

# febuxostat

NEW DRUG

Hyperuricaemia: risk of gout attacks

## Abstract

For patients with chronic symptomatic hyperuricaemia who fail to respond to a low purine diet, *allopurinol* is the standard drug used to prevent complications. This xanthine oxidase inhibitor can, in rare instances, cause severe skin reactions. *Probenecid*, a uricosuric agent, with which there is also long experience, is a second-line option.

*Febuxostat*, another xanthine oxidase inhibitor, is now authorised for the treatment of hyperuricaemia.

Two randomised double-blind trials in 762 and 1072 patients tested various doses of *febuxostat* compared with a standard dose of *allopurinol* (300 mg/day). *Febuxostat* normalised uric acid levels more frequently than *allopurinol*. However, overall, more patients suffered gout attacks with *febuxostat* than with *allopurinol* during the first two months of treatment, despite preventive measures (30-35% versus 22%). Between 3 and 6 months of treatment neither drug reduced the

incidence of gout attacks more effectively than placebo. After one year of treatment about two-thirds of patients suffered gout attacks, with no difference between the *febuxostat* and *allopurinol* groups.

In these trials there were more premature treatment withdrawals with *febuxostat* than with *allopurinol*.

The adverse effects of *febuxostat* are poorly documented, especially cardiac, hepatic, haematological and thyroid disorders. In the short term, severe cardiac disorders, based on a composite endpoint, were 4 to 5 times more frequent with *febuxostat* than with *allopurinol*. Treatment withdrawals due to hepatic disorders were more frequent with *febuxostat* than with *allopurinol* (2.8% versus 0.4%). The relative frequency of severe cutaneous disorders with *febuxostat* and *allopurinol* is not known.

Clinical evaluation does not include any head-to-head trials of *febuxostat* versus *probenecid*.

In practice, patients with hyperuricaemia should continue to receive *allopurinol* as first-line treatment, and *probenecid* as second-line treatment if *allopurinol* is ineffective.

## NOTHING NEW



For the prevention of recurrent gout attacks in patients with hyperuricaemia, a moderate dose of *allopurinol* carries a lower initial risk of gout attacks than *febuxostat*, even if *febuxostat* has stronger hypouricaemic effects. Hepatic and cardiac adverse effects appear to be more frequent with *febuxostat*. *Allopurinol* remains the first-line drug treatment in this setting, while the best second-line option is *probenecid*, a drug with which *febuxostat* has not been compared.

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Uric acid is the metabolic end product of exogenous and endogenous purines. Hyperuricaemia is generally defined as plasma uric acid concentrations exceeding 0.42 mmol/l (70 mg/l) in men and postmenopausal women, or 0.36 mmol/l in premenopausal women (1). These concentrations are associated with a risk of sodium urate crystal deposition in synovial fluid and in other tissues (1).

## Do not confuse hyperuricaemia and gout

Drug therapy is not necessary for asymptomatic hyperuricaemia (2).

The presence of sodium urate crystals in synovial fluid can cause acute inflammatory reactions, thus provoking gout attacks. Persistent hyperuricaemia is sometimes associated with the development of visible or palpable crystal

deposits (tophi) at various sites, especially in the joints. These peri- and intra-articular deposits can erode the cartilage, leading to destructive gouty arthropathy. More rarely, sodium urate crystal deposition in the kidneys can cause renal lithiasis or even interstitial nephropathy (1).

Long-term hyperuricaemic therapy is often needed for symptomatic patients. The objective is to reduce the production of uric acid and/or to promote its renal elimination. After failure of a low purine diet, the standard drug is *allopurinol*, a purine analogue, that acts both on uric acid production (by inhibiting xanthine oxidase, an enzyme involved in purine metabolism), and on renal uric acid elimination. The main adverse effect is the onset, in rare cases, of cutaneous hypersensitivity reactions (Lyell or Stevens-Johnson syndrome) (3,4). A uricosuric drug such as *probenecid* represents an alternative.

## febuxostat

(ADENURIC®)

Tablets

- 80 mg of *febuxostat* per tablet
- 120 mg of *febuxostat* per tablet

### ■ Licensed indications:

"Chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis)". [EU marketing authorization, centralised procedure]

hypouricaemic agent;  
xanthine oxidase inhibitor

➤ **Febuxostat** (Adenuric<sup>®</sup>, Beaufour Ipsen) is a xanthine oxidase inhibitor unrelated to purine and pyrimidine bases. It is now also authorised in the European Union for the treatment of hyperuricaemia. Is its risk-benefit balance any more favourable than that of *allopurinol* in the prevention of gout attacks?

**Gout attacks early in the course of treatment**

Clinical evaluation of *febuxostat* in this setting is mainly based on two trials versus *allopurinol*. *Allopurinol* was given at a dose of 300 mg/day, while the maximum recommended daily dose is 800 mg to 900 mg in some countries. In addition, the *allopurinol* dose was not adjusted according to the blood concentration of uric acid (3,5,6). There are no trials comparing *febuxostat* with *probenecid*.

**The one-year Fact trial: many treatment withdrawals.** This double-blind controlled trial included 762 patients with gout and hyperuricaemia (> 80mg/l) (6). After randomisation they received *febuxostat* 80 mg/day, *febuxostat* 120 mg/day, or *allopurinol* 300 mg/day for one year. All patients received *naproxen* or *colchicine* for the first eight weeks in order to prevent gout attacks at the beginning of treatment.

During the first 8 weeks of treatment the incidence of gout attacks was higher with *febuxostat* 120 mg/day (36% versus 21%, p<0.001). During the rest of the trial about two-thirds of patients had gout attacks, with no statistically significant difference between the groups. Nor was there a difference in the percentage reduction in the number or surface area of tophi in the 156 patients who had tophi at baseline.

The primary endpoint was the percentage of patients with uric acid levels below 60 mg/l at the 3-month visit. The two doses of *febuxostat* were more effective than *allopurinol* (53% of patients with 80 mg, 62% with 120 mg and 21% with *allopurinol*).

At the end of the trial, there was a significantly greater improvement in quality of life with *allopurinol* than with *febuxostat* (6).

There were a large number of premature treatment withdrawals, usually due to gout attacks or adverse effects. These discontinuations were statistically more frequent with *febuxostat* 120 mg/day (39.2%) and *febuxostat*

80 mg/day (34.5%) than with *allopurinol* (26.5%).

**The 28-week Apex trial.** This randomised double-blind trial included 1072 patients (6), who received 80 mg, 120 mg or 240 mg of *febuxostat*, 300 mg of *allopurinol* or placebo daily for 28 weeks.

During the first 8 weeks of treatment the incidence of gout attacks was 28% with *febuxostat* 80 mg, 36% with 120 mg and 46% with 240 mg, 23% with *allopurinol* and 20% with placebo. This incidence was statistically higher with the 120 mg and 240 mg doses of *febuxostat* than with the other treatments. During the rest of the trial the incidence of gout attacks did not differ significantly between the groups (52% in the placebo group), with the exception of the *febuxostat* 240 mg/day group (57%).

There was no difference between the five groups in the reduction in the number and size of tophi.

The percentage of patients whose uric acid levels were below 60 mg/l at 3 months was significantly higher with *febuxostat* 80 mg/day (72%), 120 mg/day (79%), and 240 mg/day (92%) than with *allopurinol* (39%) or placebo (1%).

The rate of premature treatment withdrawals was 35% with *febuxostat* 80 mg/day, 26% with 120 mg, 36% with 240 mg and 21% with *allopurinol* (6).

**Risk of cardiac and hepatic disorders still uncertain**

In the two trials versus *allopurinol* about one-quarter of patients had an adverse effect attributable to treatment, with no significant difference between the groups (6).



**Hepatic disorders require monitoring.** In the Fact trial the adverse effect most frequently responsible for treatment cessation was an abnormal liver function test result: there were 5 withdrawals with *febuxostat* 80 mg (1.9%), 7 with *febuxostat* 120 mg (2.8%), and 1 with *allopurinol* (0.4%) (p=0.04 versus *allopurinol*) (5).

This apparent hepatotoxicity of *febuxostat* warrants rigorous pharmacovigilance.



**Cardiac disorders.** In the two comparative trials the incidence of cardiovascular events was estimated on the basis of an endpoint combining cardio-

vascular death, non-fatal myocardial infarction, non-fatal stroke, and non-fatal cardiac arrest. The incidence was 4 to 5 times higher with *febuxostat* than with *allopurinol* (1.3 versus 0.3 per 100 patient-years) (6). During long-term unblinded follow-up studies of patients included in these trials, the incidence was similar with *febuxostat* and *allopurinol* (about 1.20 per 100 patient-years).

In the Fact trial there were 4 deaths in the *febuxostat* groups and none in the *allopurinol* group (5); two of these deaths were due to cardiovascular causes (heart failure and cardiac arrest). The European Medicines Agency (EMA) report does not mention any deaths in the other comparative trial (6). The EMA has asked the company to conduct a long-term study designed to compare the cardiovascular risks of *febuxostat* and *allopurinol* as part of its risk management programme (6).



**Hypothyroidism?** About 6% of patients treated long-term with *febuxostat* had an increase in their thyroid stimulating hormone level, compared to about 3% of patients treated with *allopurinol* (6). Thyroid disorders are also included in the risk management programme.



**Increased platelet count: long-term consequences?**

An increase in the platelet count was statistically more frequent with *febuxostat* than with *allopurinol* during long-term follow-up of comparative trials (8% versus <1%) (6). The possible clinical consequences are not known.



**Headache.** In the double-blind comparative trials, 2% of patients had headaches that the investigators attributed to *febuxostat* (6).



**Oedema.** Oedema occurred in 4% of patients treated with *febuxostat* in comparative trials, versus less than 1% with placebo (6).



**Cutaneous disorders?** In the comparative trials about 7% of patients treated with *febuxostat* or *allopurinol*

developed skin rashes, an incidence similar to that observed with placebo (6). No cases of Lyell or Stevens-Johnson syndrome occurred during these trials. However, these syndromes are rare and

it is not known whether they occur more or less frequently with *febuxostat* than with *allopurinol*.



**Interactions likely.** *Febuxostat* is a weak inhibitor of cytochrome P450 isoenzyme CYP 2D6 (6,7). The clinical consequences are not known. Xanthine oxidase inhibition leads to an increase in the plasma concentrations of *mercaptopurine* and *azathioprine*, two immunosuppressants (8).

Although a pharmacokinetic study showed no interaction between *febuxostat* and *warfarin*, a few cases of haemorrhage occurred in patients treated with both drugs in clinical trials (6,7).

#### **Febuxostat: too many unknowns**

In patients with hyperuricaemia, dietary measures should be the first-line treatment. Drugs should be reserved for patients in whom dietary measures fail. Clinical evaluation of *febuxostat* highlights the importance of not confusing surrogate markers and clinical outcome measures that are relevant to patients.

In the two main comparative trials, *febuxostat* was more effective than *allopurinol* in reducing hyperuricaemia, but this increased mobilisation of uric acid crystals led to a higher frequency of gout attacks at the beginning of treatment, despite preventive measures. In the longer term, the reduction in hyperuricaemia did not lead to a reduction in the incidence of gout attacks during at least the first 6 months of treatment. *Febuxostat* was no more effective than *allopurinol* at one year.

In summary, if treatments for hyperuricaemia are to have a tangible clinical benefit, they must be used preventively and regularly for long periods. However, *febuxostat* is less acceptable to patients, due to its numerous adverse effects.

*Allopurinol* remains the standard first-line drug in this setting. In second-line treatment, *febuxostat* has not been compared with *probenecid*, a drug that has been in use for many years and whose adverse effects (including sometimes intense drug interactions) are well documented. In contrast, the adverse effects of *febuxostat* are poorly documented, due to a lack of post-marketing follow-up studies. It is therefore better to continue to use *probenecid* in second-line treatment.

**©Review prepared and translated  
by the Prescrire Editorial Staff  
(no conflicts of interest)**



#### **ASSESSMENT ELSEWHERE**

The following extracts are from the conclusions reached by the Canadian health technology agency concerning *febuxostat* (Adenuric®).

**Issues in Emerging Health Technologies (Canada):** "(...) superior to *allopurinol* for lowering uric acid levels (...). Its efficacy in preventing gout attacks was similar to that of *allopurinol*. Despite a similar rate of adverse effects, individuals on *febuxostat* were more likely to stop treatment than those on *allopurinol*" (1).

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1- "Febuxostat for Prevention of Gout Attacks" *Issues in Emerging Health Technologies* n° 87, August 2006. www.cadth.ca accessed 30 July 2008: 4 pages.

#### **Literature search**

Our literature search was based on continuous prospective scrutiny of contents listings of the main international journals, *Current Contents-Clinical Medicine*, and member bulletins of the *International Society of Drug Bulletins (ISDB)* at the Prescrire library; routine consultation of a clinical pharmacology textbook (Martindale *The Complete Drug Reference*); and routine consultation of the websites of the *European Medicines Agency (EMA)* and the *US Food and Drug Administration (FDA)*, up to 25 June 2008.

We also searched the following databases: *Embase/Excerpta Medica Drugs and Pharmacology (1991-2nd quarter 2008)*, *Medline (1966-June week 2, 2008)*, *Reactions (1983-May 2008)*, and *The Cochrane Library (CDSR, Dare, Centra, HTA, Nhsed; 2008 issue 2)*, and the following websites: *Cadth, CVZ, DERP, Inami, Iqwig, NICE, Scottish Consortium and SIGN*, up to 24 June 2008.

Despite our request for information, Beaufort Ipsen did not provide us with any information.

- 1- "Antigout drugs. Gout and hyperuricaemia". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 25 March 2008: 3 pages.
- 2- Prescrire Rédaction "Ne pas traiter les hyperuricémies asymptomatiques" *Rev Prescrire* 1995; 15 (147): 33-35.
- 3- "Allopurinol". In: "Martindale The Complete Drug Reference" The Pharmaceutical Press, London. www.medicinescomplete.com accessed 16 June 2008: 13 pages.
- 4- Prescrire Editorial Staff "Drug-induced Lyell and Stevens-Johnson syndromes" *Prescrire Int* 2009; 19 (99): 20-22.
- 5- Becker MA et al. "Febuxostat compared with allopurinol in patients with hyperuricemia and gout" *N Engl J Med* 2005; 353 (23): 2450-2461 + (letters) 354 (14): 1532-1533.
- 6- European Medicines Agency - CHMP "European Public Assessment Report (first published)-Adenuric. Scientific discussion"; 51 pages posted on the EMA website on 28 May 2008.
- 7- Bruce SP "Febuxostat: a selective xanthine oxidase inhibitor for the treatment of hyperuricemia and gout" *Ann Pharmacother* 2006; 40: 2187-2194.
- 8- European Commission "Résumé des caractéristiques du produit - Adenuric" 21 April 2008: 14 pages.

## **PRESCRIRE'S RATINGS**

Our judgement is based on the therapeutic advance of the new product.

It considers not only the inherent value of each product in terms of its risk-benefit balance, but also its advantages and disadvantages relative to existing products available in France. Note that the relative value of new products can vary from one country to another.



**BRAVO:** The product is a major therapeutic advance in an area where previously no treatment was available.



**A REAL ADVANCE:** The product is an important therapeutic innovation but has certain limitations.



**OFFERS AN ADVANTAGE:** The product has some value but does not fundamentally change the present therapeutic practice.



**POSSIBLY HELPFUL:** The product has minimal additional value, and should not change prescribing habits except in rare circumstances.



**NOTHING NEW:** The product may be a new substance but is superfluous because it does not add to the clinical possibilities offered by previous products available. In most cases it concerns a me-too product.



**JUDGEMENT RESERVED:** The editors postpone their rating until better data and a more thorough evaluation of the drug are available.



**NOT ACCEPTABLE:** Product without evident benefit but with potential or real disadvantages.

## **Quality of information from pharmaceutical companies**

In response to our systematic requests



Company provided detailed information including unpublished data and packaging items.



Company provided information limited to administrative and published data.



Company provided minimal information, mainly administrative data.



Company provided no information.