

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

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First published online 22 May 2015

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.

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take a placebo, allopurinol 300 mg (100 mg in renal impairment) or febuxostat 80 mg, 120 mg or 240 mg daily. Serum urate was measured every four weeks during the 28-week study. The primary end point was the proportion of patients with their last three urate concentrations below 6 mg/dL (0.36 mmol/L). This outcome was achieved by 48% of the patients taking febuxostat 80 mg, 65% of those taking 120 mg and 69% of those taking 240 mg. Only 22% of the allopurinol group and none of the placebo group achieved the same outcome. In the few patients with renal impairment (serum creatinine 1.5–2 mg/dL or 133–177 micromol/L) none of those taking allopurinol (10 patients) or placebo (5 patients) had the required reduction in urate concentrations, compared with four of the nine patients taking febuxostat 80 mg.¹

The other pivotal trial also used the same end point of a urate concentration below 6 mg/dL (0.36 mmol/L) for the last three months of therapy. However, this trial studied 52 weeks of treatment. It randomised 762 patients to take daily doses of allopurinol 300 mg, febuxostat 80 mg or febuxostat 120 mg. There was a significantly greater response to febuxostat therapy. The primary end point was reached by 53% of those taking 80 mg and 62% of those taking 120 mg compared with 21% of those taking allopurinol. In the 156 patients with tophi at the start of the study, the median percentage reduction in area was 83% with 80 mg, 66% with 120 mg and 50% with allopurinol. This difference is not statistically significant.²

Another trial (see Table) also compared allopurinol 300 mg to febuxostat 40 mg or 80 mg. Its primary end point was a final urate concentration below 6 mg/dL (0.36 mmol/L) after six months of treatment. Approximately 65% of the 2268 patients in the trial had mild or moderate renal impairment (estimated creatinine clearance 60–89 mL/min or 30–59 mL/min). The target urate concentration was reached by 45% of the patients taking febuxostat 40 mg, 67% of those taking 80 mg and 42% of the allopurinol group. In patients with renal impairment the respective responses were 50%, 72% and 42%.³

In the pivotal trials more patients withdrew from the febuxostat groups than from the allopurinol groups.^{1,2} The most common adverse event leading to withdrawal was abnormal liver function tests. Liver function should therefore be tested before and during treatment with febuxostat.

When treatment to lower urate concentrations begins there can be a flare-up of gout. Flare-ups affected more of the patients taking febuxostat than allopurinol. Prophylaxis with a non-steroidal anti-inflammatory drug or colchicine is recommended for up to six months after starting febuxostat.

The incidence of rash with febuxostat is not significantly different from the incidence with allopurinol. There have been rare reports of serious hypersensitivity reactions including anaphylaxis. In the pivotal trials there were more cardiovascular events with febuxostat than with allopurinol.^{1,2} An open-label extension of these studies, involving 1086 patients followed for up to 40 months, reported serious adverse cardiac events in 4% of patients taking febuxostat 80 mg and in 3% of the allopurinol group.⁴ The product information states that febuxostat is not recommended in patients with ischaemic heart disease or congestive heart failure.

More common adverse effects of febuxostat include diarrhoea, nausea and headache. In general, these symptoms had a similar frequency in patients taking allopurinol.

In the extension study more than 80% of the patients taking febuxostat continued to have urate concentrations below 6 mg/dL (0.36 mmol/L). There was also a decrease in the number and size of tophi.⁴ Although the efficacy of febuxostat 80 mg was significantly greater than the efficacy of allopurinol in the pivotal trials, the allopurinol dose was fixed.^{1,2} In practice the dose of allopurinol can be adjusted according to the response. The Australian Medicines Handbook also advises on how to prescribe allopurinol in renal impairment. While the trials included higher doses, the recommended starting dose for febuxostat in Australia is 40 mg, only increasing to 80 mg if the serum urate is greater than 0.36 mmol/L after 2–4 weeks.

Febuxostat is indicated for patients who have chronic symptomatic hyperuricaemia with evidence of urate deposition, such as tophi. It is currently not indicated for hyperuricaemia due to causes other than gout. The likely role of febuxostat will be in patients with chronic gout who cannot be managed with allopurinol.

T manufacturer provided the product information

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First published online 6 May 2015