South Australian Policy Advisory Committee on Technology (SAPACT)

Health Technology Assessment (HTA) Decision Summary

Government of South Australia

SA Health

Sponsor's update (5 May 2020):
The sponsor has removed product from the TGA ARTG with effect from 31 March 2020.
Product is no longer available for use in Australia.

Xiaflex® (Collagenase Clostridium Histolyticum) for treatment of Dupuytren's contracture

SAPACT MEETING DATES	16th SAPACT Meeting, 23 November 2018
APPLICATION #	1607
TECHNOLOGY	Xiaflex (Collagenase Clostridium Histolyticum) (Actelion Pharmaceuticals Australia Pty Ltd)
TECHNOLOGY CLASSIFICATION	Schedule 4 Prescription Only Medicine for a novel procedural treatment
PATIENT INDICATION (TGA)	Xiaflex is TGA-indicated for the treatment of Dupuytren's contracture in adult patients with a palpable cord.

SAPACT DECISION

☒ Restricted recommendation for clinical use with financial or operational restrictions.

In 2016 and 2018, SAPACT received application referrals from CALHN and SALHN clinicians to evaluate the use of Xiaflex in SA Health. Xiaflex is the first novel non-surgical treatment option available for the treatment of Dupuytren's contracture. SAPACT commenced the HTA process, inclusive of the development of a SAPACT Evidence Synopsis in 2016 and from 2016-18, monitored the 2-year clinical outcomes results from CALHN as well as the updated published scientific evidence.

SAPACT Advisory Recommendations

Based on the consideration of safety, clinical-effectiveness and cost-effectiveness, SAPACT advised restricted recommendation for clinical use of Xiaflex with financial or operational restrictions.

Patient selection

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 (causing contracture of the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint of the affected finger).

AND Patient must have no more than two rays affected on the treated hand.

AND Patient must otherwise require surgical fasciectomy for this condition.

Dosage and Administration (TGA Product Information Xiaflex March 2016):

- Xiaflex is only to be administered by qualified doctors who are experienced in the diagnosis of Dupuytren's disease and are experienced in injection procedures of the hand. All qualified doctors must have either experience in the surgical management of Dupuytren's disease or been an investigator in the clinical trial program. Prior to use of Xiaflex, all qualified doctors must have undergone a prescriber education and training program by Actelion Pharmaceuticals Australia Pty Ltd including training in the appropriate administration of Xiaflex.
- Ensure appropriate equipment, monitoring of vital signs and treatments are available to address any severe local or systemic reactions including the potential for anaphylaxis that may occur following injection of Xiaflex.
- The recommended dose of Xiaflex is 0.58 mg per injection into a palpable Dupuytren's cord. Each vial of Xiaflex and sterile diluent for reconstitution should only be used for a single injection. If cords of two affected joints on the same hand are to be treated during a treatment visit, separate vials and syringes should be used for each reconstitution and injection.
- The volume of reconstituted Xiaflex to be administered into the Dupuytren's cord differs depending on the type of joint being treated.
- Approximately 24 -72 hours after injection, a finger extension procedure may be performed, as necessary, to facilitate cord disruption.
- If a satisfactory response has not been achieved, the injection and finger extension procedures may be repeated after approximately 4 weeks.
- Injections and finger extension procedures may be administered up to 3 times per cord at approximately 4-week intervals.
- Inject up to two cords or two affected joints in the same hand according to the injection procedure during a treatment visit. Two palpable cords affecting two joints may be injected or one palpable cord affecting two joints in the same finger may be injected at two locations during a treatment visit. Each injection contains a 0.58 mg dose.
- If the disease has resulted in multiple contractures, additional cords may be treated at other treatment visits approximately 4 weeks apart, as determined by the physician.
- Patients should be instructed to return to see their physician approximately 24 - 72 hours after injection for an examination of the injected hand and a possible finger extension procedure(s) to disrupt the cord(s).

REGULATORY APPROVALS

☒ **ARTG**: 7/08/2013	☒ **US FDA**: 3/2/2010	☒ **EU CE mark**: 2011

ARTG ID: 199584 Schedule 4 Prescription Only Medicine Xiaflex® is TGA-indicated for: • The treatment of Dupuytren's contracture in adult patients with a palpable cord. • The treatment of adult men with Peyronie's disease with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy.	SA Health
QUALITY OF EVIDENCE	
Quality of Evidence	SAPACT developed an SAPACT Evidence Synopsis on Xiaflex in 2016 and from 2016-18, monitored the 2-year clinical outcomes results from CALHN as well as the updated published scientific evidence. The best available evidence (Level 1) was a comprehensive systematic review and economic evaluation of Xiaflex (Brazzelli 2015 HTA Journal). The systematic review appraised the quality of the included studies and found that the RCTs and non-randomised comparative studies assessing different surgical techniques varied across studies, with inconsistencies in the type of surgical methods assessed, definition and measurement of efficacy and length of follow-up. No head-to-head RCTs of collagenase versus surgery were identified. The. Five RCTs (493 participants) comparing collagenase with placebo, three RCTs (334 participants) comparing various surgical procedures, two non-randomised studies (105 participants) comparing collagenase with surgery, five non-randomised studies (3571 participants) comparing various surgical procedures and 15 collagenase case series (3154 participants).
CLINICAL NEED	
Burden of Illness	Dupuytren's contracture is a progressive condition characterised by the development of fibrotic cords causing deformities in the MCP and/or PIP joints and functional disability of the hand. Based on application, it is estimated that Australia has 7750 patients (9046 hands).
Need	Xiaflex injections have changed the treatment of Dupuytren's contracture as the first non-surgical treatment option for this condition. Xiaflex is classified by TGA as a Schedule 4 Prescription Only Medicine for a procedural treatment and its existing comparator is surgery (surgical fasciectomy, open or percutaneous needle fasciotomy). Fasciectomy is a significant surgical procedure involving an approximately 60 - 90min operative procedure, 6-12 weeks post-op recovery, significant risk of complications including nerve damage (numbness), skin breakdown, infection and haematoma, and has a recurrence rate of 27-80%. Xiaflex provides an alternative less invasive treatment option.
CLINICAL BENEFIT	
Safety	In terms of comparative safety, PBAC accepted that Xiaflex® was found to be non-inferior or possibly superior to surgical fasciectomy. The most frequent patient-reported adverse events in patients treated with Xiaflex® 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. 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. No studies reported tendon rupture. Adverse events related to anaesthesia were not reported.
Effectiveness	Xiaflex® had a lower clinical success rate (65.4%) compared to surgical fasciectomy (80.8%). Patients treated with Xiaflex® had higher rates of recurrence compared to fasciectomy if recurrence is defined as contracture of ≥ 20° or ≥ 30° occurring up to 4 years after initial treatment. If more than 2 fingers require treatment – surgery is the recommended option. Xiaflex® is an option to the gold standard of fasiectomy in some patients.
SUITABILITY OF PATIENT GROUP	
Suitability of Patient Group	<u>Patient selection</u> 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 (causing contracture of the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint of the affected finger). AND Patient must have no more than two rays affected on the treated hand. AND Patient must otherwise require surgical fasciectomy for this condition.
FINANCIAL CONSIDERATION	
Device costs	Costs differ depending on the number of Xiaflex injections per joint. Cost of Xiaflex injection: ~ $1,300/injection (up to $3900 per course of 3 injections) Each injection consists of a single dose of 0.58mg of Xiaflex into the cord affecting a primary joint. Up to 3 injections may be received in a cord and inject up to two cords or two affected joints in the same hand. Clinic cost for outpatient injection: ~ $250; Clinic cost for manipulation: ~ $400; Hand Therapy (cost of visit and splint): ~ $180 Total cost for Xiaflex per patient (with an affected joint) in SA Health: ~$2200 - $4730
Value for	Cost of comparator - open fasciectomy from Geelong Hospital, Victoria (Chan 2016)

Money	In-theatre costs (Anaesthesia + Booking & Admission + Operating theatre utilization + Sterilizing services + Surgical Staff): ~$3000/hour, which translates to $3140/case (1 case: 1.07hour) Outpatient clinic costs (0.5 hr per session): $305/case Total cost of open fasciectomy: $3440/case (compared to $2200-4730/joint using Xiaflex). Patients who have more than two rays affected on the treated hand should undergo surgery.
Funding Approvals	PBAC evaluated Xiaflex in July 2014 and recommended that Xiaflex be subject to a risk sharing arrangement (RSA) with Actelion Pharmaceuticals Ltd that requires a 100% rebate for use of Xiaflex above an agreed level of expenditure. However, till date, Actelion Pharmaceuticals Ltd has not progressed PBAC's recommendation. Therefore, Xiaflex is not available on the Pharmaceutical Benefits Scheme (PBS) for the treatment of Dupuytren's contracture (Email correspondence with PBAC on 15 September 2016).
FEASIBILITY OF ADOPTION	
Organisational Feasibility	The treatment and evaluation program should be planned and approved at the LHNs and ensure that appropriate protocols and risk management are in place.
Credentialing and Competency	The Clinician(s) should be appropriately trained, credentialed and approved by the SA Health Credentialing and Scope of Practice Committee to administer Xiaflex injections for the treatment of Dupuytren's contracture (refer to paragraph 3.4.3 New Clinical Procedures, Technologies and Treatments of the SA Health Credentialing Policy Directive). Only one cord must be treated at a time. Xiaflex is not suitable for prescribing by nurse practitioners.
CONSISTENCY WITH EXPECTED SOCIETAL/ ETHICAL/ LEGAL VALUES	
Values	Xiaflex provides an alternative, less invasive option compared to surgical interventions or amputation in the most severe cases.
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