

**7.2 COLLAGENASE CLOSTRIDIUM HISTOLYTICUM,  
900 microgram injection [1 x 900 microgram vial]  
(&) inert substance [1 x 3 mL vial],  
Xiaflex<sup>®</sup>, Actelion Pharmaceuticals Australia Pty Ltd**

**1 Purpose of Application**

1.1 The major re-submission sought an Authority Required listing for collagenase clostridium histolyticum (CCH) for the treatment of Dupuytren’s contracture in patients with ≤2 affected rays (fingers) who are unable to simultaneously place the affected finger and palm flat on a table due to a Dupuytren’s contracture with a palpable cord.

**2 Requested listing**

2.1 The re-submission sought the following General Schedule listing:

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Proprietary Name and Manufacturer	
COLLAGENASE <i>CLOSTRIDIUM HISTOLYTICUM</i> 0.9 mg vial lyophilised powder and vial of diluent	1	0	Xiaflex	Actelion

<b>Authority required</b> Treatment of Dupuytren’s contracture, in patients with two or less rays affected, by specialists who have been trained and certified in its use, for patients who are unable to simultaneously place the affected finger and palm flat on a table due to a Dupuytren’s contracture with a palpable cord, and who would otherwise require surgery.
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2.2 Listing was sought on the basis of a cost comparison between CCH and surgical fasciectomy, using a similar approach to the previous submission.

2.3 The re-submission sought a more restrictive listing than the previous submission by limiting the use of CCH to patients with ≤ 2 rays affected who would otherwise require surgery. The PBAC recalled that it had previously considered that subsidy of CCH should be restricted to patients with Dupuytren’s contracture with 2 or less affected rays who would otherwise undergo surgical fasciectomy (CCH PBAC minutes July 2013, para 7.5).

2.4 The re-submission proposed that all physicians administering CCH must have undergone a prescriber education and training program by Actelion Pharmaceuticals Australia Pty Ltd. Details of the training program were discussed in the re-submission and appeared unchanged from the July 2013 submission.

2.5 The pre-sub-committee response (PSCR, p4) agreed with the Secretariat suggested restriction which aimed to reformat the requested restriction to meet current electronic media requirements.

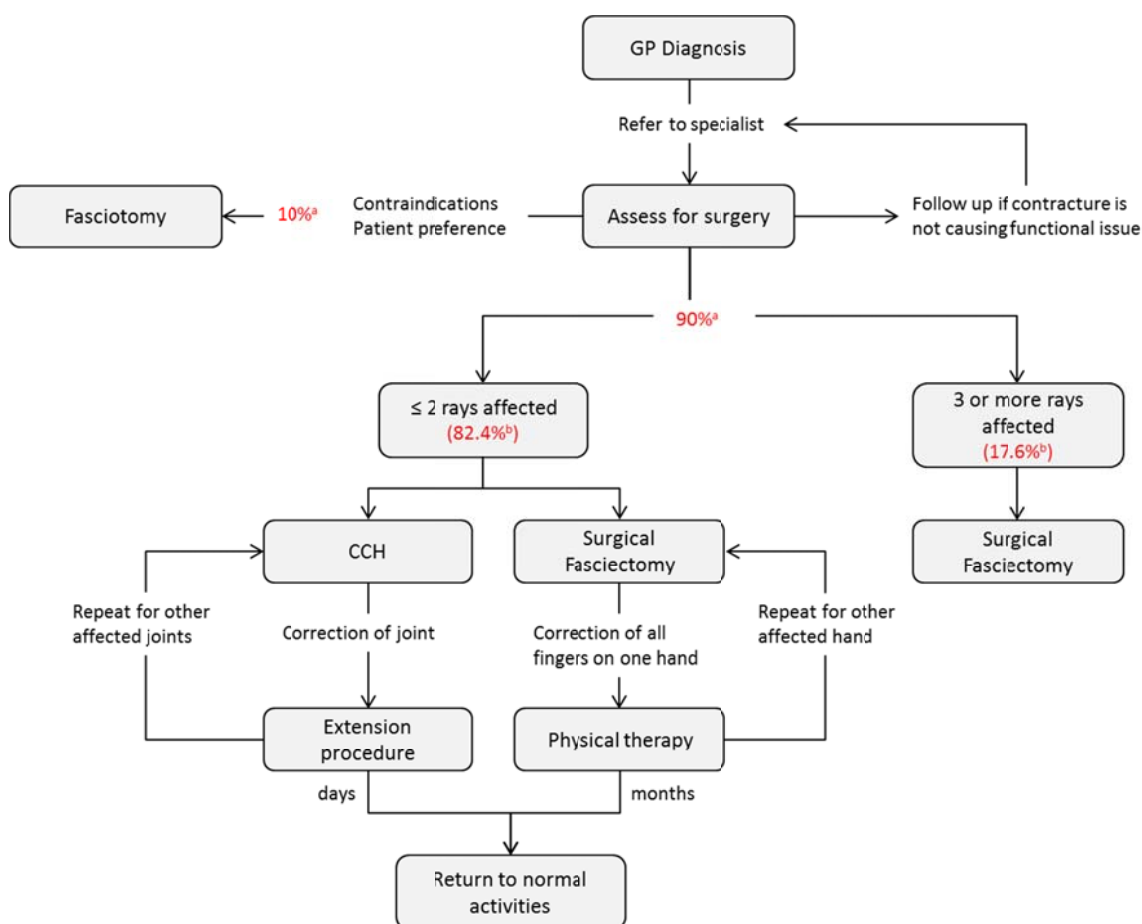
*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**3 Background**

- 3.1 Collagenase *Clostridium histolyticum* (CCH, Xiaflex<sup>®</sup>) was registered by the TGA on 7 August 2013 for the treatment of Dupuytren's contracture in adult patients with a palpable cord.
- 3.2 CCH was previously considered by the PBAC at the July 2013 meeting for "the treatment of Dupuytren's contracture, by specialists who have been trained in its use, for patients who are unable to simultaneously place the affected finger and palm flat on a table due to a Dupuytren's contracture with a palpable cord". The major submission was rejected on the basis of inadequate evidence supporting the claim of non-inferiority and an unacceptably high price. The PBAC considered that a further price reduction was essential; that the future listing should be restricted to patients with  $\leq 2$  rays affected; and that fasciotomy should be included in both the clinical management algorithm and the economic analysis.

#### **4 Clinical place for the proposed therapy**

- 4.1 Dupuytren's contracture is a progressive fibro-proliferative disorder involving irreversible contraction of the palmar fascia of the hand and fingers, primarily affecting the metacarpal-phalangeal (MCP) and/or proximal inter-phalangeal (PIP) joints of the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> fingers. Dupuytren's contracture is associated with progressive functional disability of affected hands, with an average time for progression from a mild to a severe contracture of 4.7 years (Rodrigo et al. 1976). Recurrence of disease following successful treatment is common. Current treatment is surgical fasciectomy (excision of the Dupuytren's cord), open or percutaneous needle fasciotomy (division of the cord by needle or fine blade) or amputation in the most severe cases. Long term, aggressive and recurrent disease (i.e. severe contracture) responds less favourably to treatment due to remodelling of surrounding ligaments and joints.
- 4.2 CCH hydrolyses the collagen subtypes that predominate in the diseased Dupuytren's cord (mostly type I and III collagens), causing disruption of the cord (completed by manual manipulation of the affected digit if required) and improved elasticity and mobility of the affected joint. For the more restrictive listing requested in the re-submission, treatment with CCH was expected to be limited to less severely affected hands (i.e. hands with  $\leq 2$  affected rays), and may be used in patients who would otherwise be treated with surgical fasciectomy or open/percutaneous needle fasciotomy.
- 4.3 The re-submission's clinical treatment algorithm is depicted below.



Source: Executive Summary, Fig.E2, p4

For more detail on PBAC's view, see section 7 "PBAC outcome"

## 5 Comparator

- 5.1 The re-submission nominated surgical fasciectomy as the comparator. This is the appropriate comparator as accepted by the PBAC at the July 2013 meeting. The PBAC also noted that fasciotomy should be regarded as an appropriate secondary comparator (CCH PBAC minutes, July 2013, para 5.1). The re-submission rejected this proposition and fasciotomy was excluded from consideration in the clinical evidence and economic evaluation.

For more detail on PBAC's view, see section 7 "PBAC outcome"

## 6 Consideration of the evidence

### Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician discussed 4 aspects of treatment with CCH. These were:
- 1) the clinical role of CCH;
  - 2) what the clinician perceived a typical CCH treatment episode involves;
  - 3) the number of injections likely to be used in clinical practice; and
  - 4) limitations on CCH prescribing expected in practice.

The clinician further addressed the Committee’s questions pertaining to post-surgery follow up and what was considered the best clinical measure of recurrence. Overall, the PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (6) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with CCH including the ability to return to work earlier, providing full correction of deformity, significantly lower comparative costs for individual patients and from a healthcare system perspective compared to surgery as patients can be managed as ‘out-patients’ and acceptable safety.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

### Clinical trials

- 6.3 No new randomised trials comparing CCH with placebo or surgical fasciectomy were identified. Three new surgical fasciectomy observational studies were identified (Bainbridge 2012a, Dias 2013b and Karabeg 2012), and included in the re-submission. The studies identified in the updated and original literature searches and included in the re-submission are presented in the table below.

#### Studies presented in the re-submission for surgical correction of Dupuytren’s contracture

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>New studies identified and included in the re-submission</b>		
Bainbridge 2012(a) <sup>c</sup>	Current trends in the surgical management of Dupuytren’s disease in Europe: an analysis of patient charts.	<i>European Orthopaedics and Traumatology</i> 2012a;3:31-41.
Dias 2013(b) <sup>c</sup>	Patterns of Recontracture After Surgical Correction of Dupuytren Disease.	<i>Journal of Hand Surgery</i> 2013;38(10): 1987-1993.
Kan 2013 <sup>c</sup>	The consequences of different definitions for recurrence of Dupuytren’s disease.	<i>Journal of Plastic, Reconstructive and Aesthetic Surgery</i> 2013;66(1):95-103.
Karabeg 2012 <sup>a,b,c</sup>	Results of surgery treatment of Dupuytren’s contracture in 115 patients.	<i>Medical Archives</i> 2012;66(5):329-331.
<b>Studies presented in the re-submission and July 2013 submission</b>		
Abe 2004 <sup>b</sup>	Surgery for Dupuytren’s disease in Japanese patients and a new preoperative classification.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 2004; 29:B(3):235.
Adam 1992 <sup>b</sup>	Prognosis in Dupuytren’s disease.	<i>The Journal of Hand Surgery</i> 1992; 17A:312.
Andrew 1991 <sup>b,c</sup>	Segmental aponeurectomy for Dupuytren’s disease: a prospective study.	<i>Journal of Hand Surgery (Brit)</i> 1991; 16 B(3):255.
Anwar 2007 <sup>a,b,c</sup>	Results of surgical treatment of dupuytren’s disease in women: a review of 109 consecutive patients.	<i>The Journal of Hand Surgery (USA)</i> 2007; 32(9):1423.
Anwar 2009 <sup>a,b,c</sup>	The lateral digital flap for dupuytren’s fasciectomy at the proximal interphalangeal joint - A study of 84 consecutive patients.	<i>The Journal of Hand Surgery (Eur)</i> 2009; 34(1):90.
Armstrong 2000 <sup>b</sup>	Dermofasciectomy in the management of Dupuytren’s disease.	<i>The Journal of Bone and Joint Surgery (Brit)</i> 2000; 82(1):90.
Ashley 1953 <sup>c</sup>	A two-stage operation for Dupuytren’s contracture, with a report of 38 cases.	<i>Plastic and Reconstruction Surgery</i> 1953;12(1):79.
Balaguer 2009 <sup>b</sup>	Histological staging and dupuytren’s disease recurrence or extension after surgical treatment: A retrospective study of 124 patients.	<i>Journal of Hand Surgery (Eur)</i> 2009; 34(4):493.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>New studies identified and included in the re-submission</b>		
Beyerman 2004 <sup>d</sup>	Severe contracture of the proximal interphalangeal joint in Dupuytren's disease: Does capsuloligamentous release improve outcome?	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 2004; 29 B(3):240.
Bismil 2012 <sup>c</sup>	The development of one-stop wide-awake Dupuytren's fasciectomy service: a retrospective review.	<i>Journal of The Royal Society of Medicine Short Reports</i> 2012; 3(7):48.
Bulstrode 2005 <sup>b,c</sup>	The complications of Dupuytren's contracture surgery.	<i>The Journal of Hand Surgery (USA)</i> 2005; 30(5):1021.
Citron 2005 <sup>b,c</sup>	Recurrence after surgery for Dupuytren's disease: A randomised trial of two skin incisions.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 2005; 30(6):563.
Clibbon 2001 <sup>b,c</sup>	Palmar segmental aponeurectomy for Dupuytren's disease with metacarpophalangeal flexion contracture.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 2001; 26 B(4):360.
Coert 2006 <sup>c</sup>	Results of partial fasciectomy for Dupuytren disease in 261 consecutive patients.	<i>Annals of Plastic Surgery</i> 2006; 57(1):13.
De Maglio 1996 <sup>b</sup>	Dupuytren's disease: recurrence and extension treated by selective aponeurectomy.	<i>Chirurgia degli Organi di Movimento</i> 1996; 81(1):43.
Denkler 2005 <sup>a,c</sup>	Dupuytren's fasciectomies in 60 consecutive digits using lidocaine with epinephrine and no tourniquet.	<i>Plastic and Reconstruction Surgery</i> 2005; 115(3):802.
Dias 2006 <sup>b,c</sup>	Dupuytren's contracture: an audit of the outcomes of surgery.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 2006; 31(5):514.
Dickie 1967 <sup>b</sup>	Dupuytren's contracture, a review of the late results of radical fasciectomy.	<i>British Journal of Plastic Surgery</i> 1967; 20(3):311.
Donaldson 2010 <sup>a,c</sup>	The association between intraoperative correction of Dupuytren's disease and residual postoperative contracture.	<i>Journal of Hand Surgery (Eur)</i> 2010; 35(3):220.
Ebskov 1997 <sup>c</sup>	Day care surgery for advanced Dupuytren's contracture.	<i>The Journal of Hand Surgery</i> 1997; 22 B(2): 191.
Edmunds 2011 <sup>c</sup>	A new surgical approach to Dupuytren's disease.	<i>Journal of Hand Surgery (Eur)</i> 2011; 36(6):485.
Engstrand 2009 <sup>a,c</sup>	Evaluation of activity limitation and digital extension in dupuytren's contracture three months after fasciectomy and hand therapy interventions,	<i>Journal of Hand Therapy</i> 2009; 22(1): 21.
Evans 2002 <sup>c</sup>	A clinical report of the effect of mechanical stress on functional results after fasciectomy for Dupuytren's contracture.	<i>Journal of Hand Therapy</i> 2003; 15(4): 331.
Foucher 1992 <sup>c</sup>	A modified open palm technique for Dupuytren's disease. Short and long term results in 54 patients.	<i>International Orthopaedics</i> 1995; 19(5):285.
Foucher 1995 <sup>b,c</sup>	Open palm technique for Dupuytren's disease. A five-year follow-up.	<i>Annals of Hand and Upper Limb Surgery</i> 1992; 11(5):362.
Gleberman 1982 <sup>c</sup>	Wound complications in the surgical management of Dupuytren's contracture: A comparison of operative incisions.	<i>The Hand</i> 1982; 14(3): 248.
Hakstian 1966 <sup>b</sup>	Long-term results of extensive fasciectomy.	<i>British Journal of Plastic Surgery</i> 1966; 19(2):140.
Hall 1997 <sup>b</sup>	Skin replacement in Dupuytren's disease.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 1997; 22(2):193.
Hogemann 2009 <sup>b</sup>	Results of total aponeurectomy for Dupuytren's contracture in 61 patients: A retrospective clinical study.	<i>Archives of Orthopaedic and Trauma Surgery</i> 2009; 129(2):195.
Honner 1971 <sup>a,b</sup>	Dupuytren's contracture. Long term results after fasciectomy.	<i>The Journal of Bone and Joint Surgery</i> 1971; 53(2):240.
Horner 1971 <sup>c</sup>	Dupuytren's contracture. Analysis of 100 consecutive surgical cases.	<i>Rocky Mt Medical Journal</i> 1971; 68(10): 49.
Hueston 1963 <sup>b</sup>	Recurrent Dupuytren's contracture.	<i>Plastic and Reconstruction Surgery</i> 1963; 31(1): 66.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>New studies identified and included in the re-submission</b>		
Jurisc 2008 <sup>b</sup>	Dupuytren's disease characteristics in Primorsko-goranska County.	<i>Collegium Antropologicum</i> 2008; 32(4):1209.
Kartik 1963 <sup>d</sup>	Data on the recurrence and the progression of Dupuytren's contracture.	<i>Acta Chirurgiae Plasticae</i> 1963; 5(4): 253.
Kjeldal 1988 <sup>a,c</sup>	Out-patient surgery for Dupuytren's disease under intravenous regional anaesthesia.	<i>The Journal of Hand Surgery</i> 1988; 13 B(3):257.
Kobus 2007 <sup>b,c</sup>	Evaluation of treatment results of patients with Dupuytren's contracture - Our clinical experience.	<i>Ortopedia Traumatologia Rehabilitacja</i> 2007; 9(2):134.
Loos 2007 <sup>c</sup>	50 years' experience with Dupuytren's contracture in the Erlangen University Hospital--a retrospective analysis of 2919 operated hands from 1956 to 2006.	<i>BMC Musculoskeletal Disorders</i> 2007; 8:60.
Macnicol 1984 <sup>c</sup>	The open palm technique for Dupuytren's contracture.	<i>International Orthopaedics</i> 1984; 8(1):55.
Maekela 1991 <sup>b,c</sup>	Dupuytren's contracture: the long-term results after day surgery.	<i>Journal of Hand Surgery (Brit)</i> 1991; 16 B(3):272.
Matton 1982 <sup>a,c</sup>	Our experience with 186 operated Dupuytren hands. Comparison of two techniques.	<i>Acta Orthopaedica Belgica</i> 1982; 48(5): 775.
Mavrogenis 2009 <sup>b,c</sup>	Partial fasciectomy for Dupuytren's contractures.	<i>Journal of Surgical Orthopaedic Advances</i> 2009; 18(2):106.
McFarlane 1966 <sup>b</sup>	Dupuytren's contracture. The management of one hundred patients.	<i>The Journal of Bone and Joint Surgery</i> 1966; 48(6):1095.
Meathrel 2004 <sup>d</sup>	Abductor digiti minimi involvement in Dupuytren's contracture of the small finger.	<i>Journal of Hand Surgery (USA)</i> 2004; 29(3):510.
Misra 2007 <sup>a,c</sup>	Predicting the Outcome of Surgery for the Proximal Interphalangeal Joint in Dupuytren's Disease.	<i>The Journal of Hand Surgery</i> 2007; 32(2): 240.
Moermans 1991 <sup>a,b,c</sup>	Long-term results after segmental aponeurectomy for Dupuytren's disease.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 1996; 21 B (6):797.
Moermans 1995 <sup>b</sup>	Segmental aponeurectomy in Dupuytren's disease.	<i>Journal of Hand Surgery (Brit)</i> 1991; 16 B(3):243.
Nieminen 1986 <sup>b</sup>	Resection of the palmaris longus tendon in surgery for Dupuytren's contracture.	<i>Annales Chirurgiae et Gynaecologiae</i> 1986; 75(3):164.
Olmeda 1986 <sup>b</sup>	The treatment of Dupuytren's contracture by radical aponeurectomy.	<i>Italian Journal of Orthopaedics and Traumatology</i> 1986; 12(3):305.
Orlando 1974 <sup>c</sup>	Dupuytren's contracture: a review of 100 patients.	<i>British Journal of Plastic Surgery</i> 1974; 27(3):211.
Rank 1978 <sup>b,c</sup>	Surgery for Dupuytren's contracture: A long-term review.	<i>Australia New Zealand Journal of Surgery</i> 1978; 48(4):398.
Razemon 1982 <sup>c</sup>	Lateral digital rotation flaps in the treatment of forms of Dupuytren's contracture.	<i>Annales de Chirurgie de la Main</i> 1982; 1(3):199.
Rebello 1995 <sup>b</sup>	Dupuytren's disease: Analysis of 110 patients on a long-term follow-up.	<i>European Journal of Plastic Surgery</i> 1995; 18(1):32.
Robins 1993 <sup>c</sup>	Day care surgery for Dupuytren's Contracture.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 1993; 18B:494.
Rodrigo 1976 <sup>c</sup>	Treatment of Dupuytren's contracture. Long term results after fasciotomy and fascial excision.	<i>The Journal of Bone and Joint Surgery</i> 1976; 58-A(3):380.
Rombouts 1989 <sup>b</sup>	Prediction of recurrence in the treatment of Dupuytren's disease: evaluation of a histologic classification.	<i>The Journal of Hand Surgery</i> 1989; 14A: 644.
Roy 2006 <sup>a,b</sup>	Fasciectomy and conservative full thickness skin grafting in Dupuytren's contracture.	<i>Acta Orthopaedica Belgica</i> 2006; 72(6): 678.
Sennwald 1990 <sup>c</sup>	Fasciectomy for treatment of Dupuytren's disease and early complications.	<i>The Journal of Hand Surgery</i> 1990; 15(5): 755.
Shaw 1996 <sup>c</sup>	Dupuytren's disease treated by palmar fasciectomy and an open palm technique.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 1996; 21 B(4):484.
Sinha 2002 <sup>a</sup>	Functional benefit of Dupuytren's surgery.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 2002; 27B(4):378.

Trial ID/First Author	Protocol title/ Publication title	Publication citation
<b>New studies identified and included in the re-submission</b>		
Tonkin 1984 <sup>b</sup>	Dupuytren's contracture: a comparative study of fasciectomy and dermofasciectomy in one hundred patients.	<i>The Journal of Hand Surgery</i> 1984; 9(2): 156.
Tonkin 1985 <sup>d</sup>	The proximal interphalangeal joint in Dupuytren's disease.	<i>The Journal of Hand Surgery</i> 1985; 10(3): 358.
Tripoli 2008 <sup>b,c</sup>	The "Jacobsen Flap" for the treatment of stages III-IV dupuytren's disease: A review of 98 cases.	<i>Journal of Hand Surgery (Eur)</i> 2008; 33(6):779.
Ullah 2009 <sup>b,c</sup>	Does a 'firebreak' full-thickness skin graft prevent recurrence after surgery for Dupuytren's contracture? A prospective, randomised trial.	<i>The Journal of Bone and Joint Surgery</i> 2009; 91-B(3):374.
van Giffen 2006 <sup>b</sup>	Dupuytren's disease: Outcome of the proximal interphalangeal joint in isolated fifth ray involvement.	<i>Acta Orthopaedica Belgica</i> 2006; 72(6): 671.
van Rijssen 2006 <sup>c</sup>	A Comparison of the Direct Outcomes of Percutaneous Needle Fasciotomy and Limited Fasciectomy for Dupuytren's Disease: A 6-Week Follow-Up Study.	<i>Journal of Hand Surgery (Brit &amp; Eur)</i> 2006; 31(5):717.
van Rijssen 2012 <sup>a,b</sup>	Five-year results of a randomised clinical trial on treatment in Dupuytren's disease: percutaneous needle fasciotomy versus limited fasciectomy.	<i>Plastic and Reconstruction Surgery</i> 2012; 129(2): 469.
Vigroux 1992 <sup>a,b,c</sup>	A natural history of Dupuytren's contracture treated by surgical fasciectomy: The influence of diathesis (76 hands reviewed at more than 10 years).	<i>Annals of Hand and Upper Limb Surgery</i> 1992; 11(5):367.
Weckesser 1964 <sup>b,c</sup>	Results of wide excision of the palmar fascia for dupuytren's contracture: special reference to factors which adversely affect prognosis.	<i>Annals of Surgery</i> 1964; 160:1007.

Source: Appendix C to the re-submission; constructed during the evaluation.

<sup>a</sup> Included in comparison of clinical success.

<sup>b</sup> Included in comparison of recurrence.

<sup>c</sup> Included in comparison of safety data.

<sup>d</sup> Not included in any relevant comparison in the re-submission.

6.4 The assessment of the risk of bias in the CCH trials was unchanged from the previous submission. The PBAC previously considered it appropriate to exclude the DUPY 303 trial from the analyses given its small sample size and early termination (CCH PBAC minutes July 2013, para 6.4). The risk of bias in the surgical fasciectomy observational studies was high. Given the inclusion of the observational studies and the lack of analysis of statistical variance, the risk of bias in the informal comparison was high.

6.5 Similar to the previous submission, the 71 surgical fasciectomy observational studies were grouped by outcomes or safety data comparable to those reported in the CCH pooled data. Data from the recently completed CCH long term extension study AUX CC 860 (patients continuing from the CORD I and CORD II trials) were included in the comparison of recurrence rates (not reported in the CCH placebo trials) and the economic evaluation.

### **Comparative effectiveness**

6.6 The results of the CCH versus placebo trials were unchanged from the previous submission (see table below).

#### **Results of the CCH placebo controlled trials**

Trial ID	CCH n/N (%)	Placebo n/N (%)	Risk difference (95% CI)	Relative risk (95% CI)	NNT
DUPY 303	21/23 (91.3%)	0/12	0.91 (0.75, 1.07)	23.3 (1.5, 354.1)	1.1
CORD I	130/203 (64.0%)	7/103 (6.8%)	0.57 (0.49, 0.65)	9.4 (4.6, 19.4)	1.8
CORD II	20/45 (44.5%)	1/21 (4.8%)	0.40 (0.23, 0.57)	9.3 (1.3, 65.0)	2.5
Pooled result			0.63 (0.37, 0.88)	9.9 (5.1, 19.1)	1.6
Pooled result (excluding DUPY 303)			0.50 (0.33, 0.67)	NR	2.0

Source: Table 27, p.98 of the re-submission.

Abbreviations: CCH, collagenase *Clostridium histolyticum*; NR, not reported.

- 6.7 Similar to the previous submission, an informal comparison between CCH and surgical fasciectomy was presented, without statistical analysis.
- 6.8 Results in terms of clinical success rate for CCH were updated with a post-hoc subgroup analysis of patients with  $\leq 2$  affected rays per hand, consistent with the more restrictive listing requested. The subgroup analysis was based on pooled individual patient data from the CCH CORD I, CORD II and DUPY 303 trials, with sensitivity analyses excluding DUPY 303 (terminated prior full enrolment). Results in terms of clinical success rate for surgical fasciectomy were updated to include results from Karabeg (2012); identified in the updated literature search. Subgroup analyses for patients with  $\leq 2$  affected rays per hand were not presented for surgical fasciectomy.
- 6.9 Results in terms of recurrence rate for CCH were derived from the recently completed long term extension study AUX CC 860 (interim results from this study were used in the previous submission). The re-submission argued that recurrence defined as “treated joints requiring further medical or surgical intervention” is preferred to the pre-specified and amended definitions of recurrence reported in the AUX CC 860 study (recurrent contracture  $\geq 30^\circ$  and  $\geq 20^\circ$ ). Recurrence rates reported in the surgical fasciectomy studies were translated into cumulative rates and pooled in order to improve comparability with the CCH AUX CC 860 results, assuming a time to event distribution similar to that reported for CCH in study AUC CC 860. Fasciectomy observational studies 30-50 years old and those with non-comparable outcomes were excluded from the comparison.
- 6.10 The primary definition of recurrence used in the re-submission (defined as a patient requiring further medical or surgical intervention up to 4 years after initial treatment) is the least stringent definition of recurrence which may not capture all recurrence events and provides the most favourable recurrence rate for CCH treated patients. The PSCR (p1.) contended that such a definition is the most relevant recurrence definition for use in the economic evaluation as it triggers the only meaningful cost implications due to recurrence in practice. The ESC questioned this contention as recurrence defined in terms of  $\geq 20^\circ$  or  $\geq 30^\circ$  contracture appeared to significantly favour surgical fasciectomy. There was insufficient justification provided for why recurrence defined in terms of  $\geq 20^\circ$  or  $\geq 30^\circ$  contracture favoured fasciectomy yet the requirement for surgical/medical intervention was less for CCH patients. The similar rate of medical/surgical intervention reported in the re-submission may have been an artefact of the differences in reporting (by joint/person, inclusion or exclusion by successful initial treatment).
- 6.11 Further, the definition of recurrence is not comparable for many studies, specifically the CCH study reports rate of medical/surgical intervention for successfully treated joints, whereas many surgical studies report repeat surgical intervention for all (successfully and unsuccessfully) treated individuals (which may have been treated for more than one joint). To highlight the potential significance of the definition, in the

AUX-CC-860 study, 198 of 644 (30.7%) subjects who received CCH had at least one intervention by year 5 [AUX-CC-860-CSR. 11.4.1.8. and Table 23 (p58)]. In contrast, based on the same study, 105 of 623 (16.9%) successfully treated joints had an intervention by year 5. The ESC considered that the combining of initial and recurrent surgical fasciectomy MBS data over a 15 year period into a rate of recurrence comparable to rates reported in the clinical trials and observational studies may not be appropriate, as it does not differentiate between re-treatment following initial surgical fasciectomy and successive re-treatment episodes.

- 6.12 The ESC further noted that the recurrence rates reported in the surgical fasciectomy studies were highly variable with respect to the recurrence definition used and time points reported. Recurrence rates were translated into cumulative rates and pooled in order to improve comparability with the CCH AUX CC 860 results, assuming a time to event distribution similar to that reported for CCH in study AUX CC 860. In addition, the ESC noted that the studies often reported insufficient detail about the cohort and recurrence definition to clearly evaluate whether the recurrence values reported were sufficiently comparable to those of the CCH studies. There is a high risk of bias for comparisons of recurrence rates between CCH and fasciectomy even with exclusion of fasciectomy observational studies 30-50 years old and those with clearly non-comparable outcomes.
- 6.13 Results of the informal comparison are shown in the table below.

**Informal comparison of CCH versus surgical fasciectomy for clinical success and recurrence rates**

Outcome	CCH	Fasciectomy
<b>Clinical success rate: reduction of contracture to <math>\leq 5^\circ</math> (excluding DUPY 303)</b>		
<b>Re-submission base case:</b> used in the economic evaluation	65.4% <sup>a</sup> ( $\leq 2$ ray subgroup)	80.8% <sup>b</sup>
July 2013 submission: all studies	60.5% <sup>c</sup>	69% <sup>d</sup>
Accepted by PBAC: (July 2013 meeting)	50%	69%
<b>Recurrence rate</b>		
<b>Re-submission base case:</b> used in economic evaluation	13.6%	13.6% (assumed)
Re-submission: requiring medical or surgical intervention up to 4 years	13.6%	15.0% <sup>e</sup>
Re-submission: recurrent contracture to $\geq 30^\circ$ up to 5 years	31.8%	24.7% <sup>e</sup>
July 2013 submission: recurrent contracture to $\geq 30^\circ$ up to 4 years	28%	21%
July 2013 submission: recurrent contracture to $\geq 20^\circ$ up to 4 years	42%	24%

Source: Table 55, p.147 of the re-submission; CCH July 2013 submission.

Abbreviations: CCH, collagenase *Clostridium histolyticum*; PES, Pharmaceutical Evaluation Section.

<sup>a</sup> 68.1% including DUPY 303. <sup>b</sup> Fasciectomy observational studies selected in the PES July 2013 Evaluation including Karabeg (2012). <sup>c</sup> Fasciectomy observational studies selected in the PES July 2013 Evaluation. <sup>d</sup> All observational studies reporting outcomes regardless of age of study or comparability. <sup>e</sup> Imputed in the re-submission.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Comparative harms**

- 6.14 In comparison with the previous submission (July 2013), no new safety data were presented. The most frequent patient-reported adverse events in patients treated with CCH were peripheral oedema, contusion, injection site haemorrhage, injection site pain, pain in extremity, tenderness, pruritus and lymphadenopathy (enlarged/swollen lymph nodes). Events reported were generally mild to moderate in severity, transient and related to the injection site and disruption of the Dupuytren's cord.

- 6.15 The most frequently reported complications associated with surgical fasciectomy were digital nerve or artery injuries, complex regional pain syndrome, joint stiffening (flare reaction), infections requiring treatment and paraesthesia. Rates varied widely between studies but weighted average rates were low.
- 6.16 No studies reported tendon rupture. Adverse events related to anaesthesia were not reported.
- 6.17 The informal comparison between CCH and surgical fasciectomy provided no comparative statistical analyses of benefits and harms. The table below shows the benefits and harms of treatment with CCH compared to placebo, based on the DUPY 303, CORD I and CORD II trials.

Summary of comparative benefits and harms for CCH versus placebo

Trial	CCH n/N	Placebo n/N	Relative risk (95% CI)	Event rate/100 patients*		Risk difference (95% CI)
				CCH	Placebo	
<b>Benefit: clinical success</b>						
DUPY 303	21/23	0/12	23.3 (1.5, 354.1)	91.3	0	0.91 (0.75, 1.07)
CORD I	130/203	7/103	9.4 (4.6, 19.4)	64.0	6.8	0.57 (0.49, 0.65)
CORD II	20/45	1/21	9.3 (1.3, 65.0)	44.5	4.8	0.40 (0.23, 0.57)
Meta-analysis			9.9 (5.1, 19.1)	63.1	5.9	0.63 (0.37, 0.88)
<b>Harms: meta-analyses of CCH trials</b>						
Peripheral oedema	206/272	7/140	13.27 (6.62, 26.57)	75.7	5.0	0.76 (0.61, 0.92)
Contusion	138/249 <sup>a</sup>	4/125 <sup>a</sup>	14.18 (3.94, 51.01)	55.4	3.2	0.54 (0.41, 0.67)
Injection site haemorrhage	80/249 <sup>a</sup>	4/125 <sup>a</sup>	10.42 (4.15, 26.18)	32.1	3.2	0.35 (0.28, 0.42)

Source: Compiled during the evaluation.

Abbreviations: CCH, collagenase *Clostridium histolyticum*.

<sup>a</sup> CORD I and CORD II trials only.

- 6.18 The PBAC noted that, on the basis of the placebo-controlled trials presented in the re-submission, for every 100 patients treated with CCH in comparison to placebo:
- approximately 57 additional patients would achieve clinical success (based on the results of the meta-analysis);
  - approximately 70 additional patients would have peripheral oedema;
  - approximately 52 additional patients would have a contusion; and
  - approximately 29 additional patients would have injection site haemorrhage.

For more detail on PBAC's view, see section 7 "PBAC outcome"

### Clinical claim

- 6.19 The re-submission described CCH as inferior in terms of comparative success rate and rate of recurrence, non-inferior in terms of recurrence resulting in subsequent medical or surgical intervention and superior in terms of safety compared to surgical fasciectomy.
- 6.20 The ESC considered that the claim of inferiority to surgical fasciectomy is reasonable in terms of comparative success rate and rate of recurrence based on the clinical study outcomes of recurring contracture  $\geq 20^\circ$  or  $\geq 30^\circ$ . The claim of non-inferiority to surgical fasciectomy in terms of recurrence resulting in subsequent medical or surgical intervention may not be reasonable as there was insufficient justification for the plausibility of this observation (i.e. more recurrent contractures of  $\geq 20^\circ$  or  $\geq 30^\circ$  for CCH treated patients yet similar rates of corrective medical/surgical interventions) and because this definition of recurrence does not capture the loss of benefit in

patients not opting for retreatment. The imputed recurrence rates for surgical fasciectomy further biased results in favour of CCH.

- 6.21 The PBAC had previously accepted that CCH is non-inferior or possibly superior to surgical fasciectomy in terms of safety. No new safety concerns were raised for CCH.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Economic analysis**

- 6.22 The re-submission presented an updated cost comparison between CCH and surgical fasciectomy, using a similar approach to the previous submission. The ESC noted that given the clinical claim of inferior efficacy, the evaluation questioned whether a cost-utility analysis may have been more appropriate to establish whether any additional savings are worth the health loss. The PSCR (p3) contended that once increased surgical retreatment is incorporated into the economic analysis, overall, there will be no difference in effectiveness as individuals for who CCH is not successful will undergo surgery and therefore a cost analysis is reasonable. The ESC noted that the quality and therefore reliability of data obtained from the surgical studies to populate any potential cost-utility analysis would be low and so this approach to the economic analysis would in practice, as opposed to in theory, be unlikely to provide any additional certainty compared to the current approach.

Source: Xiaflex\_Clinical\_Economic\_Evidence.xls; <sup>a</sup> Includes surgeon and GP visits, physiotherapy, occupational therapy and home nurse visits; corrected for error in the number of surgeon visits; <sup>b</sup> Includes patients with recurrence and those not successfully treated initially;  
<sup>c</sup> All patients requiring re-treatment assumed to have surgical fasciectomy, and therefore the out-of-pocket and productivity costs

- 6.23 The number of recovery period health services for each category was based on the responses of participating physicians and surgeons in the sponsor commissioned physician survey (19 responders from 89 approached: 21% response rate). The evaluation identified that the re-submission had incorrectly subtracted initial surgeon

visits from the number of “recovery period” visits reported in the survey for both CCH and fasciectomy (corrected during the evaluation and shown in italics in the above table). Costs associated with recovery period health services were higher for surgical fasciectomy compared to the previous submission due to the addition of more physiotherapy visits, community nurse visits, occupational therapy, out-of-pocket expenses and lost productivity. The PBAC considered that whilst these recovery period health services costs may be incurred in practice, the estimation of these costs via a sponsor commissioned physician survey raised concerns over the reliability of the results and therefore the PBAC considered that these costs should be set aside.

6.24 As a base case, the re-submission estimated a cost savings of \$724.49 (corrected) for each hand treated compared to surgical fasciectomy (uncorrected estimate CCH \$6,171.91; fasciectomy \$6,953.58; a savings of \$781.66). The ESC advised that the re-submission’s base case inappropriately included productivity loss. Patient out-of-pocket expenses may or may not be appropriate in various circumstances but were considered to be inadequately justified in the re-submission. When out-of-pocket and productivity loss costs are removed, CCH results in savings of \$28.42 per hand treated compared with surgical fasciectomy.

6.25 The PSCR (p3-4) contended that productivity loss and patient out-of-pocket costs are important to patients and doctors in the real world setting and that it would be implausible that no savings are made in terms of productivity loss/out-of-pocket costs. The ESC however considered that the inclusion of productivity loss in particular was inadequately justified and inappropriately included in the base case estimate. This consideration was influenced by the PBAC Guidelines (Version 4.3, Appendix 9) which suggest the following:

*“Unlike direct health benefits, the economic benefit to society through patients’ return to, or maintenance of, productive capacity is both difficult and controversial to estimate accurately. This is because the available methods and their application remain unresolved. Therefore, although changes in production as an outcome of therapy may be included in supplementary analyses in submissions to PBAC, they should not be included in the base case analysis.*

*There are several difficulties in estimating the net present value of production changes. These estimates are underpinned by three assumptions:*

- *for short-term absence, production will be made up on the return to work*
- *employers usually have excess capacity in the labour force to cover absenteeism*
- *for long-term absence, production will be made up by a replacement worker otherwise unemployed.*

*Where estimation of production changes can be justified in the submission, address each of the three underlying assumptions listed above...”*

6.26 The PBAC considered that it would be appropriate for productivity loss and out-of-pocket expenses to be excluded from the cost analysis due to the difficulty in providing reliable estimates of the productivity values that took into account the issues highlighted by the ESC, the incompleteness of the out-of-pocket estimates which were only derived for the fasciectomy MBS item, and the inability to separate results which excluded productivity costs and retained out-of-pocket costs.

6.27 The evaluation noted that the rate of injection per joint used in the re-submission (1.22 injections per joint) was not adequately justified, and the rate derived from the CCH clinical trials (1.65 injections per joint) may be preferred. The PSCR (p4) contended that “...the within-trial re-treatment requirement of 1.65 per joint is expected to have poor applicability to the PBS-subsidised use of CCH because, most

notably, the use of local anaesthesia was prohibited during the post-injection extension procedure in the trials. The base case estimate of 1.22 injections was informed by POINT-X where the use of local anaesthesia was indeed allowed.” The ESC considered this justification may be reasonable. However, the PBAC noted that whilst use of local anaesthesia in post-injection extension procedures may have some biological plausibility in reducing the number of injections, the PBAC disagreed with the use of an average number of injections per joint that is derived from an observational study rather than the randomised trials. The PBAC doubted the comparability of the outcomes of POINT-X to the outcomes of the CORD trials and considered that, in the cost analysis, the average number of CCH injections should be derived from the pivotal trials (i.e. 1.65 injections).

- 6.28 In relation to potential use of CCH in patients with 3 or more affected joints, the ESC noted that the PSCR (p4) contended that “...as the number of affected joints increases, so does the time taken to treat Dupuytren’s contracture with CCH increases (i.e., max one injection/one joint per month), while the time taken to treat Dupuytren’s contracture with surgery remains the same. Patients with more affected joints would hence require the treatment with CCH over a period of ~4 - 5 months (or more); which would be far longer than the surgical alternative even when its slow recovery is taken into account. Patient preference for CCH over fasciectomy would be hence compromised in these patients.” The ESC considered this contention reasonable. The PBAC agreed that an economic comparison limited to patients with 2 or less rays affected was acceptable, given that a risk sharing arrangement could mitigate the risk of CCH use in patients with more than 2 affected rays.
- 6.29 The PBAC recalled that it had previously requested advice from MSAC and the Department to clarify whether the current practice of hand surgeons claiming MBS item 46366 (subcutaneous fasciotomy) for administration of CCH is appropriate, or whether it would be necessary to create a specific MBS item to administer CCH for the treatment of Dupuytren’s contracture. It was noted that the Department was still to provide this clarification. In view of this, the PBAC approached the consideration of the cost analysis on the assumption that a new MBS item is not needed for CCH administration and that there are no differences in utilisation of other MBS items that may not already be accounted for in the cost analysis. Should these assumptions be incorrect, the price of CCH would need to adjust for this. The PBAC also requested that, consistent with its recent considerations of the costs of injecting botulinum toxin via the MBS, MSAC or the Department should review the model and advise on more accurate cost estimates, for example in place of the respective MBS fee for each of the identified MBS services, including fasciectomy. The PBAC noted that this would also more accurately estimate out-of-pocket payments. The price of CCH would also need to adjust for this advice.
- 6.30 The ESC noted that the cost comparison was sensitive to the number of CCH injections per joint, the definition of recurrence, and the inclusion of productivity losses. Under a number of scenarios presented in sensitivity analyses, CCH was dominated by surgical fasciectomy (i.e. is less effective and more expensive). The outcomes of the sensitivity analysis of the cost comparison ranged from a savings of [REDACTED] per hand treated with CCH (the re-submission base-case) to an additional cost of [REDACTED] per hand treated with CCH. In view of the large variation in the best estimate of the equivalent overall treatment costs of CCH compared to fasciectomy, the PBAC recommended that the cost analysis be based on the following parameters and values shown in the table below. All other parameters and their respective values are to be as specified in the base case estimate from the pre-PBAC response to the July 2014 PBAC meeting. Based on the values specified in the table below, the price of CCH that achieves an equivalent overall treatment cost compared to



- 6.35 The PBAC noted that, compared to the July 2013 submission, estimated drug utilisation had increased significantly (4,419 prescriptions in Year 5 of the July 2013 submission compared to 7,689 in the re-submission). The PBAC noted that the net financial implications to the PBS/MBS would be significantly lower than those estimated in the table above if the PBS listing price of CCH is set in accordance with the PBAC's view of the best estimate of various parameters of the cost analysis outlined above under 'Economic Analysis'.
- 6.36 The PBAC considered that the re-submission's estimated PBS utilisation may be underestimated for the following reasons:
- higher than expected use of CCH arising from:
    - use of CCH earlier in the treatment algorithm to delay surgical fasciectomy;
    - use of CCH in place of surgical fasciotomy;
    - use in patients with more than 2 affected rays;
  - potential for lower clinical success rates, higher recurrent contracture rates and corrective retreatment episodes than that observed in clinical trials, thereby underestimating the number of retreatments for failed initial treatments and recurrent disease; and
  - potential for the average number of injections per joint to be higher than that claimed by the re-submission.
- 6.37 A Risk Sharing Arrangement (RSA) based on the predicted number of treatments required per patient was considered impractical by the PBAC in the July 2013 consideration. The re-submission proposed a RSA based on a budget cap with a rebate of approximately [REDACTED] off the revised price of [REDACTED].
- 6.38 The PBAC considered, among other matters, that its assessment of the cost parity of CCH to surgical fasciectomy would be acceptable if the measures below were implemented to contain risks associated with the cost of CCH to the PBS:
- a Risk Share Agreement (RSA) between the sponsor and the Government;
  - the RSA should include a cap based on an annual number of hands treated as estimated by the re-submission, an average number of 1.65 injections per joint, an average of 1.3 affected joints per ray and uptake rates as estimated per the re-submission; and
  - a 100% rebate for use beyond the cap.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended listing collagenase clostridium histolyticum as an Authority required benefit for the treatment of Dupuytren's contracture in patients meeting certain criteria, on a cost analysis basis that assumes equivalent overall treatment costs between and surgical fasciectomy, but accounting for a lower treatment success rate with CCH compared to surgical fasciectomy as well as higher retreatment and recurrent contracture rates for patients treated with CCH compared to surgical fasciectomy.
- 7.2 The PBAC noted the re-submission's request for a more restrictive listing than the previous submission through limiting the use of CCH to patients (a) with  $\leq 2$  rays affected and (b) who would otherwise require surgery. Whilst the PBAC agreed with the intent of these two particular elements of the restriction and the inclusion of them in the restriction, the PBAC considered that it would be difficult to audit whether these

two requirements are being met and therefore their inclusion in the restriction does not completely resolve the PBAC's previous concerns that CCH would be used earlier in the clinical treatment algorithm to delay surgery.

- 7.3 The re-submission's nominated main comparator of surgical fasciectomy had been previously accepted by the PBAC at the July 2013 meeting. Although the PBAC had previously considered that CCH may potentially replace fasciectomy in clinical practice, the PBAC had also considered in July 2013 that fasciectomy is a secondary comparator.
- 7.4 The PBAC noted that the re-submission's base case estimate of clinical success rate was 65.4% for CCH, and 80.8% for fasciectomy and that these results had increased in magnitude to those accepted by the PBAC in July 2013 (50% success rate for CCH, 69% success rate for fasciectomy). The PBAC further noted that in the comparison of recurrence rates, patients treated with CCH had higher rates of recurrence compared to fasciectomy if recurrence is defined as contracture of  $\geq 20^\circ$  or  $\geq 30^\circ$  occurring up to 4 years after initial treatment. The PBAC did not accept the re-submission's definition of recurrence (patients who received medical or surgical intervention up to 4 years after initial treatment) as it considered that a  $20^\circ - 30^\circ$  contracture is likely to translate into a patient being unable to place a hand flat on a table and therefore recurrence by degree of contracture is a reasonable definition of recurrence. This was consistent with the advice of the clinician presenting at the hearing.
- 7.5 As a result of the observed lower success rate and higher rate of recurrence (defined by degree of contracture) for CCH compared to fasciectomy, the PBAC reaffirmed its view that CCH is inferior to fasciectomy in terms of comparative effectiveness if retreatment is not accounted for. In terms of comparative safety, the PBAC recalled that it had previously accepted that CCH is non-inferior or possibly superior to surgical fasciectomy.
- 7.6 The re-submission's overall approach to the economic comparison of CCH to surgical fasciectomy using a cost analysis was considered acceptable. The cost analysis accounted for differences in success rates between CCH and surgical fasciectomy by factoring in retreatment of recurrent contractures. However, determining the equivalent overall treatment costs of CCH and surgical fasciectomy was subject to variation in estimates of numerous costs relating to both drug usage and recovery period health service costs. The PBAC noted that estimates of overall treatment costs were particularly sensitive to: 1) the average number of CCH injections used per joint; 2) inclusion of productivity loss and out-of-pocket costs; and 3) the definition of a recurrent contracture. The PBAC's best estimate of these 3 parameters and additional parameters relating to the estimate of the overall treatment costs are outlined under 'Economic Analysis'. Subject to any issues raised in relation to the MBS, these estimates form the basis for the derivation of equivalent overall treatment costs between CCH and surgical fasciectomy and the price at which CCH is considered acceptable for PBS listing.
- 7.7 The PBAC recommended that CCH be subject to a risk sharing arrangement (RSA) that requires a 100% rebate for use of CCH above an agreed level of expenditure.
- 7.8 The PBAC considered that should a price for CCH significantly above that determined by the PBAC's current best estimate of the overall treatment costs and/or a less stringent risk share arrangement be sought, then a major re-submission with a stronger clinical evidence base (e.g. a randomised controlled trial directly comparing

CCH to surgical fasciectomy that collects data on healthcare resource use) would be required.

- 7.9 The PBAC advised that CCH is not suitable for prescribing by nurse practitioners.
- 7.10 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.11 The PBAC noted that this submission is not eligible for an Independent Review.

**Outcome:**  
Recommended

## 8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max Qty	No. of Rpts	Proprietary and Manufacturer	Name
COLLAGENASE CLOSTRIDIUM HISTOLYTICUM				
collagenase clostridium histolyticum 900 microgram injection [1 x 900 microgram vial] (& inert substance [1 x 3 mL vial], 1 pack	1	0	Xiaflex <sup>®</sup>	AT

<b>Category/Program</b>	GENERAL – General Schedule (GE)
<b>Indication:</b>	Dupuytren's contracture
<b>Restriction:</b>	Authority required
<b>Treatment criteria:</b>	Must be treated by a surgeon who is certified following completion of injection administration training provided by the sponsor.
<b>Clinical criteria:</b>	<p>Patient must be unable to simultaneously place the affected finger and palm flat on a table due to a Dupuytren's contracture with a palpable cord.</p> <p>AND</p> <p>Patient must have no more than two rays affected on the treated hand.</p> <p>AND</p> <p>Patient must otherwise require surgical fasciectomy for this condition.</p>
<b>Prescriber instructions:</b>	Only one cord must be treated at a time. PBS-subsidised treatment with collagenase clostridium histolyticum is limited to a maximum of three injections per cord. Details of the specific cord being treated must be recorded in the patient's medical records.
<b>Administrative Advice:</b>	<p><u>NOTE:</u> No increase in the maximum quantity or number of units may be authorised.</p> <p><u>NOTE:</u> No increase in the maximum number of repeats may be authorised.</p>

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**10 Sponsor's Comment**

Actelion Pharmaceuticals Ltd will continue to work with the PBAC to make Xiaflex available to the public on the PBS.