/Ligament rupture or injury	Routine pharmacovigilance Targeted questionnaire Risk Management Committee Additional pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Re-treatment study (AUX-CC864) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)
Medication errors	Routine pharmacovigilance

Important Identified Risks	Pharmacovigilance Activities
	Risk Management Committee Additional pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)
Important potential risks	
Injection site bleeding in patients with coagulation disorders, including those on concurrent anti-coagulation therapy	Routine pharmacovigilance Risk Management Committee Additional pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)
Severe systemic hypersensitivity/anaphylaxis	Routine pharmacovigilance Targeted questionnaire Risk Management Committee Additional pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)
Reactions related to cross-reactivity with endogenous MMPs (including musculoskeletal syndrome and development/exacerbation of autoimmune disorders)	Routine pharmacovigilance Targeted questionnaire Risk Management Committee Additional pharmacovigilance Long-term safety follow-up study (AUX-CC-860) Prospective open-label study (B1531002) Non-interventional post-approval commitment study (B1531005)

Important Identified Risks	Pharmacovigilance Activities
Important missing information	
Re-treatment with collagenase *Clostridium histolyticum*	Routine pharmacovigilance Risk Management Committee Additional pharmacovigilance Re-treatment study (AUX-CC864)
Use in pregnancy	Routine pharmacovigilance Risk Management Committee Additional pharmacovigilance

Risk minimisation activities

The risk minimisation plan for Australia, as described in the ASA, provides the following activities (Table 19):

Table 19. Risk Minimisation Activities

Routine Risk Minimisation Activities	Product Information (PI) Consumer Medicine Information (CMI)
Additional Risk Minimisation Activities	Prescriber education and training program Educational brochure Audio-visual material Online and peer-to-peer training Prescriber certification A controlled distribution system

Evaluator comment

Education and training programme

The ASA describes the proposed content of the education program which seems reasonable however the actual educational materials are under development. As the educational materials are integral to the risk minimisation plan, it was recommended that the provision of educational materials satisfactory to the TGA prior to supply of the product in Australia would be imposed as a condition of registration.

Prescriber certification

The sponsor will maintain a list of the names of prescribers who have undertaken the specified training and therefore regarded as "Certified Prescribers". It was recommended that the sponsor should describe what, if any, requirements there are for re-certification and how this will be implemented. Additionally it is expected that the requirement for prescriber certification will be made clear in the education program. These details and/or amendments to the ASA can be provided when the educational materials are provided to the TGA for review.

Controlled distribution system

The sponsor has outlined a controlled distribution system whereby product will only be distributed to pharmacies that hold a valid prescription from a "Certified Prescriber". According to the ASA the intended prescriber population will be restricted to "*only those physicians experienced in injection procedures of the hand and in the treatment of patients with Dupuytren's contracture and who have been trained in the appropriate administration of Xiaflex*". The sponsor's controlled distribution system should ensure that all prescribers should meet the latter requirement but it is not clear how doctors who are not "experienced in injection procedures of the hand" will be necessarily excluded from participating in the education and from becoming "Certified Prescribers". A targeted marketing strategy may assist in this regard (that is, marketing to hand and plastic surgeons only). In the absence of any other alternative the evaluator considers that the proposed distribution system was acceptable from a RMP standpoint.

It was recommended that the sponsor report (in Periodic Safety Update Reports (PSURs) or separately) the success of the distribution system as a risk minimisation activity including reporting of any occurrence where the product was inadvertently used by a non-certified prescriber.

Additionally the rationale for and the mechanism of the controlled distribution system should be made clear to prescribers in the education program.

Effectiveness of the risk minimisation activities

The sponsor proposes to measure the effectiveness of the risk minimisation activities through "*close monitoring and by dedicated review within the PSURs*". At present this would appear acceptable. However, if "real-world" adverse events were seen above the level seen in clinical trials or a new safety concern came to light the TGA expects that the risk minimisation plan will be amended as needed to address specific concerns.

Summary of recommendations

The OPR provided these final recommendations in the context that the submitted RMP is supportive to the application; the implementation of the Collagenase *Clostridium histolyticum* EU RMP (version 8.0, date 20 April 2012) + Xiaflex Australian-specific Annex (version 1.0, date 26 April 2013) and any future updates as a condition of registration:

NB The sponsor has advised that an updated version of the EU RMP was recently provided to the European regulator for review. The sponsor should provide the TGA with a list of material changes to the Ongoing Safety Concerns, pharmacovigilance plan and risk minimisation plan with an assurance that the activities proposed in the evaluated EU RMP (version 8.0) and ASA will be fully implemented in Australia.

1. According to the RMP there is one planned study, namely B1531005 which is a non-interventional post-approval commitment study to evaluate the outcomes of the various treatment options for Dupuytren's contracture. Although the evaluator has no particular objection to this study, limited detail is provided and the protocol should be provided to the TGA for evaluation.
2. Section 2.2 of the ASA describes the pivotal and supportive studies relating to the application. This section should also describe an overview of the studies proposed as part of the pharmacovigilance plan including their applicability to Australia.
3. The sponsor has described the general content of the education program in the ASA which seems reasonable however the actual educational materials are under development. As the educational materials are integral to the risk minimisation plan, it was recommended that

the provision of educational materials satisfactory to the TGA prior to supply of the product in Australia would be imposed as a condition of registration.

4. The sponsor will maintain a list of the names of prescribers who have undertaken the specified training and therefore regarded as "Certified Prescribers". It is recommended that the sponsor should describe what, if any, requirements there are for re-certification and how this will be implemented. Additionally it is expected that the requirement for prescriber certification will be made clear in the education program. These details and/or amendments to the ASA can be provided when the educational materials are provided to the TGA for review.
5. It was recommended that the sponsor report (in PSURs or separately) the success of the distribution system as a risk minimisation activity including reporting of any occurrence where the product was inadvertently used by a non-certified prescriber.
6. Additionally, the rationale for and the mechanism of the controlled distribution system should be made clear to prescribers in the education program.
7. An amendment was recommended regarding the statement in the draft PI relating to anaphylaxis in accordance with the clinical evaluator's recommendations.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The quality (biological) evaluator has no objections to the registration of Xiaflex on quality grounds including with regards to formulation, manufacture, stability, shelf life, sterility, specifications, labelling and microbiology. It was recommended that the sponsor be required as conditions of registration to notify the TGA of any out of specification results following the completion of the reconstitution stability studies at the end of shelf life which are expected at the end of 2013 and to provide batches of the product for TGA's assessment prior to supply.

The Pharmaceutical Subcommittee (PSC) of Advisory Committee on Prescription Medicines (ACPM) also reviewed this item at the 150th meeting on 25 March 2013 and provided advice on a number of matters. The committee advised on further bioburden testing however the sterility evaluator has advised this was not needed since the product is aseptically manufactured prior to terminal sterilisation, including filtration through two 0.22 µm filters followed by aseptic filling and a prefiltration bioburden limit that was acceptably low. The committee also commented on the absence of information regarding the relationship between potency and clinical efficacy thereby making it difficult to ensure consistency between batches and the significant amount of polymorphisms in the collagenases. The quality evaluator has advised that all released lots of the product have met potency release tests specifications and that the genetic substitutions seen are not spontaneous mutations but rather genetic variations that are not deleterious to enzymatic activity. The sponsor was asked to comment on PSC's advice regarding the relationship between potency and clinical efficacy. The committee also raised a concern regarding the lack of long term studies, high rate of seroconversion and potential impact on re-presenting patients.

Nonclinical

The proposed indication providing identified risks were adequately addressed by the clinical evaluator. The nonclinical studies were well designed and conducted in compliance with GLP. Injection site toxicity was assessed including inadvertent venous injection, intrapenile injection

and repeat dose intravenous injection. Cultured explants of Dupuytren's cord and Peyronie's plaques showed the drug is active but non-collagenous elements such as blood vessels and nerves were preserved with no damage to adjacent tissue.

No safety pharmacology concerns were identified from the studies and there did not appear to be secondary pharmacodynamic effects of toxicological concern. Systemic exposure is limited and/or non-quantifiable. Following IV administration, $t_{1/2}$ was low at about 0.1 to 0.5 hours. Local subcutaneous injection into non-vascularised tissue showed limited and/or non-quantifiable exposure in plasma following single and repeat dosing. Repeat dosing in animals showed anti-drug antibodies but no evidence of antibody mediated adverse effects or collagenolytic activity. However there was no data to determine if these antibodies had neutralising potential or could cross react with matrix metalloproteinases (MMPs).

There was no evidence of systemic toxicity following subcutaneous, intrapenile, intramuscular or intratendon injections but local reactions did include: swelling, discolouration, bleeding, inflammation, collagen lysis, fibroplasia/neovascularisation, sinus erythrocytosis in lymph nodes and arterial intramural haemorrhage with no effects on adjacent nerves, blood vessels or elastic fibres.

The liver was identified as a target organ following IV administration however the injection site peri-vascular inflammation and fibrosis along with hepatic toxicity are not considered likely in clinical use given the limited systemic absorption and exposure margins used in the animal studies. Collagenase clostridium histolyticum is not teratogenic and no adverse findings were noted in fertility/embryonic development studies. Given the lack of systemic absorption then carcinogenicity studies, genotoxicity studies and reproductive toxicity studies were not required. The issue of anti-drug antibodies and potential for cross-reactivity with MMPs remains along with a potential concern of maternal anti-drug antibodies and its effects on the human fetus. Xiaflex is classified as a Category B1 drug in pregnancy and is not recommended for use; treatment should be postponed until after pregnancy.

Clinical

The clinical evaluator has reviewed the submitted data, which included:

- 45 reports of bioanalytical and analytical methods
- 2 pharmacology studies.
- 3 controlled clinical studies (DUPY-303, AUX-CC-857 and AUX-CC-859)
- 4 uncontrolled open label studies
- 4 other clinical studies
- 3 integrated summaries: efficacy, safety and immunogenicity
- 4 reports of post-marketing experience

The clinical evaluator recommended approval in the evaluation report (Clinical Evaluation Report (CER)). The following concerns were highlighted by the evaluator:

- Immunogenicity
- The need for doctor training and distribution of the product only to those doctors who have completed the training.
- Recurrence rate of contractures

Pharmacology

The pharmacology studies noted the following findings:

- Collagenase clostridium histolyticum shows no quantifiable systemic absorption following a single local injection followed by finger extension.
- Collagenase may diffuse from the injection site and the amount diffused is unclear however this is based on using methylene blue, which is a smaller molecule.
- Collagenase is not a substrate for CYP450 enzymes or other drug metabolising pathways.
- Excretion, drug interaction studies, multiple dose pharmacokinetic studies and secondary pharmacodynamic studies have not been conducted/assessed given the lack of systemic absorption but it appears collagenase is inactivated locally most likely as a result of complex formation with alpha-2 macroglobulin.
- Immunogenicity assessment from the pooled studies showed 85.7% of subjects were positive for antibodies to AUX-I and/or AUX-II at 30 days post injection rising to all subjects after 3-4 injections. Log titres were two fold higher after the second injection and titres declined over time but remained positive in >82% after 2 years.
- An assessment of potential cross-reactivity with endogenous human collagenases showed a low sequence homology with matrix metalloproteinases of 24-53% and differences in chain length. Assays to measure cross-reactivity with MMPs found no cross reactivity with MMPs 1,2,3,8 or 13.
- Neutralising antibodies against AUX-I were seen in 11% of samples and for AUX-II in 22% of samples from Study 857 in which 100% of subjects seroconverted.

Efficacy

A dose ranging study was conducted and determined that of the three doses tested (2500, 5000 and 10000 units) versus placebo, all were found to be better with success rates of 50%, 45.5% and 78.3% respectively compared to 0% in placebo, however only the 10000 unit dose (equivalent to 0.58 mg dose as proposed in the draft PI) was significantly effective at both joints of PIP and MP. The adverse events rate was 78%, 82% and 91% for the three doses respectively versus 65% for placebo. Given this information, it was decided the 10000 unit dose was the most appropriate.

Pivotal trials (857 and 859)

These were Phase III, US and Australian, multicentre, randomised (stratified by MP or PIP joint and by baseline flexion), double blind, placebo controlled, parallel design superiority trials comparing *collagenase clostridium histolyticum* 0.58 mg (0.25 mL for MP joints and 0.20mL for PIP joints, maximum 3 injections at monthly intervals with up to five additional injections in the open label period but maximum 3 injections per cord) and placebo in 308 subjects (Study 857) and 66 subjects (Study 859) with Dupuytren's contracture (fixed flexion deformity of at least one finger other than the thumb that was ≥20° and ≤100° for MP contracture (≤80° for PIP) caused by a palpable cord that had never been treated with collagenase and a positive "table top test" (the inability to simultaneously place the affected finger(s) and palm flat against a table top)) for a 90 day randomised period followed by a 9 month open label extension period. Key exclusion criteria were: chronic muscular, neurological or neuromuscular disorder affecting the hands, collagenase treatment within 30 days, receiving doxycycline within 14 days, anticoagulants within 7 days and recent stroke, bleeding or a disease affecting the hands. Subjects were monitored for 60 min postinjection for adverse events, underwent forced finger extension at 24 hours (three attempts allowed) and had hand splinting each night for 4 months with daily finger exercises. Baseline characteristics were similar in both studies and mostly

balanced (62-66 years, 70-87% male, mean 3 joints affected (range 1 to 13) with slightly more MP than PIP joints affected, mean contracture of 49-50° in Study 857 and 50-53° in Study 859, half with family history of Dupuytren's, 20-28% hand trauma, <76% alcohol use, prior surgery in Study 857 was 36% on collagenase versus 42% on placebo). Protocol deviations occurred in 10.7% on collagenase versus 12.5% on placebo in Study 857 with a high rate in Study 859 of 78% and 71% respectively (only two were considered major). Study discontinuation was 6.4% on collagenase in Study 857 (0% in Study 859) and 3.8% on placebo in Study 857 (9.5% in Study 859) mainly due to consent withdrawal and loss to follow-up. Three injections were given to 47.5% of collagenase subjects in Study 857 (60% in Study 859) versus 89.4% of placebo subjects in Study 857 (90.5% in Study 859). The studies had 80% power to establish superiority of collagenase clostridium histolyticum to placebo using a clinical success rate of contracture reduction to ≤5°with 54 subjects however this was increased to allow for dropouts.

The primary efficacy endpoint of clinical success rate of reduction in contracture to ≤5° as measured by finger goniometry 30 days post last injection was statistically significantly superior for collagenase clostridium histolyticum versus placebo:

Study 857: 64.0% versus 6.8%, absolute difference = 57.2% (95%CI 46.8-66.8, p<0.001)

- First injection success rate was 38.9% versus 1%
- Average number of injections was 1.7 versus 2.9
- First/Last injection success rate at MP joint: 45.1/76.7% versus 0/7.2%, p<0.001
- First/Last injection success rate at PIP joint: 27.1/40% versus 2.9/5.9%, p<0.002, p<001

Study 859: 44.4% versus 4.8%, absolute difference = 39.6% (95%CI 13.7-62.3, p<0.001)

- First injection success rate was 26.7% versus 4.8%
- Average number of injections was 1.7 versus 2.8
- First/Last injection success rate at MP joint: 45/65% versus 9.1/9.1%, p=NA, p<0.001
- First/Last injection success rate at PIP joint: 12/28% versus 0/0%, p=NA, p=0.069

Pooled efficacy: Clinical success at MP joint of 75.2% versus 7.5% and PIP joint of 36.8% versus 4.5%.

Clinical success was still evident if subjects who had missed their 30 day assessment were considered as not having reached success and was also seen at a higher rate for those with less severe degrees of severity but still seen in those with greater degree of severity at baseline (eg MP: 57.7% versus 0% in Study 857 and 60.0% versus 0% in Study 859), CER, p70-71. For joints that did not reach clinical success, about half did not receive the full treatment regimen mainly due to a lack of palpable cord.

The rate of clinical improvement (≥50% reduction in contracture from baseline) was significantly higher on collagenase at 84.7% versus 11.7% in Study 857 and 77.8% versus 14.3% in Study 859, p<0.001. Physician global assessment was 86% on collagenase versus 3% on placebo and subjects satisfaction (very/quite) was 87% versus 32%. Subgroup analysis showed no notable differences for age, gender, weight and BMI but a lower response in the Australian sites compared to the US sites.

Other studies

Other studies conducted are discussed in the CER (Attachment 2) but briefly showed the following:

Study 858: This 9 month open label extension to Study 857 was in subjects (286 initial collagenase subjects and 100 initial placebo subjects) who could have up to 5 additional injections (total of 8 over the 12 months of Studies 857 and 858). Of the 523 joints in the

combined analysis (combined with the initial Study 857), the rate of clinical success was 50.5% (MP =66.5% and PIP=29%) using an average 1.4 injections. Overall, 13% and 27% of MP and PIP joints respectively did not achieve clinical success after 3 injections. Physician rating and subject rating on success were high. Non-responders also showed some clinical response with 60% of MP and 37% of PIP joints with ≥50% reduction in contracture.

Studies 854 and 856: These were Phase III, open label, 9 month studies of up to 5 injections (maximum 3 per joint) in 386 and 201 subjects respectively (589 and 293 cords treated respectively) in patients with advanced Dupuytren's disease. Study completion was 93% and 84% respectively (discontinuation mainly due to consent withdrawal and loss to follow up) and subjects were male (87% and 82%), mean age of 63-65 years, 2.7-2.8 joints affected and 42% and 31% respectively for prior surgical treatment. Clinical success (reduction in contracture to ≤5°) was as follows:

- First injection success rate in 55-59% of MP joints and 19-33% of PIP joints.
- Last injection success rate was in 67-71% of MP joints and 27-41% of PIP joints
- Greater response in the less severely affected joints than the more severely affected (Study 854: 76% versus 32% and Study 856: 66% versus 29%).
- The average number of injections for clinical success was 1.2 for MP joints and 1.3-1.4 for PIP joints.
- Failure to achieve clinical success after 3 injections occurred in 6.1-6.9% for MP joints and 9.8-22.1% for PIP joints in the studies.
- Recurrence of contracture occurred in 2.3-7.1% of joints.

Study 303: This was a phase III, double blind, randomised, placebo controlled study with follow up for five years in 35 subjects. **Study 404** was an open label extension for up to five years in those subjects (n=19) who did not achieve clinical success (reduction in contracture to ≤5°) or had other joints to treat from the initial Study 303. Each joint could be injected up to three times and if clinical success was achieved prior to three injections then secondary or tertiary joints could be treated. The trial had a change in sponsorship and was prematurely terminated thereby providing limited information and an inadequate sample size with follow up for a median 401 days in Study 303 and 142 days in Study 404. The results were:

- First injection success rate: 70% versus 0% for placebo
- Last injection success rate: 91% for all joints after up to 3 injections versus 0% for placebo
- The average number of injections was 1.4.

Study 851 and its extension 852 and Study 853 were prematurely terminated due to a manufacturing issue and provided no meaningful data.

Study 101 had limited information and an evaluation of it was not possible.

Study 860: This was a non-treatment follow up study of subjects from Studies 854, 856, 857, 858 and 859 once a year for 4 years to examine recurrence rates, disease progression and long term safety. Of the possible 950 enrolled subjects, 634 were followed up; 75% had at least one successfully treated joint with the majority being MP joints of low baseline severity and joints not successfully treated were mainly PIP joints (71%). At Year 2, the recurrence rate for subjects who had been successfully treated was 19% (MP was 14% and PIP was 34%).

Pooled analysis across 6 trials: A box plot of results against antibody titres for cohorts of subjects who received the same number of injections did not show any correlation between clinical outcome and antibody titre and no trend for poorer outcome with increasing titre.

Recurrence rates: The recurrence rate was 42% at 4 years (62% PIP and 35% MP). Of those joints that were successfully treated in the primary study of AUX-CC-860, 12.8% had received medical or surgical intervention by the 4 year visit.

Safety

Overall patient exposure was 1,082 subjects who received at least one injection of 0.58 mg collagenase (1780 cords treated with 2630 injections). The median study participation was 275 days for subjects who had at least one dose and 366 days for subjects with 12 months post first dose data (n=268 subjects, 509 cords and 771 injections). Some 30% of subjects receiving at least one dose were from Australia. Treatment emergent adverse events were higher on collagenase than placebo at 97.8% versus 54% with mild, moderate and severe at 32.4% versus 35.8%, 55.9% versus 15.3% and 9.6% versus 2.9% respectively. The most frequent TEAEs from Sstudies 857, 859 and 303 compared with placebo tended to be in the hand and were: peripheral oedema (75.7% versus 5.1%), contusion (50.7% versus 2.9%), injection site pain (39% versus 3.6%), injection site haemorrhage (34.9% versus 2.9%), pain in extremity (33.1% versus 3.6%), tenderness (22.8% versus 0%), ecchymosis (23.2% versus 0%), lymphadenopathy (15.1% versus 0%) and pruritus (12.1% versus 0.7%). Other adverse events included skin laceration, lymph node pain, blood blister, auxillary pain, erythema and injection site pruritus. The profile of events from the other studies using subjects with 12 months post first dose data and subjects who had at least one dose was similar to these data and showed that 72.5% had moderate to severe TEAEs. Post treatment, the only TEAEs occurring ≥2% of subjects were recurrence of contractures (3%) and pain in extremity (2.3%) with severe events at 3.7%.

Adverse reaction rate was close to the TEAE rate in the pivotal studies and severe reactions occurred in 9.2% of subjects (none in placebo) and included: injection site pain (2%), extremity pain (2%), peripheral oedema (1.6%), contusion (1.6%), injection site haemorrhage (1.3%), tenderness, injection site cellulitis, ligament injury, skin laceration, tendon rupture, chest wall pain and irritability (all <1%). Most adverse reactions commenced on the injection day (80.6%). The adverse reaction rate from all subjects who had at least one dose was similar to the adverse event rate. The rate of adverse reactions in the post-treatment period from the non-pivotal studies was 7.8%. The rate of adverse reactions was fairly constant by the number of injections administered, except for pruritus which increased and the mean duration of peripheral oedema, contusion, injection site pain and extremity pain did not increase with increasing number of injections.

Seven deaths that were considered unrelated occurred during the programme (three myocardial infarction, iliac artery stenosis, liver cancer, pulmonary fibrosis complications and ruptured aortic aneurysm). Serious adverse events (non-fatal) occurred in 7.7% of subjects and included tendon rupture (n=3), ligament injury, tendonitis, finger deformity, Dupuytren's contracture and sensory disturbance of the hand, DVT and complex regional pain syndrome. The tendon ruptures and one ligament injury all occurred at the fifth PIP joint. Discontinuation due to adverse events was low at 1.1% in the pivotal studies due to injection site pain, dizziness and complex regional pain syndrome. In the other studies, the rate was 0.8% and due to various cancers and myocardial infarction in addition to the previous events.

The pivotal studies showed no notable mean changes in laboratory parameters or between collagenase and placebo however there were two with low platelets and two with low haemoglobin compared with none in the placebo group and increased blood urea nitrogen in three and increased aspartate aminotransferase (AST) in one subject with one of each on placebo. Vital signs showed no clinically relevant changes and hand grip strength showed no adverse findings. Post-marketing experience from the US showed over a year there were 7300 vials sold with 146 non-serious reports and 14 serious reports with the most frequent being skin laceration (48), peripheral oedema (41), contusion (37), drug ineffective (19), extremity

pain (14), injection site haematoma (12) and lymphadenopathy (10). Serious events included one atrial fibrillation with allergic reaction, one fatal myocardial infarction in a 79 year old patient with cardiac risk factors 5 days post injection, one pulmonary embolism one month post-injection, one fatal aortic dissection 2 hours post-injection, one fatality from ruptured aortic aneurysm one month post-injection, 2 tendon ruptures, 1 tendon damage and 5 skin tears needing grafting.

There were eight immunological events classed as hypersensitivity reactions (3 local reactions of the hand that were related), three urticarias and no systemic anaphylaxis. Only pruritus showed a relationship with increasing number of injections. There was no increase in antibody titres with severe events. There were no musculoskeletal events of polyarthritis, osteolysis, shoulder pain or reduction in range of motion. Special populations of age, gender, weight and diabetes history showed no obvious differences.

Risk management plan

The Office of Product Review has accepted the Collagenase clostridium histolyticum EU RMP, Version 8.0 (20 April 2012) plus Xiaflex Australian specific Annex (Version 1.0, 26 April 2013) and recommended further changes as outlined in their report.

The pharmacovigilance plan consists of routine pharmacovigilance with a targeted questionnaire and risk management committee (will meet quarterly to review nonclinical and clinical study data as well as spontaneous reports and pertinent medical literature) and additional pharmacovigilance that includes further clinical trials involving long term safety follow-up, an open label study and a non-interventional post-approval commitment study. The RMP evaluator considered that the pharmacovigilance plan was acceptable.

Risk minimisation plan involves a prescriber education and training program that includes educational brochures, audio-visual material, online based training and peer to peer training. Training will also be linked to a prescriber certification program and there will be a controlled distribution system linked to prescriber certification that will form conditions of registration.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the Pre-ACPM Response and follow up where appropriate with the Office of Product Review:

- The protocol for Study B1531005, which is a non-interventional post-approval commitment study to evaluate the outcomes of the various treatment options for Dupuytren's contracture, should be provided to the TGA for evaluation.
- Section 2.2 of the ASA describes the pivotal and supportive studies relating to the application. This section should also describe an overview of the studies proposed as part of the pharmacovigilance plan including their applicability to Australia.
- The sponsor has described the general content of the prescriber education and training program in the ASA which seems reasonable however the actual educational materials are under development. As the educational materials are integral to the risk minimisation plan, it was recommended that the provision of educational materials satisfactory to the TGA prior to supply of the product in Australia be imposed as a condition of registration [Note this needs to be provided to the TGA prior to registration].
- The sponsor will maintain a list of the names of prescribers who have undertaken the specified training and therefore regarded as "Certified Prescribers". It was recommended that the sponsor should describe what, if any, requirements there are for re-certification and how this will be implemented. Additionally it is expected that the requirement for prescriber certification will be made clear in the education program. These details and/or

amendments to the ASA can be provided when the educational materials are provided to the TGA for review.

- It was recommended that the sponsor report (in PSURs or separately) the success of the distribution system as a risk minimisation activity including reporting of any occurrence where the product was inadvertently used by a non-certified prescriber.
- Additionally, the rationale for and the mechanism of the controlled distribution system should be made clear to prescribers in the prescriber education and training program.

Risk-benefit analysis

Delegate considerations

Efficacy and recurrence rate of contractures

Collagenase clostridium histolyticum demonstrated a statistically superior clinical success rate to placebo in reducing the contracture to 5° or less at the primary joint in both pivotal Studies 857 and 859 (Australian trial) with a success rate after having up to 3 injections of 64.0% versus 6.8%, absolute difference = 57.2% (95%CI 46.8-66.8, p<0.001) for Study 857 and 44.4% versus 4.8%, absolute difference = 39.6% (95%CI 13.7-62.3, p<0.001) for Study 859. A positive response was seen after the first injection with less collagenase injections required than placebo (mean of 1.7 collagenase injections). Clinical success was seen at MP and PIP joints but less at PIP joints and those with more severe contraction. Subjects were representative of the target population and results were consistent across subgroups and showed physician and patient satisfaction. The primary endpoint is considered rigorous and clinically meaningful given its measure was close to full finger extension. Five open label extension periods that allowed non-primary joints to be treated with up to 5 injections (maximum 3 per joint) in the 9 month period showed consistent efficacy with the pivotal trials. Five trials were prematurely terminated due to change of sponsorship or manufacturing issues and provided limited information. Pooled immunogenicity data showed no relationship between treatment success and antibody titre levels.

Compared to surgical treatment, collagenase offers a non-surgical treatment option that avoids anaesthetic risks and possible surgical risks such as nerve or vessel injury and wound infections. Although trials directly comparing Xiaflex with surgical treatment would have been preferable to placebo controlled trials, their design would have been methodologically difficult and the lack of a currently approved pharmacological treatment makes a placebo control an appropriate option. Literature reports indicate full correction of MP joint contracture in 70-89% of cases and 13-29% of PIP joint cases. The pivotal trial showed a success rate of 65-77% for MP joint contractures and 28-40% for PIP joint contractures which is consistent with the surgical results for MP joints but less so for PIP joints.

The recurrence rate of contractures following treatment with Xiaflex at 9-12 months was 4% which increased to 19% at 2 years (34% PIP and 14% MP) and to 42% at 4 years (62% PIP and 35% MP). The recurrence rates in the literature for surgical interventions vary but range from 12-73% for fasciectomy/aponeurectomy and 33-100% for fasciotomy/aponeurotomy according to the sponsor. Data provided from the sponsor shows a range from 2-85% (percutaneous needle fasciotomy was 65% at 2.75 years and 85% at 5 years). Treatment with Xiaflex seems to be in the range of recurrence rates reported for surgical options but 5 year data from the ongoing trial AUX-CC-860 should provide further clarity (expected in the tird quarter of 2013).

Safety and RMP

Xiaflex was used in 1082 subjects and almost all showed adverse events that were considerably higher than placebo with nearly all being classified as treatment related and mostly occurring on injection day with the majority resolved by the next injection. Adverse events were mostly associated with the hand and included peripheral oedema (75.7% versus 5.1%), contusion (50.7% versus 2.9%), injection site pain (39.0% versus 9.5%), injection site haemorrhage (34.9% versus 2.9%) and pain in the extremity (33.1% versus 3.6%). These may be related to the product or as a response to collagen lysis. Other frequent (>10%) TEAEs were tenderness, ecchymosis, lymphadenopathy and pruritus. Most events were mild (32%) or moderate (56%) and resolved prior to the next treatment. Peripheral oedema occurred after each injection and only pruritus increased with further injections. None of the seven deaths were considered treatment related. There were nine treatment related serious adverse events that included 3 tendon ruptures (0.3%), ligament injury; tendonitis; finger deformity; Dupuytren's contracture and sensory disturbance of hand; DVT; and complex regional pain syndrome.

Postmarketing data of one year noted 160 reports with 14 serious cases including 2 tendon ruptures, 1 tendon damage and 5 skin tears requiring grafting which are of concern. Tendon rupture and ligament damage, especially at the fifth finger PIP joint, is a risk. Localised haemorrhage is a potential concern and patients on anticoagulants would need to avoid treatment (the PI includes a precaution). Discontinuation due to adverse events was infrequent. Laboratory values and vital signs were unremarkable and there was no reduction in hand grip strength. Antibodies developed in 85% of subjects after the first injection which increased to all subjects by the 3-4 injections. Immunological events found no cases of systemic anaphylaxis, three cases of urticaria and three cases of local hand allergic type reactions. The database, however, may be too small to detect anaphylactic reactions. There was no overall association between increasing injection number, and by inference increasing antibody titre, and TEAEs except for pruritus. There was also no obvious association between the severity of events and antibody titre and there were no musculoskeletal events that may have indicated inhibition of endogenous collagenases however this remains a potential concern. Safety was consistent across subgroups and patients on tetracyclines and anticoagulants were excluded from the trials (precaution in the PI). The use of Xiaflex is for the treatment of one cord only at a time. A study was conducted by the sponsor in patients with two cords concurrently treated that indicated no serious adverse events however this study was only in 12 patients and has not been evaluated by the TGA. The sponsor has also indicated from an ongoing study in 254 patients recruited in Europe (up to 5 months open label treatment plus 6 months follow up) that no new safety concerns have been identified. This study should be submitted to the TGA post-registration.

Long term data, anti-drug antibodies and re-presenting patients

Given this product contains a non-human protein then patients will develop antibodies. Although these antibodies did not appear to impact on efficacy or safety as such and there was no systemic absorption, antibodies nevertheless were detected. There is a concern therefore for patients who re-present for treatment given the high seroconversion rate in developing anti-drug antibodies. During the clinical studies, after the first injection, antibodies were detected in 92% of patients against AUX-I and 86% of patients against AUX-II which increased to 100% by the third or fourth injection against both collagenases. No severe hypersensitivity reactions or anaphylaxis occurred but there were cases of urticaria and pruritus which increased with further injections. Follow up at two years following the initial injection showed 92.3% of patients were antibody positive for AUX-I and 95% were antibody positive for AUX-II. By Year 4, 85.4% were positive for those receiving one injection and 98-99% were positive for those receiving 2 injections. This shows that anti-drug antibodies remain in the vast majority of patients even if they only received one injection. Since the proteins in Xiaflex have homology with human MMPs, then it is possible that the antibodies could interfere with human MMPs. The

clinical data have not raised concerns regarding exacerbation of autoimmune diseases or musculoskeletal syndrome however the exposure is too limited to detect these rare events. Therefore it remains a possibility and long term monitoring is therefore needed to assess this potential risk. The draft PI addresses these issues and the sponsor should outline any further data on this subject and how it intends to address this in the RMP.

Training program

The clinical evaluator and RMP evaluator have both highlighted the importance of a training program for prescribers which is strongly endorsed. Xiaflex should only be administered by doctors who have completed the training program and the sponsor has addressed this through the RMP. Training should include reconstitution of the product, volumes to inject, dosing interval, injection technique, finger manipulation post injection, information on likely adverse reactions including potential for allergic reactions and their management (and the availability of adrenaline, oxygen and intravenous fluids) and information on MMP cross-reactivity and potential for autoimmune conditions and musculoskeletal syndrome. The risks of usage beyond the approved indication should also be covered. The sponsor has advised that the training materials will include educational brochures, audio-visual material, online based training and peer to peer training. Training will also be linked to a prescriber certification program and there will be a controlled distribution system linked to prescriber certification. Product will only be distributed to pharmacies that hold a valid prescription from a "Certified Prescriber".

Injection volume

The proposed vial contains 0.9 mg of drug substance however the proposed dosage is 0.58 mg with a variable volume to inject depending on the joint. This leaves a potential excess of drug substance and potential for overdosing when drawing up the amount. The sponsor conducted a study into this to show how much could be withdrawn from the vial by a healthcare professional after the required volume had been withdrawn. The amounts remaining in the vial varied from 0.05 mL to 0.08 mL depending on the joint which indicates a reasonable overage. However this doesn't address the potential for the initial drawing up of the vial to include too much drug substance. The labels on the box state use in one patient on one occasion only but they do not inform that the entire contents should not be drawn up nor do they state to discard remaining contents. A statement on the label should be included to address this matter.

Data deficiencies

Long term data is limited but a 5 year report is due soon which will be a condition of registration. Data on the use of Xiaflex at other injection sites around the body are unavailable. There is limited information on potential risks in subjects who undergo surgery following Xiaflex treatment however safety data from Study AUX-CC-860 at Year 4 did not report any issues relating to surgery of previously treated cords. Pregnancy and lactation effects have not been assessed and therefore the potential effects of anti-drug antibodies on the developing fetus are unknown (PI recommends against use).

Conditions of registration

The following are proposed as conditions of registration:

1. The implementation in Australia of the collagenase clostridium histolyticum EU Risk Management Plan (EU RMP), (version 8.0, 20 April 2012) plus Xiaflex Australian specific Annex (version 1.0, 26 April 2013), included with submission PM-2012-01472-3-3, and any subsequent revisions, as agreed with the TGA.
2. The sponsor will be required to complete the reconstitution stability studies on the drug product batches at the end of shelf life (36 months), when those batches become available at the end of 2013, and notify the TGA of any out of specification results.

3. It is a condition of registration that independent batches of Xiaflex Collagenase clostridium histolyticum, AA4500 Powder for Injection vial (0.9 mg/vial) with sterile diluent vial (3 mL/vial) [AUST R 199584] imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS). The sponsor should supply:
    a. A Certified Product Details (CPD) document.
    b. Certificates of Analysis of all active ingredient (drug substance) and final product.
    c. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents.
    d. Evidence of the maintenance of registered storage conditions during transport to Australia.
    e. Three vials of each batch for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

    These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The conditions remain in place until you are notified in writing of any variation.
4. An electronic draft of the Certified Product Details (CPD), as described in Appendix 7 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.
5. Xiaflex is only administered by doctors who are experienced in the diagnosis and management of Dupuytren's disease and who have undergone a prescriber education and training program that includes reconstitution of the product, volumes to inject, dosing interval, injection technique, post injection finger manipulation and management, information on likely adverse reactions including potential allergic reactions and their management (including vital signs monitoring, adrenaline, IV fluids, oxygen), information on matrix metalloproteinase cross-reactivity and potential for autoimmune conditions, information on musculoskeletal syndrome and risks of usage outside the approved indication and information on reporting adverse events. This program, including its educational materials, has been agreed with the TGA.
    a. The rationale for and the mechanism of the controlled distribution system should be made clear to prescribers in the prescriber education and training program.
6. There will be a prescriber certification program, including re-certification requirements, and a controlled distribution system for Xiaflex as agreed with the TGA.
    a. The sponsor is to report, in PSURs or separately, the success of the distribution system as a risk minimisation activity including reporting of any occurrence where the product was inadvertently used by a non-certified prescriber.
7. Xiaflex is only to be administered in a setting with the ability to monitor vital signs and treat allergic reactions including administer adrenaline, oxygen and intravenous fluids.
8. The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
    a. Studies B1531002 and B1531005.
    b. Study AUX-CC-860, 5 year study report.

c. Any other studies that identify safety concerns or provide updated safety information from the ongoing program.

Summary

Xiaflex exhibits moderate clinical efficacy and a safety profile that appears confined to the treated limb. A number of issues have been discussed above including contracture recurrence rates, local reactions, tendon rupture, ligament damage, skin lesions, antibody development, injection volume, potential for allergic reactions, cross-reactivity with endogenous MMPs, the need for a prescriber education and training program, a prescriber certification program and a controlled distribution system, usage by doctors in a setting capable of treating allergic reactions, potential concern in pregnancy and the need for ongoing monitoring through an RMP. Providing these are adequately addressed by the sponsor, then the submission appears approvable at this stage with acceptable quality, safety and efficacy of the product.

Recommendation

The Delegate was inclined to **approve** this submission at this stage by Actelion Pharmaceuticals Australia Pty Ltd to register Xiaflex (collagenase clostridium histolyticum) 0.9 mg powder for injection based on the quality, safety and efficacy of the product being satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit Discussion:

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

The sponsor should address the following issues in the Pre-ACPM response

- Provide an update on the possibility of anti-drug antibodies causing a safety concern, including in relation to cross-reactivity with endogenous human proteins (MMPs), and in particular with autoimmune conditions or musculoskeletal syndrome, based on any further studies or post-marketing experience and summarise how this is being further investigated and addressed in the RMP.
- Provide further details of the ongoing clinical trial program beyond that provided to the clinical evaluator in response to the consolidated TGA request for information, Question 4 on Eefficacy, including any studies into other potential uses such as Peyronie's disease.
- Comment on PSC's advice below regarding the relationship between potency and clinical efficacy "*Noted the sponsor's justification for not providing information on the relationship between potency specifications and clinical efficacy. The PSC raised concerns that the absence of information makes it difficult to ensure consistency in activity between batches. The Committee agreed that it was difficult to assess how in vitro assay relates to clinical activity.*"
- Discuss why the clinical success rate was lower in Australian Study 859 than US Study 857.
- Provide information on reports of lymphangitis from clinical trials and the postmarketing period.
- Explain further why the vial needs to contain 0.9 mg when the dose is only 0.58 mg.
- Please c*omment on how doctors who are not "*experienced in injection procedures of the hand" will be necessarily excluded from participating in the education and therefore becoming "Certified Prescribers" in the controlled distribution system.
- The sponsor has advised that an updated version of the EU RMP was recently provided to the European regulator for review. The sponsor should provide the TGA with a list of material changes to the Ongoing Safety Concerns, pharmacovigilance plan and risk

minimisation plan with an assurance that the activities proposed in the evaluated EU RMP (version 8.0) and ASA will be fully implemented in Australia.

- Please address the recommendations by the RMP evaluator.
- Provide a timeframe for when the prescriber education and training program, including its educational materials, can be submitted to the TGA for agreement prior to registration.
- Provide a timeframe for when the prescriber certification program and a controlled distribution system, including re-certification requirements, can be submitted to the TGA for agreement prior to registration.

ACPM's advice is requested on the following issues

- Is there potential for use beyond the approved indication and if so, are the risks associated with such use adequately addressed in the PI and RMP?
- Is the safety profile acceptable and partially consistent with what would be expected if the patient had undergone surgery instead?

Response from sponsor

The sponsor stated that there are currently no pharmacological therapies for the treatment of Dupuytren's contracture and as such there is an evident unmet medical need. Compared to the current treatment preference in Australia of fasciectomy, Xiaflex offers a non-surgical treatment option that is broadly as effective as fasciectomy but that avoids anaesthetic risks and possible surgical risks such as nerve or vessel injury and wound infections. Furthermore, recovery from treatment with Xiaflex is substantially shorter (around 1 week or less) compared with fasciectomy (4-12 weeks).

The first question the Delegate raised to the ACPM was whether there is potential for use beyond the approved indication. The sponsor is implementing substantial barriers to minimise the possibility for use beyond the approved indication. The sponsor will be directing marketing campaign materials towards surgeons who have a sub-specialty in hand surgery and/or physicians with active membership of the Australian Hand Surgery Society (AHSS). In addition, as part of the "certification" procedure linked to the controlled distribution, the product will only be supplied to those surgeons who have undergone the education and training program and who make a signed declaration that:-

a. they are experienced in injection procedures of the hand, and

b. they are experienced in the treatment of patients with Dupuytren's contracture.

The sponsor believed that these measures will satisfactorily reduce the risk of use beyond the approved indication.

The Delegate raised a number of points requiring the sponsor's clarification, as follows:

1. ***Provide an update on the possibility of anti-drug antibodies causing a safety concern, including in relation to cross reactivity with endogenous human proteins (MMPs), and in particular with autoimmune conditions or musculoskeletal syndrome, based on any further studies or post marketing experience and summarise how this is being further investigated and addressed in the RMP***

There is a theoretical concern that collagenase clostridium histolyticum antibodies could cross-react with endogenous human matrix metalloproteinases (MMPs), resulting in the development of new-onset autoimmune disorder or the exacerbation of pre-existing autoimmune disease. In addition, anti-drug antibodies (ADAs) could theoretically lead to an MMP inhibitor–associated musculoskeletal syndrome.

The available literature indicates that the closest structural and functional vertebrate analogues, MMPs, are substantially different from collagenase clostridium histolyticum. Furthermore, there are a number of structural differences in the amino acid homology, catalytic and collagen binding and function between collagenase clostridium histolyticum and the mammalian collagenolytic MMPs that make antibody cross-reactivity less likely in any species.

The potential for anti-AUX-I or anti-AUX-II antibodies to cross-react with mammalian MMPs was evaluated *in vitro* using an enzyme-linked immunosorbent assay with serum samples taken from patients who were administered Xiaflex.

- No evidence for MMP inhibition was observed.
- Validated assays are now available to assess the mammalian MMPs (MMP -1, -2, -3, -8, and -13) bioactivity in serum. The validation work demonstrated that the methods can be used for the determination of the inhibition of MMP -1, -2, -3, -8, and -13 when spiked into human serum. This work provides a suitable assay for monitoring MMP inhibitory activity of neutralizing antibodies to AUX-I and AUX-II (should any be identified).
- A review of all TEAEs from completed clinical programs and global postmarketing safety surveillance up until February 2013 revealed no signals identified for a combination of adverse events (severe systemic hypersensitivity, onset of musculoskeletal syndrome or new onset/exacerbation of autoimmune disorders) suggestive of cross reactivity with endogenous human MMPs of anti- AUX-I and anti-AUX-II antibodies.

In summary, at the time of this response, there was clinical evidence from the global safety surveillance undertaken that indicates evidence of cross-reactivity of anti-drug antibodies (anti-AUX-I and anti-AUX-II) with endogenous human MMPs.

Within the RMP, the occurrence of immune-mediated reactions, severe systemic hypersensitivity/anaphylaxis and reactions potentially related to cross-reactivity with endogenous MMPs (including musculoskeletal syndrome and development/exacerbation of autoimmune disorders) are being monitored via routine pharmacovigilance (including use of a targeted questionnaires) to capture additional information. The occurrence of these reactions is also specifically being investigated in two postmarketing clinical studies [AUX-CC-860 (long-term follow-up of subjects treated with collagenase clostridium histolyticum in Studies AUX-CC-854, AUX-CC-856, AUX-CC-857, AUX-CC-858, and AUX-CC-859), and Study B1531005 (non-interventional EU post approval commitment study to evaluate the outcomes of the various treatment options for Dupuytren's contracture).

2. ***Provide further details of the ongoing clinical trial program beyond that provided to the clinical evaluator in response to Question 4 on Efficacy, including any studies into other potential uses such as Peyronie"s disease.***

A table summarising all the ongoing clinical trials including those beyond Dupuytren's contracture was provided with the sponsor's pre-ACPM response.

3. ***Comment on the PSC's advice below regarding the relationship between potency and clinical efficacy 'Noted the sponsor's justification for not providing information on the relationship between potency specifications and clinical efficacy. The PSC raised concerns that the absence information makes it difficult to ensure consistency in activity between batches. The committee agreed that it was difficult to assess how in vitro assay relates to clinical activity.'***

The sponsor was not deliberately silent on a relationship between the potency specification and clinical efficacy. By its nature, the potency test methods (that is, SRC and GPA) are intended to be an *in vitro* surrogate for clinical efficacy. These release test methods measure the enzymatic activity of the AUX-I (collagenase Type I) and AUX-II (collagenase Type II) intermediates in both the Drug Substance (DS) and Drug Product (DP) as part of the release process. In particular, the

SRC test method utilises a synthetic Type I collagen substrate which is cleaved by AUX-I/II thus providing a direct measurement of the DS and DP enzyme activity. Type I collagen is relevant as a surrogate as this collagen type is found in the *in vivo* Dupuytren's contracture cord.

The basis of the established potency relative to reference specifications was developed utilizing more than 20 batches of DS and DP produced with the commercial manufacturing process. These potency specifications were used to release clinical materials, thus providing a link to the consistent enzymatic activity observed *in vitro* with the observed *in vivo* efficacy seen in the clinic.

4. Discuss why the clinical success rate was lower in Australian Study 859 than US Study 857.

Subjects in Australia had more bilateral disease and more PIP joints of high severity, suggesting that subjects in Australia may have had more severe disease.

While the percentage of subjects with a reduction in contracture to 5° or less was similar between the United States and Australia for primary MP joints, the success rate for primary PIP joints tended to be higher in the United States compared with Australia. Of the PIP joints that did not achieve the primary endpoint, 72.2% (13/18) in Australia did not receive the full collagenase clostridium histolyticum treatment regimen compared with 50.0% (21/42) in the United States. In both countries, the reason most commonly cited for not receiving the full treatment regimen of up to three injections was "no palpable cord to inject".

5. Provide information on reports of lymphangitis from clinical trials and the post marketing period.

Further to a request from the Committee for Medicinal Products for Human Use (CHMP), following a meeting on the 23 August 2012, the European Marketing Authorisation Holder (MAH) agreed to add the adverse drug reaction term of "lymphangitis" to Section 4.8 of the Summary of Product Characteristics (SmPC).

In clinical studies, the safety population included 1082 subjects who had received at least 1 dose of collagenase clostridium histolyticum. Lymphangitis was reported in 11 (1.0%) of these subjects. In postmarketing reports through to 27 February 2013, 6 cases of lymphangitis were reported. Based on clinical studies with collagenase clostridium histolyticum, the frequency of lymphangitis has been shown to be about 1%. The CHMP concluded that a causal relationship between Xiaflex and lymphangitis is at least a reasonable possibility. Consequently the addition of lymphangitis as an adverse drug reaction to the SmPC with the frequency "uncommon" was requested by the CHMP. Detailed information on reports of lymphangitis was also provided with this pre-ACPM response submission.

6. Explain further why the vial needs to contain 0.9 mg when the dose is only 0.58 mg.

Each vial of drug product is filled at a target of 0.9 mg of collagenase clostridium histolyticum per vial in order to ensure the specified therapeutic dose of 0.58 mg can be withdrawn.

The sponsor conducted a study under protocol 50-1-0004, "*Evaluation of Volume that Can Be Withdrawn by a Healthcare Provider from a Xiaflex™ Vial after Withdrawal of the Appropriate Dosage Volume*", to evaluate the volume of reconstituted drug product that can be withdrawn from the vial by a healthcare provider (HCP) after removal of the required dosing volume, as prepared for administration for both metacarpophalangeal (MP) and proximal interphalangeal (PIP) joint injections. The reconstitution, dose removal and removal of remaining volume, including recording of that volume, was conducted by qualified HCPs (medical doctors, registered nurses, physician assistants, pharmacists) who participated in the Xiaflex clinical studies of Dupuytren's contracture, in order to replicate the "real world" use of the drug product.

The analysis of the results was conducted by Auxilium personnel and reported in report 50 - 1-0005, "*Report of Evaluation of Volume that Can Be Withdrawn by a Healthcare Provider from a Xiaflex™ Vial after Withdrawal of the Appropriate Dosage Volume*". The theoretical volume remaining in the vial after reconstitution and removal of the dose for a MP joint is 0.14 mL. For a PIP joint, it is 0.11 mL. The study demonstrated that the actual amount that can be withdrawn from a vial after removing a clinical dose is generally lower than the theoretical volume: 0.08 mL for MP joints and 0.05 mL for PIP joints. Generally, the volume varies from 0.07 mL to 0.1 mL for MP and 0.04 mL to 0.06 mL for PIP (95% CI). However, the "worst case" was 0.03 mL for MP joints and 0 mL for PIP. These results demonstrate that the overage in the vial is necessary to allow an HCP to comfortably remove a dose from the vial and establish that 0.9 mg is the minimal amount of collagenase clostridium histolyticum per vial required to permit withdrawal of the appropriate dosage volume.

Protocol 50-1-0004 and report 50-1-0005 have been provided to the TGA.

7. Please comment on how doctors who are not 'experienced in injection procedures of the hand' will be necessarily excluded from participating in the education and therefore becoming 'Certified Prescribers' in the controlled distribution system.

A tailored marketing program will be used to target physicians who would routinely see and treat patients with Dupuytren's contracture, that is,surgeons who have a sub-specialty in hand surgery and/or physicians with active membership of the Australian Hand Surgery Society (AHSS). These physicians will be offered training, education and certification for Xiaflex use. Part of the certification process will require that physicians make a signed declaration that a) they are experienced in injection procedures of the hand, and b) they are experienced in the treatment of patients with Dupuytren's contracture.

8. The sponsor has advised that an updated version of the EU RMP was recently provided to the European regulator for review. The sponsor should provide the TGA with a list of material changes to the Ongoing Safety Concerns, pharmacovigilance plan and the risk minimisation plan with an assurance that the activities proposed in the evaluated EU RMP (version 8.0) and the ASA will be fully implemented in Australia.

Version 9.0 of the EU RMP was produced as a routine update. There were no material changes to the Ongoing Safety Concerns, pharmacovigilance plan or the risk minimisation plan. Version 9.0 of the EU RMP was submitted to EMA on 25 April 2013. Except where indicated within the ASA the sponsor assured the TGA that the activities proposed in the evaluated EU RMP (version 8.0) and the ASA will be fully implemented in Australia.

9. Please address the recommendations by the RMP evaluator.

a. The protocol for study B1531005 should be provided to the TGA for evaluation

The protocol was sent to the TGA on 7 May 2013.

b. Section 2.2 of the ASA should also describe an overview of the studies proposed as part of the Pharmacovigilance Plan including their applicability to Australia

The sponsor confirmed that this will be done when the ASA is updated prior to registration.

c. As the Education Materials were still under development it was recommended that provision of educational materials satisfactory to the TGA prior to supply of the product in Australia be imposed as a condition of registration.

All education content will be included in the updated ASA and provided to the TGA prior to registration.

d. The sponsor will maintain a list of the names of prescribers who have undertaken the specified training and therefore regarded as "certified prescribers". It was recommended that the sponsor should describe what, if any, requirements there are

for re-certification and how this will be implemented. Additionally, it was expected that the requirement for prescriber certification will be made clear in the education program. These details and/or amendments to the ASA can be provided when the educational materials are provided to the TGA for review.

A re-certification process was not planned. Certified prescribers will have full access to all training and education materials via the web portal once certified. Through the pharmacovigilance actions proposed within the RMP the sponsor will monitor adverse events and evaluate on an ongoing basis whether re-certification would be valuable as an additional risk minimization activity. No re-training/re-certification is conducted in any other territory where the product is approved.

The requirement for prescriber certification will be made clear in the education program.

e. It was recommended that the sponsor report (in PSURs or separately) the success of the distribution system as a risk minimisation activity including reporting of any occurrence where the product was inadvertently used by a non-certified prescriber.

The sponsor confirmed that they will monitor and report these points as requested.

f. Additionally, the rationale for and the mechanism of the controlled distribution system should be made clear to prescribers in the education program.

The sponsor ensured the TGA that this would be made clear to prescribers in the education program.

g. An amendment was recommended regarding the statement in the draft PI relating to anaphylaxis in accordance with the clinical evaluator's recommendations.

The amendments recommended by the clinical evaluator have been included in the Australian PI.

h. Provide a timeframe for when the prescriber education and training program, including its educational materials, can be submitted to the TGA for agreement prior to registration.

The sponsor aimed to submit the amended ASA containing all educational, training and certification content, and details of the controlled distribution system (and the amendments requested within the Delegate's Overview and RMP Evaluation Report) to the TGA by 15 July 2013.

i. Provide a timeframe for when the prescriber certification program and a controlled distribution system, including re-certification requirements, can be submitted to the TGA for agreement prior to registration.

Please see above response. As described above, the sponsor had no plans for a re-certification program although the need for this will be monitored on an ongoing basis.

Advisory committee considerations

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

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Xiaflex (containing collagenase clostridium histolyticum) to have an overall positive benefit–risk profile for the indication as proposed**;**

> *Xiaflex is indicated for the treatment of Dupuytren's contracture in adult patients with palpable cord.*

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the following:

- Subject to satisfactory negotiation of the Risk Management Plan, specifically the educational program and certification of qualified prescribers
- That "qualified prescribers" should be confined to those doctors who have experience in the diagnosis and surgical management of Dupuytren's disease and have undergone a prescriber education and training program approved by the TGA and be capable of treating allergic reactions.
- The rationale for and the mechanism of the controlled distribution system should be made clear to prescribers in the prescriber education and training program.
- A statement in the CMI to reflect the RMP requirements regarding use only by practitioners with suitable experience and training to use the product, such as:

the procedure should only be used by approved practitioners who will be able to display (or show you) such an authorisation.

Proposed PI/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:

- Statements in the *Adverse Events* section of the PI and relevant sections of the CMI to ensure the prominence of important adverse events such as lymphangitis and tendon rupture
- A statement on the potential long term risk of auto-immune disease

The ACPM advised that the 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 (collagenase clostridium histolyticum) 0.9 mg lyophilised powder vial for intralesional inejction, indicated for:

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

Specific conditions applying to these therapeutic goods

1. The collagenase clostridium histolyticum EU Risk Management Plan (EU-RMP), version 8.0, dated 20 April 2012, and Xiaflex Australian specific Annex (version 2.0, 12 July 2013) included with submission PM-2012-01472-3-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

   An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required. The reports are to at least meet the requirements for Periodic Safety Update Reports (PSURs) as described in the European Medicines Agency's Guideline on Good

Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report, Part VII.B. "Structures and processes". Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

The annual submission may be made up of two Periodic Safety Update Reports each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

2. The sponsor is required to complete the reconstitution stability studies on the drug product batches at the end of shelf life (36 months), when those batches become available at the end of 2013, and notify the TGA of any out of specification results.

3. The independent batches of Xiaflex Collagenase clostridium histolyticum, AA4500 Powder for Injection vial (0.9 mg/vial) with sterile diluent vial (3 mL/vial) [AUST R 199584] imported into Australia are not to be released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS). The sponsor should supply:

    i. A Certified Product Details (CPD) document.

    ii. Certificates of Analysis of all active ingredient (drug substance) and final product.

    iii. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents.

    iv. Evidence of the maintenance of registered storage conditions during transport to Australia.

    v. Three vials of each batch for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

    These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The conditions remain in place until you are notified in writing of any variation.

4. An electronic draft of the Certified Product Details (CPD), as described in Appendix 7 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM), should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

5. Xiaflex is only to be supplied to qualified doctors who are experienced in the diagnosis of Dupuytren's disease and are experienced in injection procedures of the hand. All qualified doctors must have either experience in the surgical management of Dupuytren's disease or been an investigator in the clinical trial program. Prior to use of Xiaflex, all qualified doctors must have undergone a prescriber education and training program by Actelion Pharmaceuticals Australia Pty Ltd including training in the appropriate administration of Xiaflex. The prescriber education and training program must include reconstitution of the product, volumes to inject, dosing interval, injection technique, post injection finger manipulation and management, information on likely adverse reactions including potential allergic reactions and their management (including vital signs monitoring, adrenaline,

intravenous fluids, oxygen), information on matrix metalloproteinase cross-reactivity and potential for autoimmune conditions, information on musculoskeletal syndrome and risks of usage outside the approved indication and information on reporting adverse events. This program, including its educational materials, has been agreed with the TGA on 18 July 2013.

i. The rationale for and the mechanism of the controlled distribution system should be made clear to prescribers in the prescriber education and training program.

ii. The prescriber education and training program must inform doctors that Xiaflex is only to be administered in a setting with the ability to monitor vital signs and treat allergic reactions including the ability to administer adrenaline, oxygen and intravenous fluids**.**

6. There will be a prescriber certification program and a controlled distribution system for Xiaflex, as agreed with the TGA on 18 July 2013.

   The sponsor is to report, in PSURs or separately, the success of the distribution system as a risk minimisation activity including reporting of any occurrence where the product was inadvertently used by a non-certified prescriber.

7. The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:

   a. Studies B1531002 and B1531005.

   b. Study AUX-CC-860, 5 year study report.

   c. Any other studies that identify safety concerns or provide updated safety information from the ongoing program.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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