NEW DRUGS

New drugs

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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.

Prucalopride

Approved indication: constipation

Resotrans (Janssen-Cilag)

1 mg, 2 mg film-coated tablets

Australian Medicines Handbook section 12.4

Constipation sometimes does not respond to the usual treatments (see Managing constipation in adults, Aust Prescr 2010;33:116-9). Patients with an unsatisfactory response to laxatives can be considered for treatment with prucalopride.

Prucalopride is an agonist of the serotonin $5HT_4$ receptors. These receptors are found in the gut and stimulating them increases motility.

The drug is taken once a day. The tablets have a high oral bioavailability and can be taken with or without food. There is little metabolism of prucalopride. Most of the dose is excreted unchanged in the urine. A lower dose is recommended for elderly patients and those with severe renal or hepatic impairment. The half-life of prucalopride is one day.

The main double-blind clinical trials of prucalopride were carried out in the 1990s. Research into the product was temporarily suspended and the trials were not published until a decade later. The studies included three placebo-controlled trials with identical designs. They involved patients with a history of chronic constipation who had two or less bowel movements per week. These patients took prucalopride 2 mg or 4 mg, or placebo for 12 weeks. The primary efficacy endpoint in the trials was the proportion of patients who reported an average of three or more spontaneous bowel motions each week.[1,2,3]

The results (see Table) showed that more patients respond to prucalopride than to placebo, but the 4 mg dose is no better than the 2 mg dose. It is therefore the 2 mg dose which is approved for use in Australia.

During the trials the most frequent adverse effects seen with prucalopride were headache, nausea, abdominal pain and diarrhoea. Adverse events are more frequent at the start of treatment. The proportions of patients discontinuing treatment following adverse events were 1.9–6.7% with placebo, 4–8.2% with prucalopride 2 mg, and 6–15.1% with prucalopride 4 mg.[1,2,3] Adverse events also led to the withdrawal of 8% of the 1455 patients who continued to take (open-label) prucalopride after the main trials concluded.[4]

Cisapride and tegaserod were $5HT_4$ agonists that were removed from the market because of concerns about serious cardiovascular adverse effects. At present prucalopride does not appear to affect the QTc interval on the ECG or cause significant ischaemia. However, the product information advises caution if prescribing prucalopride for patients taking drugs which prolong the QTc interval.

Prucalopride is contraindicated in patients with ileus, obstruction or inflammatory bowel disease. It should not be used following bowel surgery.

As 86.6–90.8% of the trial participants were female,[1,2,3] the European regulatory agency approved prucalopride for use by women only. Women taking prucalopride must also use effective contraception as the drug is not recommended in pregnancy or breastfeeding. If prucalopride causes diarrhoea the efficacy of oral contraception may be reduced.

In Australia, prucalopride can be considered for adult men and women who have not responded to at least two laxatives for at least six months. Although some patients will respond to prucalopride, approximately 70% will not (Table). Consideration should be given to stopping prucalopride if it has not been effective after four weeks of treatment.

T T manufacturer provided additional useful information

Table **Response rates in trials of prucalopride**

TRIAL LOCATION	NUMBER OF PATIENTS	PLACEBO	PRUCALOPRIDE 2 MG	PRUCALOPRIDE 4 MG
USA[1]	620	12%	30.9%	28.4%
International[2]	713	9.6%	19.5%	23.6%
USA[3]	641	12.1%	23.9%	23.5%

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The T-score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

† 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)

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

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A: ANSWERS TO SELF-TEST QUESTIONS

1 True
2 True
3 True
4 True