

New drugs

Fidaxomicin

Approved indication: Clostridium difficile infection

Dificid (Specialised Therapeutics)

200 mg tablets

Australian Medicines Handbook section 5.1

Clostridium difficile infection usually responds to metronidazole or vancomycin,¹ however up to a third of patients have recurrent infection. Fidaxomicin is a narrow spectrum macrocyclic antibiotic with bactericidal activity against *C. difficile*, staphylococci and enterococci, but not Gram negative bacteria. It works by blocking bacterial RNA polymerase and inhibiting protein synthesis.

Fidaxomicin has been compared to vancomycin in two randomised controlled trials.^{2,3} Patients with life-threatening or fulminant infection, toxic megacolon or a history of recurrent infection (more than one episode in past 3 months) were excluded, as were those with inflammatory bowel disease.

In the trials, patients with a positive stool toxin test were randomised to oral fidaxomicin 200 mg twice a day or vancomycin 125 mg four times a day for 10 days. Clinical cure rates for fidaxomicin were non-inferior to vancomycin in the intention-to-treat populations and rates of recurrence were significantly lower with fidaxomicin than with vancomycin (see Table).^{2,3}

In the combined phase III trial data, the most common adverse events in the fidaxomicin groups included nausea (11%), vomiting (7.3%), headache (6.6%), abdominal pain (5.9%), diarrhoea (5%) and constipation (4.4%). Hypersensitivity has been reported and is a contraindication to fidaxomicin use.

After oral administration, there is minimal systemic absorption of fidaxomicin. It is hydrolysed to the active metabolite, OP-1118, and most of the dose

is excreted in the faeces. Co-administration with P-glycoprotein inhibitors such as cyclosporin, ketoconazole or verapamil may increase systemic fidaxomicin, however dose adjustments are not recommended. Inhibition of cytochrome P450 2C9 and 3A4/5 could potentially occur in the gastrointestinal tract and may affect the bioavailability of other drugs.

Due to lack of data, fidaxomicin should be used with caution in patients with hepatic or renal impairment. Fidaxomicin is a pregnancy category B1 drug with little data in humans. It is also not known if it is excreted in breast milk so caution is urged in pregnant and breastfeeding women.

Fidaxomicin appears to be a safe and effective alternative to vancomycin for diarrhoea caused by *C. difficile*. It is not yet known how it will compare to metronidazole which is recommended for mild to moderate disease managed in the community.¹ There is limited evidence for fidaxomicin's use in severe infections as these patients were excluded from the trials. Repeated courses of fidaxomicin have not been studied, however recurrence was less common with fidaxomicin than with vancomycin. The safety and efficacy of fidaxomicin in children has not been established.

T T manufacturer provided additional useful information

REFERENCES *†

- McFarlane M, Hajkowicz K. Controlling *Clostridium difficile*. Aust Prescr 2013. First published online 15 May 2013.
- Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422-31.
- Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012;12:281-9.

First published online 15 May 2013



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.

Table **Efficacy of fidaxomicin versus vancomycin in patients with Clostridium difficile infection** ^{1,2}

	Trial 1 ²		Trial 2 ³	
	fidaxomicin	vancomycin	fidaxomicin	vancomycin
Clinical cure rates [‡] (patient numbers)	88.2% (253/287)	85.8% (265/309)	87.7% (221/252)	86.8% (223/257)
Recurrence rates [#] (patient numbers)	15.4% (39/253)	25.3% (67/265)	12.7% (28/221)	26.9% (60/223)

[‡] resolution of diarrhoea (no more than 3 unformed stools for 2 consecutive days) and no need for further therapy after the treatment course

[#] recurrence of diarrhoea (3 or more unformed stools per day) within 4 weeks of finishing the treatment course, positive stool toxin test and need for retreatment

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

- * 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).