

New drugs

Dienogest

Approved indication: endometriosis

Visanne (Bayer)

2 mg tablets

Australian Medicines Handbook section 17.4

Endometriosis is a common condition, affecting up to 10% of women. It occurs when endometrial cells proliferate outside the uterus, for example on the ovaries or in the peritoneum. It is associated with symptoms such as chronic pelvic pain, and pain during menstruation and sexual intercourse.

Drug treatments for endometriosis aim to suppress ovarian function and include androgens (e.g. danazol), gonadotropin-releasing hormone agonists (e.g. goserelin) and progestogens.

Dienogest is a progestogen-only hormone preparation for the treatment of endometriosis. It works by suppressing oestradiol production and preventing the growth of the endometrium. Dienogest is already available in Australia in combination with an oestradiol in some oral contraceptive pills (Aust Prescr 2007;30:50-5, Aust Prescr 2015:38;6-11).

In an open-label, dose-finding trial of 68 women, daily dienogest 2 mg or 4 mg significantly reduced the severity of endometriosis, scored by laproscopic examination at baseline and 24 weeks later. It also decreased rates of pain during sexual intercourse from 52% to around 6%. Rates of premenstrual pain, dysmenorrhoea and diffuse pelvic pain were also reduced. The trial concluded that dienogest 2 mg once a day was the lowest effective dose.¹ (A 1 mg dose of dienogest was also included in the trial, but randomisation was stopped prematurely due to irregular bleeding in all four patients receiving this dose.)

In a 12-week placebo-controlled trial involving 198 women, daily dienogest 2 mg significantly reduced pelvic pain compared with placebo on a 100-mm visual analogue scale (by 27.4 mm vs 15.1 mm).² The clinical significance of this difference was unclear. In a 52-week open-label extension of this study, 87 women continued dienogest and 81 who had taken placebo started the drug. Treatment continued for up to 52 weeks. The mean pain score declined from 27.89 mm to 9.72 mm in previously treated patients, and from 40.73 mm to 13.49 mm in those who switched from placebo. At the end of treatment the mean score for all patients was 11.52 mm.³ However, approximately

a quarter of the women still used analgesia for their symptoms. A group of 34 women were followed up for 24 weeks after treatment finished. Their mean pain score increased slightly to 14.56 mm.³

Dienogest has been compared to the gonadotropin-releasing hormone agonist leuprolide (leuprorelide) in an open-label non-inferiority study of 252 women. After 24 weeks of treatment, pelvic pain – assessed by a 100-mm visual analogue score – had reduced from 60.2 mm to 12.7 mm with daily dienogest 2 mg and from 57.9 mm to 11.9 mm with leuprorelide (3.75 mg by depot intramuscular injection every four weeks). The trial concluded that dienogest was non-inferior to leuprorelide.⁴ (A non-inferiority margin of 15 mm was pre-specified on a 100-mm visual analogue scale.)

Similarly dienogest was found to be as effective as buserelin (given intranasally), another gonadotropin-releasing hormone agonist. However, dienogest was associated with more vaginal bleeding than the comparator.⁵

In a safety cohort of 727 women, the most frequently reported adverse effects with dienogest were headache (9%), acne (5.1%), nausea (4.2%), weight gain (3.6%), breast tenderness (3.3%), depressed mood (3.0%) and flatulence (3.0%). As severe depression has been reported with dienogest,⁴ patients with a history of depression should be monitored closely.

Changes in menstrual bleeding patterns were common in the trials, but did not usually lead to discontinuation. After 9–12 months, bleeding was normal in 22.8% of women but had stopped (28.2%), become infrequent (24.2%), frequent (2.7%), irregular (21.5%) or prolonged (4%) in others.

Dienogest is contraindicated in undiagnosed vaginal bleeding and during pregnancy and lactation. Although ovulation is inhibited in most patients, dienogest is not a contraceptive and use of a non-hormonal method is recommended while taking dienogest. The menstrual cycle resumes within two months of stopping the drug.

Dienogest should not be given to patients with an active thromboembolic disorder or a history of cardiovascular disease. The risk of cardiovascular events is associated with older age, hypertension and smoking. Diabetes and severe hepatic disease, a history of liver tumours or sex-hormone dependent malignancies are contraindications to dienogest. If cholestatic jaundice or pruritis develops, dienogest should be stopped.



Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

It was not clear from the trials if dienogest affects bone mineral density. If treatment is continued for longer than six months, consider monitoring bone mineral density.

After oral administration, dienogest is rapidly absorbed with peak serum concentrations being reached after approximately 1.5 hours. It is completely metabolised, mainly by cytochrome P450 (CYP) 3A4, and metabolites are rapidly excreted in the urine and faeces.

Inducers of CYP3A4, such as rifampicin or St John's wort, may decrease plasma concentrations of dienogest, whereas CYP3A4 inhibitors, such as fluoxetine, ketoconazole or erythromycin, may increase dienogest concentrations.

Dienogest can be started on any day of the menstrual cycle. It should be taken every day without interruption. If a tablet is missed, the next one should be taken as soon as possible and dosing continued as normal the next day. As with the contraceptive pill, vomiting and diarrhoea can reduce the efficacy of dienogest.

Dienogest reduces the pain associated with endometriosis and is comparable to gonadotropin-releasing hormone agonists. However, some women may still need analgesia for their pelvic pain.

T manufacturer provided the AusPAR and product information

REFERENCES ^A

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Febuxostat

Approved indication: hyperuricaemia

Adenuric (A Menarini)

80 mg tablets

Australian Medicines Handbook Appendix A

Some patients with gout, such as those with tophi, require treatment to reduce their plasma urate concentration. Allopurinol achieves this by inhibiting xanthine oxidase, an enzyme involved in the production of uric acid.

Febuxostat is also an inhibitor of xanthine oxidase and, like allopurinol, it is taken once a day. It is well absorbed. Most of the dose is metabolised with approximately half the dose being eliminated in the urine. No dose adjustment is recommended if the creatinine clearance is at least 30 mL/min or in patients with mild or moderate liver impairment. Inhibition of xanthine oxidase creates a risk of serious interactions with azathioprine and mercaptopurine.

The Australian approval of febuxostat is based on two main trials (see Table).^{1,2} In the largest trial, 1072 patients with hyperuricaemia were randomised to

Table Efficacy of febuxostat in chronic gout

Trial and duration	Number of randomised patients	Treatment	Proportion of patients with serum urate below 0.36 mmol/L at final visit †
APEX ¹ 28 weeks	134	placebo	1%
	267	febuxostat 80 mg	72%
	268	allopurinol 300 mg [§]	39%
FACT ² 52 weeks	257	febuxostat 80 mg	74%
	254	allopurinol 300 mg	36%
CONFIRMS ³ 28 weeks	757	febuxostat 40 mg	45%
	756	febuxostat 80 mg	67%
	755	allopurinol 300 mg [§]	42%

† Primary outcome in CONFIRMS, secondary outcome in APEX and FACT.

§ Lower doses of allopurinol were used in patients with renal impairment.