

#### Arthritis ACT

PO Box 4017  
WESTON ACT 2611  
Phone: (02) 6288 4244  
E-mail: [afact@austarmetro.com.au](mailto:afact@austarmetro.com.au)

#### Arthritis NSW

Locked Bag 16, Post Office  
NORTH PARRAMATTA NSW 2151  
Phone: (02) 9683 1622  
E-mail: [info@arthritisnsw.org.au](mailto:info@arthritisnsw.org.au)

#### Arthritis NT

6 Caryota Court  
COCONUT GROVE NT 0810  
Phone: (08) 8948 5232  
E-mail: [afnt@telstra.com](mailto:afnt@telstra.com)

#### Arthritis QLD

PO Box 2121  
WINDSOR QLD 4030  
Phone: (07) 3857 4200; 1800 011 041 freecall  
E-mail: [info@arthritis.org.au](mailto:info@arthritis.org.au)

#### Arthritis SA

Unit 1/202–208 Glen Osmond Rd  
FULLARTON SA 5063  
Phone: (08) 8379 5711  
E-mail: [info@arthritissa.org.au](mailto:info@arthritissa.org.au)

#### Arthritis TAS

Box 30 McDougall Building  
Ellerslie Road  
BATTERY POINT TAS 7004  
Phone: (03) 6224 4755; 1300 650 647 infoline  
E-mail: [hobart@arthritistasmania.com.au](mailto:hobart@arthritistasmania.com.au)

#### Arthritis VIC

263–265 Kooyong Rd  
ELSTERNWICK VIC 3185  
Phone: (03) 8531 8000; 1800 011 141 freecall  
E-mail: [afv@arthritisvic.org.au](mailto:afv@arthritisvic.org.au)

#### Arthritis WA

PO Box 34  
WEMBLEY WA 6014  
Phone: (08) 9388 2199  
E-mail: [general@arthritiswa.org.au](mailto:general@arthritiswa.org.au)

## New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial 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 either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

### Fibrin sealant

Tisseel Duo 500 (Baxter)

1.0 mL, 2.0 mL and 5.0 mL kits, each containing a syringe of sealer protein solution and a syringe of thrombin solution

Approved indication: surgical haemostasis

Australian Medicines Handbook section 7.4

This product is a sealant which can be used as an adjunct to surgical techniques for controlling blood loss. It can also be used as an adjunct in the closure of colostomies.

In addition to fibrinogen, the kits contain vials of thrombin, calcium chloride and a fibrinolysis inhibitor. The fibrinogen is reconstituted with the fibrinolysis inhibitor solution and the thrombin is mixed with the calcium chloride solution. Syringes containing the two mixtures are then loaded into a device which delivers equal volumes of each mixture to the wound. The thrombin converts the fibrinogen to fibrin which seals the wound. It takes two hours for the sealant to reach its full strength, but it reaches 70% strength in 10 minutes. The fibrinolysis inhibitor then stops the fibrin being broken down too quickly. As the preparation can take up to 40 minutes the product is unsuitable for unexpected brisk bleeding.

Topical applications of sealants have been used successfully to reduce bleeding in facial surgery, knee arthroplasty, skin grafting, vascular reconstruction and cardiac surgery. Other studies, for example of tonsillectomy, show no advantage.

There is limited published information on this particular sealant preparation. Its fibrinogen and thrombin components are derived from blood donations so there is a potential for transmitting infection. The fibrinolysis inhibitor has a bovine origin so some patients may have hypersensitivity reactions to cow protein.

A laboratory study compared a range of fibrin tissue adhesives. It found that this product took longer to prepare than a cryoprecipitate from a single donor, but had a greater binding power.<sup>1</sup> Although this fibrin sealant could be made up in advance of a procedure, it has to be discarded after four hours. It is also much more expensive than autologous preparations.<sup>1</sup>

### REFERENCE

1. Siedentop KH, Park JJ, Shah AN, Bhattacharyya TK, O'Grady KM. Safety and efficacy of currently available fibrin tissue adhesives. *Am J Otolaryngol* 2001;22:230-5.

### Tadalafil

Cialis (Eli Lilly)

10 mg and 20 mg tablets

Approved indication: erectile dysfunction

Australian Medicines Handbook section 13.3

The treatment of impotence changed when sildenafil was launched in 1998. Over 17 million men have been prescribed

sildenafil and in 2001 it generated sales of US\$1.5 billion. There is therefore a large potential market for oral treatments of erectile dysfunction.

Although it has a different structure, tadalafil acts in the same way as sildenafil. It inhibits the phosphodiesterase type 5 enzyme to reduce the inactivation of cyclic guanosine monophosphate (cGMP). This inhibition helps to maintain the smooth muscle relaxation, in the corpus cavernosum of the penis, which produces an erection. As the production of cGMP requires the release of nitric oxide in response to sexual arousal, tadalafil will have no effect in the absence of sexual stimulation.

Tadalafil is more slowly absorbed than sildenafil. The median time to the maximum concentration is two hours compared to one hour. In addition, tadalafil has a much longer half-life than sildenafil (17.5 hours versus 4 hours). It can still be effective 36 hours after a dose. Tadalafil is mainly eliminated by metabolism. This metabolism involves cytochrome P450 3A4 so there is a potential for interactions with drugs which inhibit or induce this enzyme.

Few of the clinical trials of tadalafil have been published in full. Overall the efficacy of tadalafil 20 mg for successful sexual intercourse is 75% compared with a placebo response of 32%. The efficacy is likely to be less in patients with diabetes.

Only 1.7% of patients in clinical trials stopped treatment because of adverse events, but 26% had at least one adverse effect. Headache and dyspepsia are the commonest adverse effects. As tadalafil causes vasodilatation it can provoke flushing and falls in blood pressure. It may therefore potentiate the effect of antihypertensive drugs. Tadalafil is contraindicated in patients taking nitrates. As the clinical trials excluded men with unstable cardiovascular disease, tadalafil should not be prescribed for these patients. These contraindications include men with a recent history of stroke, heart failure or myocardial infarction and those with unstable angina or uncontrolled hypertension or arrhythmia.

Although tadalafil is a more potent inhibitor of phosphodiesterase type 5 than sildenafil is, the clinical relevance is uncertain. There appear to be no published trials which compare the two drugs or investigate if patients who do not respond to one drug will respond to the other. As tadalafil causes fewer ocular adverse effects it may have a role in patients who have developed abnormal vision while taking sildenafil, however there are no reports of this usage.

**Answers to self-test questions**

1. True	3. False	5. False
2. True	4. True	6. True
7. True		
8. False		

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**Editorial office**

For general correspondence such as letters to the Editor, please contact the Editor.

Telephone: (02) 6282 6755

Facsimile: (02) 6282 6855

Postal: The Editor  
Australian Prescriber  
Suite 3, 2 Phipps Close  
DEAKIN ACT 2600  
AUSTRALIA

E-mail: [info@australianprescriber.com](mailto:info@australianprescriber.com)

Web site: [www.australianprescriber.com](http://www.australianprescriber.com)