New drugs

Collagenase *Clostridium histolyticum*

Approved indication: Dupuytren's contracture

Xiaflex (Actelion)

vials containing 0.9 mg lyophilised powder for reconstitution

Australian Medicines Handbook Appendix A

Dupuytren's contracture is characterised by overproduction and deposition of fibroblasts in the hand. Longitudinal collagen cords form which cause flexion contractures. The ring finger and small finger are most commonly affected and cause considerable disability. Standard treatment is surgery to remove or release the cord, but recurrence occurs in about half of cases.

This product contains two collagenases (AUX-I and AUX-II), produced by the bacterium *Clostridium histolyticum*. These enzymes hydrolyse collagen and are used to dissolve the collagen cords.

Two placebo-controlled randomised trials – CORD I[1] and CORD II[2] – assessed the efficacy of collagenase *Clostridium histolyticum* in adults with Dupuytren's contracture. Patients had at least one finger contracture (with a palpable cord) of 20–100° in a metacarpophalangeal joint or 20–80° in a proximal interphalangeal joint. Approximately 40–50% of enrolled patients had previously had surgery for contractures. Collagenase *Clostridium histolyticum* 0.58 mg or placebo was injected into the affected cord. The volume of the injection depended on the joint being injected. If needed, the hand was manipulated the next day to facilitate cord disruption. In CORD I, patients were allowed up to three injections given monthly, whereas in CORD II, patients could have a maximum of eight injections over 12 months. Finger contracture was measured four weeks after an injection.

Significantly more patients receiving collagenase compared to placebo had their contracture reduced to 5° or less (see Table).[1,2] The mean number of collagenase injections required was 1.5.

In the phase III trials, recurrence rates of contracture (to at least 20 degrees) in joints that had been successfully treated with collagenase were 3.3% (28 of 838 joints) after 12 months and 42% after four years.

Injection-site reactions to collagenase were the most common events and included haemorrhage (38.2% of patients), pain (34.9%), swelling (24.5%) and tenderness (24.1%). Other common adverse events were peripheral oedema (73.5%), contusion (55%), ecchymosis (20.5%) and lymphadenopathy (13.3%).

Most patients developed antibodies to collagenase and 15% had pruritus at the injection site. Anaphylaxis is a risk with this product.

Some patients developed serious injuries to the hand as result of the injection. These included tendon rupture, ligament injury and a complex regional pain syndrome. Patients should be warned to contact their doctor if they are unable to bend their finger after the swelling goes down.

As ecchymosis and haemorrhage were common, this drug should be used with caution in patients with a bleeding disorder or those taking anticoagulants. Except low-dose aspirin, anticoagulants should not be given up to seven days before treatment. Tetracyclines have been shown to inhibit collagen degradation and should be avoided up to 14 days before a collagenase injection.

Although collagenase is undetectable in plasma following an injection into the hand, it is a category B1 pregnancy drug and its use should be postponed until after pregnancy. Caution is urged during breastfeeding.

Collagenase injections provide a convenient option for people with Dupuytren's contracture who cannot have

Table **The efficacy of collagenase *Clostridium histolyticum* in adults with Dupuytren's contracture**[1,2]

	CORD I trial		CORD II trial	
	collagenase	placebo	collagenase	placebo
Number of patients	204	104	45	21
Proportion of patients with reduced contracture (to 5° or less) 4 weeks after last collagenase injection	64%	6.8%	44.4%	4.8%

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

surgery. Approximately half of patients will benefit but complications can occur and treatment has a high relapse rate. Special training is required before a doctor can administer this product.

T T manufacturer provided additional useful information

REFERENCES *†

1. Hurst LC, Badalamente MA, Hentz VR, Hotchkiss RN, Kaplan TD, Meals RA, et al. Injectable collagenase Clostridium histolyticum for Dupuytren's contracture. N Engl J Med 2009;361:968-79.
2. Gilpin D, Coleman S, Hall S, Houston A, Karrasch J, Jones N. Injectable collagenase Clostridium histolyticum: a new nonsurgical treatment for Dupuytren's disease. J Hand Surg Am 2010;35:2027-38.

First published online 12 December 2013

The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).