

# NEW DRUG EVALUATION

No. 101

January 2010

## FEBUXOSTAT

**Febuxostat (Adenuric<sup>®</sup>▼) is a non-purine xanthine oxidase inhibitor licensed for the treatment of chronic hyperuricaemia. It is more effective than placebo or allopurinol for lowering uric acid concentrations in studies of up to 40 month's duration. However, a reduction in the incidence of episodes of acute gout has not been demonstrated. Febuxostat is associated with a significant burden of adverse effects, there is currently limited long-term safety data, and it is more expensive than alternative treatments. In line with NICE guidance, it is only recommended when allopurinol is contraindicated or not tolerated.**

### *What is it?*

Febuxostat (Adenuric<sup>®</sup>▼, Ipsen) is an oral non-purine selective xanthine oxidase inhibitor.<sup>1</sup> It is licensed for the treatment of chronic hyperuricaemia where uric acid (UA) deposition has already occurred.<sup>1</sup> Available as 80 mg and 120 mg tablets, the recommended starting dose is 80 mg once daily. Serum UA concentration should be measured every 2 to 4 weeks after initiation of therapy and if > 350 micromol/L then the dose may be increased to 120 mg once daily.<sup>1</sup>

### *How effective is it?*

The clinical efficacy of febuxostat has been studied in two phase III, active comparator, double-blind, randomised controlled trials called FACT and APEX.<sup>2,3</sup> Both these studies recruited patients diagnosed with gout and with serum UA  $\geq$  476 micromol/L. Both studies also provided prophylaxis against gout flare-up during the first eight weeks of treatment consisting of daily colchicine or naproxen.<sup>2,3</sup>

FACT compared febuxostat 80 mg (n = 255) and 120 mg (n = 250) with allopurinol 300 mg (n = 251), each taken once daily for 52 weeks.<sup>2</sup> Patients had a mean age of 52 years and were predominantly male (96%). The primary outcome of serum UA < 357 micromol/L at the last three monthly measurements was achieved by 53%, 62%, and 21% respectively (p<0.001 for each comparison vs. allopurinol). The proportion of patients in each group requiring treatment for  $\geq$  1 gout flare-up between weeks 9 to 52 were 64%, 70%, and 64% respectively (p $\geq$ 0.05) and during the eight-week prophylaxis period 22%, 36%, and 21% (p<0.001 for febuxostat 120 mg vs. 80 mg and vs. allopurinol).<sup>2</sup>

The APEX study was a 28-week phase III study in over 1,000 patients who were predominantly male (94%) and had a mean age of 52 years.<sup>3</sup> Patients were randomised to once daily treatment with placebo (n = 134), febuxostat 80 mg (n = 262), 120 mg (n = 269), or 240 mg (n = 134), or allopurinol 100 mg or 300 mg (n = 268). After 28 weeks the proportion of patients in each group that met the primary outcome of serum UA < 350 micromol/L for their last three monthly visits was 0%, 48%, 65%, 69%,

and 22% respectively (p<0.001 for each febuxostat dose vs. placebo or allopurinol). In weeks 8 to 28 during which prophylaxis for gout flare-up was not provided there were no significant differences in the incidence of gout flare-ups between groups (p $\geq$ 0.05). However, the incidence of gout flare-up was significantly greater in the high dose febuxostat groups (120 and 240 mg daily) during the first eight weeks of the study (36% and 46% respectively, vs. 28% with febuxostat 80 mg, 23% with allopurinol and 20% with placebo).<sup>3</sup>

An open-label extension study called EXCEL recruited 1,086 patients from the FACT and APEX studies (85% of eligible patients) with maximum follow-up of 40 months.<sup>4</sup> The aim of the EXCEL study was to maintain serum UA between 179 to 357 micromol/L with patients permitted to switch between treatments during the first six months in order to achieve this target. On entry following partial randomisation 649 patients were treated with febuxostat 80 mg, and 292 with 120 mg, and 145 with allopurinol 100 or 300 mg. At six months the numbers in each group were 606, 388, and 92, with the proportions switching from each group being 25%, 31%, and 59% respectively. The principal reason for switching from febuxostat 120 mg was due to a low serum UA level. After one month of initial treatment 81%, 87% and 46% of patients, respectively, had serum UA within range. Between month 12 and study end (i.e. after the period during which patients were able to switch treatment) target serum UA levels were maintained by 75 to 100% of patients at each two-monthly visit.<sup>4</sup>

### *How safe is it?*

In both phase III studies the most common adverse effects encountered were respiratory infection, diarrhoea, headache, and liver function abnormalities. The overall incidence of adverse effects was similar across all groups including placebo and ranged between 75 to 85% in FACT and 68 to 75% in APEX.<sup>2,3</sup>

Some longer term data on adverse effects is reported in the EXCEL study. Adjusted event rates did not reveal any important differences between febuxostat- and allopurinol-treated patients. The most common effects were respiratory tract infections, musculoskeletal and joint-related effects, skin injuries, and headache.<sup>4</sup>

Rash, and other allergic and skin related effects occurred at similar rates between each treatment group with incidences ranging from < 1 to 2% in the FACT study, from 4 to 6% in the APEX study, and from 2 to 5% in the EXCEL study.<sup>2-4</sup>

A review of clinical evidence performed for a NICE technology appraisal identified a non-significant increased risk of cardiovascular events and deaths in febuxostat-treated groups.<sup>5</sup> Febuxostat is not recommended for patients with ischaemic heart disease or congestive heart failure.<sup>1</sup>

All suspected adverse reactions to black triangle drugs such as febuxostat should be reported to the MHRA via the Yellow Card Scheme ([www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)).

### What other options are there?

The only other licensed treatments for gout prophylaxis are allopurinol and sulfinpyrazone.<sup>6</sup> Like febuxostat, allopurinol has simple once-daily dosing<sup>6</sup> although it is commonly associated with the emergence of skin rashes with prevalence estimated at about 3%.<sup>7</sup> This is a similar rate

to that observed in each treatment group in the febuxostat studies.<sup>2-4</sup> Sulfinpyrazone is reserved for patients who are under-excretors of UA or who are resistant to, or intolerant of, allopurinol.<sup>6,8</sup>

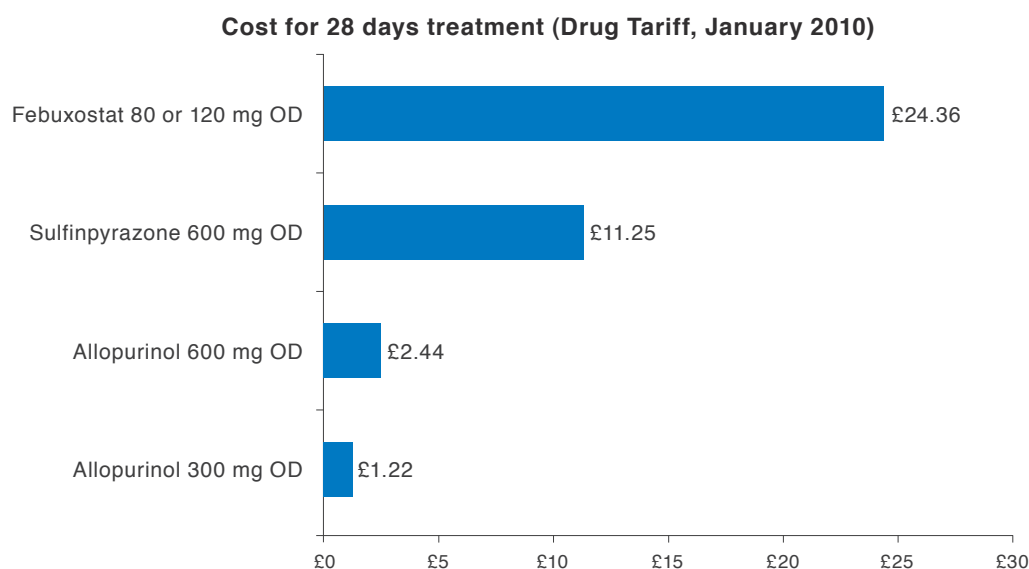
The British Society for Rheumatology recommends a target serum UA level of < 300 micromol/L for gout prophylaxis,<sup>8</sup> which is a lower target than applied in the febuxostat studies.<sup>2-4</sup>

### When should it be used?

While febuxostat reduces serum UA this has not been shown to translate to a reduction in the incidence of gout flare-ups. It is associated with important adverse effects, for example altered liver function, there is limited long-term safety data available, and it is more expensive than alternative licensed treatments.

In December 2008 NICE published a technology appraisal of febuxostat and recommended it for use only if allopurinol is contra-indicated or not tolerated.<sup>5</sup>

### How much does it cost?



NB. Doses shown are for general comparison only and do not imply therapeutic equivalence. (Febuxostat costs provided by A. Menarini Pharma UK S.R.L., January 2010).

## REFERENCES

1. Approved summary of product characteristics accessed via [www.ema.europa.eu/humandocs/PDFs/EPAR/adeneric/emea-combined-h777en.pdf](http://www.ema.europa.eu/humandocs/PDFs/EPAR/adeneric/emea-combined-h777en.pdf)
2. Becker MA et al. Febuxostat compared with allopurinol in patients with hyperuricaemia and gout. NEJM 2005; 353: 2450-61 (RCT)
3. Schumacher HR et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008;59:1540-8 (RCT)
4. Becker MA et al. Clinical efficacy and safety of successful longterm urate lowering with febuxostat or allopurinol in subjects with gout. J Rheumatol 2009;36:1273-82 (OL)
5. NICE technology appraisal No.164. Febuxostat for the management of hyperuricaemia in people with gout. Dec 2008 [www.nice.org.uk/Guidance/TA164](http://www.nice.org.uk/Guidance/TA164) (G)
6. British National Formulary No. 57, March 2009
7. Sonntag MR et al. Exanthema during frequent use of antibiotics and antibacterial drugs as well as allopurinol: Results of The Berne Comprehensive Hospital Drug Monitoring Program. Schweiz Med Wochenschr 1986; 116: 142-5
8. Jordan KM et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. Rheumatology 2007; 46: 1372-4 (G)

KEY: G – Guideline, OL – open label study, RCT – randomised controlled trial

**Regional Drug and Therapeutics Centre**  
**Wolfson Unit, Claremont Place, Newcastle upon Tyne NE2 4HH**  
**Tel: 0191 260 6188 Fax: 0191 260 6191**  
**Email: [nyrdtc.rxsupp@nuth.nhs.uk](mailto:nyrdtc.rxsupp@nuth.nhs.uk) Website: [www.nyrdtc.nhs.uk](http://www.nyrdtc.nhs.uk)**