Gout update:

Febuxostat now subsidised on Special Authority
Febuxostat selectively inhibits xanthine oxidase to lower serum urate

Febuxostat is a potent, non-purine, selective inhibitor of xanthine oxidase that inhibits the production of uric acid by preventing the normal oxidation of purines to uric acid.¹,² Febuxostat has a similar mechanism of action to allopurinol, however, it is structurally different to allopurinol and allopurinol’s active metabolite oxypurinol in that it does not have a purine ring and inhibits only xanthine oxidase and not other enzymes in the purine and pyrimidine metabolic pathways.² Febuxostat inhibits both the reduced and oxidised forms of xanthine oxidase whereas oxypurinol binds predominately to the reduced form and only weakly to the oxidised form.³ This ability to inhibit both isoforms of xanthine oxidase means that febuxostat is regarded as a more potent urate-lowering medicine than allopurinol.³

Febuxostat is well absorbed after oral doses and has a half life of five to eight hours making it suitable for once daily dosing, with or without food.⁴ It is mainly metabolised in the liver, with approximately half of the dose excreted in the faeces and the other half excreted in the urine, either unchanged or as metabolites.²,⁴ The most common adverse effects reported are nausea, diarrhoea, headache, skin rashes, gout flares and liver function abnormalities.⁵,⁶ Dizziness, sleepiness and blurred vision have also been reported so patients should initially be cautious when driving or using machinery.¹ The manufacturer does not recommend the use of febuxostat in women who are pregnant or breast feeding.⁶

The role of febuxostat in the management of people with gout

Allopurinol remains the first-line choice when a xanthine oxidase inhibitor is indicated for the reduction of serum urate levels in people with gout.⁸,⁹ In clinical use, allopurinol is frequently under-dosed, particularly in patients with renal impairment. These lower doses are often ineffective at achieving and maintaining target serum urate concentrations. While allopurinol does require dose adjustment in renal impairment, lower starting doses can be slowly increased to doses above 300 mg depending on patient tolerance, with the aim of reducing urate levels to target. Allopurinol should be used optimally in people with renal impairment before considering febuxostat. A gout flare during the introduction of allopurinol is not indicative of intolerance. Patients commencing any urate-lowering therapy are at risk of flare and should be given appropriate prophylaxis to prevent this. A frequent reason for treatment failure with allopurinol is patients not adhering to the treatment regimen; a switch to another medicine will not necessarily address this, therefore all aspects of treatment need to be optimised before considering prescribing an alternative medicine.

See: “A conversation about gout” BPJ 60 (Apr, 2014) for tips on how to manage adherence.

Probenecid (second-line) is a uricosuric drug that is often effective as monotherapy in those who do not tolerate allopurinol. The usual starting dose of probenecid is 250 mg,
Special Authority criteria for febuxostat

Febuxostat is available as 80 mg and 120 mg tablets.

The Special Authority criteria for initial approval for six months are as follows (application from any relevant practitioner):

Any of the following:
1. The patient has a serum urate level greater than 0.36 mmol/L despite treatment with allopurinol at doses of at least 600 mg/day and appropriate doses of probenecid; or
2. The patient has experienced intolerable side effects from allopurinol such that treatment discontinuation is required and serum urate remains greater than 0.36 mmol/L despite appropriate doses of probenecid; or
3. Both:
   3.1 The patient has renal impairment and serum urate remains greater than 0.36 mmol/L despite optimal treatment with allopurinol (see note); and
   3.2 The patient has a rate of creatinine clearance greater than or equal to 30 mL/min.

Renewal of the Special Authority (from any relevant practitioner), for two years, is possible where the treatment remains appropriate and the patient is benefitting from treatment.

Note: Optimal treatment with allopurinol in patients with renal impairment is defined as treatment to the creatinine clearance-adjusted dose of allopurinol then, if serum urate remains greater than 0.36 mmol/L, a gradual increase of the dose of allopurinol to 600 mg or the maximum tolerated dose.

For full details, see the Pharmaceutical Schedule, available from: www.pharmac.health.nz


twice daily, increasing to 500 mg, twice daily. If the serum urate target is not achieved, probenecid can be further increased to 1 g, twice daily. Combination treatment with allopurinol and probenecid may be helpful to achieve target urate levels in some patients. Probenecid may also be used for people who have contraindications to using allopurinol, such as previous severe hypersensitivity. However, probenecid is contraindicated in patients with a history of kidney stones. All patients commencing probenecid should be advised to drink at least two litres of fluid per day to prevent nephrolithiasis.

Febuxostat is a third-line alternative for patients who have had an adequate trial of treatment with allopurinol and probenecid, and meet Special Authority criteria for subsidy (see criteria opposite).

What are the risks and benefits of febuxostat?

Febuxostat is a relatively new medicine, approved in 2008 in Europe, in 2009 in the United States and available in New Zealand since 2013. Clinical studies have revealed a number of potential benefits and risks with febuxostat use, however, a complete risk-benefit profile has not been fully clarified. Further studies and post-marketing surveillance will help determine the longer term safety profile of febuxostat, especially in patients with cardiovascular risk factors and those with more severe renal and hepatic impairment. Ongoing research is also likely to provide more information about the effectiveness of febuxostat in relation to allopurinol when it is appropriately up-titrated.

Risks of febuxostat

The main safety issue with febuxostat is the risk of hepatotoxicity. There is some evidence that febuxostat may increase cardiovascular risk. Hypersensitivity reactions have also been reported from post-marketing surveillance. As with all gout medicines, prophylaxis is required to prevent gout flares while establishing treatment.

Potential risk of hepatotoxicity

Serum alanine aminotransaminase (ALT) concentrations exceeding three times the upper limit of normal have been observed in patients treated with febuxostat in clinical studies. The clinical significance of this is unknown, and although there have been post-marketing reports of non-fatal and fatal hepatic failure in patients taking febuxostat, probable cause has not been established. It is recommended that liver function tests (LFTs) are requested prior to initiation of treatment with febuxostat, followed by LFTs during the early
stages of treatment (e.g. at one month and three months) and then periodically thereafter based on clinical judgement. If a patient taking febuxostat has symptoms and signs suggestive of liver damage, e.g. anorexia, nausea, fatigue, right upper abdominal pain, dark urine or jaundice, request an urgent LFT.

Febuxostat can be safely used in people with mild hepatic impairment, with the dose limited to 80 mg daily. This is also likely to apply to those with moderate hepatic impairment, although the data is more limited. Patients who have abnormal LFTs, with an ALT more than three times the upper limit of normal, should stop treatment with febuxostat and not be restarted unless there is an alternative explanation for the abnormal LFTs. There is currently no data on the safety of febuxostat in patients with severe hepatic impairment.

Use with caution in patients with cardiovascular disease
The New Zealand Formulary (NZF) currently advises caution with the use of febuxostat in patients with ischaemic heart disease and congestive heart failure and the manufacturers datasheet does not recommend use in these patients.

Early clinical studies revealed a higher incidence of cardiovascular events in people treated with febuxostat than with placebo and included excess cardiovascular deaths, myocardial infarction and stroke, however, a direct relationship has not been established. Researchers found that the cardiovascular events occurred in patients with a history of atherosclerosis, previous myocardial infarction, baseline congestive heart failure and in those aged over 60 years, and concluded that these events were unrelated to febuxostat.

A more recent analysis of febuxostat use (maximum dose 80 mg) in a subset of older patients, the majority of whom had a history of cardiovascular disease (87.2%), showed low rates of cardiovascular adverse effects.

Further research is required to clarify the risks of febuxostat in patients with cardiovascular disease. A randomised controlled trial is currently underway to compare cardiovascular risks with the use of febuxostat and allopurinol (CARES).

Prophylaxis is essential during treatment initiation
Evidence suggests that there is an increased risk of gout flares during initial treatment with febuxostat compared with other urate-lowering medicines (e.g. allopurinol 200 to 300 mg).

The mechanism is not well understood, however, it is believed to be caused by rapid changes in serum urate concentrations and the resulting mobilisation of urate stores.\textsuperscript{14}

Trials comparing febuxostat and allopurinol reported that more people withdrew from treatment with febuxostat, particularly those taking the 120 mg dose, due to the increased incidence of gout flares, despite the use of prophylaxis, and other adverse effects.\textsuperscript{1, 15}

Prophylaxis should be prescribed during the initiation of treatment with febuxostat, for up to six months. Options include low-dose colchicine (0.5 mg, once or twice daily) or a low dose of an NSAID (e.g. naproxen 250 mg, twice daily) with concomitant gastroprotection treatment if required.\textsuperscript{1} Low dose steroids, e.g. prednisone ≤ 10 mg daily, can be used if colchicine and NSAIDs are not tolerated or are contraindicated.\textsuperscript{16}

**Hypersensitivity reactions have been reported**

In 2012, the UK Medicines and Healthcare products Regulatory Agency (MHRA) provided a warning about the risk of rare but serious hypersensitivity reactions with febuxostat following a review of post-marketing surveillance data.\textsuperscript{17}

Reactions included reports of patients with Stevens-Johnson syndrome and acute anaphylactic shock, the majority of which occurred within the first month of treatment.\textsuperscript{17} Some patients were reported to have a history of renal disease and/or hypersensitivity to allopurinol. Patients should be advised of signs and symptoms of severe hypersensitivity, such as skin rashes, facial oedema, fever, and febuxostat must be stopped immediately if these occur. Patients with a prior history of hypersensitivity to allopurinol and/or renal disease may have a potential for hypersensitivity to febuxostat.\textsuperscript{5}

Febuxostat is not recommended for use in patients who have a greatly increased rate of urate formation, e.g. those with malignant disease or Lesch-Nyhan syndrome, as there is currently no data on its use in these patients.\textsuperscript{5, 6}

**Medicine interactions – azathioprine and theophylline**

Febuxostat is a xanthine oxidase inhibitor therefore it may interact with medicines that are also metabolised by this enzyme, such as the cytotoxic medicines azathioprine and mercaptopurine.\textsuperscript{18} Febuxostat may increase serum levels of these medicines when taken concurrently so it is recommended that they are not used together.\textsuperscript{18} If it is essential that these medicines are used concurrently it is appropriate to consider a reduction in the dose of azathioprine or mercaptopurine, and to monitor for signs of haematological toxicity, e.g. myelosuppression.\textsuperscript{18}

Theophylline (and aminophylline) are also metabolised by xanthine oxidase so theoretically similar precautions apply if these medicines are used with febuxostat. The predicted increase in serum levels of theophylline may not be clinically significant, however, as there is some evidence to show that febuxostat 80 mg daily had no effect on the pharmacokinetics of a single dose of theophylline.\textsuperscript{19} It is currently recommended that concurrent use of these medicines is undertaken with caution, that the patient is monitored for adverse effects, such as headache, nausea and tremor, and that if these occur the dose of theophylline be reduced.\textsuperscript{5, 18}

**Benefits of febuxostat**

One of the clinical benefits of febuxostat is that the dose does not need to be adjusted in patients with mild to moderate renal impairment (i.e. creatinine clearance > 30 mL/min). The medicine appears well tolerated in older patients. There is evidence that febuxostat may be more effective than fixed-dose allopurinol (i.e. 200 – 300 mg allopurinol daily), although depending on renal function and tolerance, many patients will be taking allopurinol doses above 300 mg.

**Dose adjustment not required in patient with mild to moderate renal impairment**

Febuxostat is eliminated by both renal and hepatic pathways whereas allopurinol is largely excreted renally.\textsuperscript{2} Unlike allopurinol, therefore, febuxostat does not require dose adjustment in patients with gout who have mild to moderate renal impairment.\textsuperscript{1} There is, however, limited data on the safety of febuxostat in patients with severe renal impairment (creatinine clearance < 30 mL/min).\textsuperscript{1, 7, 20}

Allopurinol can be used in patients with renal impairment, even those with severe renal impairment, provided that the patient starts on a creatinine clearance-adjusted dose and the dose is then slowly titrated upwards as required to achieve a target serum urate level.\textsuperscript{8, 21}

**Well tolerated in older patients**

Febuxostat appears to be well tolerated in patients with gout who are older (> 65 years). When used in a population which included 374 people aged over 65 years (out of 2269 subjects) in comparison to a fixed dose of allopurinol (200 or 300 mg), febuxostat at doses of 40 and 80 mg was well tolerated and effective at achieving target urate levels.\textsuperscript{11} Within the population there were high rates of patients with co-morbidities, including a high percentage with cardiovascular disease, renal impairment and concomitant use of other medicines.
May be more effective than fixed lower doses of allopurinol. Clinical studies comparing febuxostat and allopurinol report that febuxostat doses of 80 mg and 120 mg were more effective at lowering serum urate than allopurinol 200 mg and 300 mg.\textsuperscript{15, 22} However, clinical guidelines suggest that 300 mg of allopurinol is a relatively low dose and further evidence is required to determine whether febuxostat is more effective than allopurinol when allopurinol has been titrated to effect.\textsuperscript{12}

**How should I prescribe febuxostat?**

- **Ensure an adequate trial with allopurinol and probenecid.** When initiated at low doses and up-titrated appropriately to target serum urate, allopurinol is an effective urate-lowering treatment and well tolerated by patients.\textsuperscript{21} The Special Authority criteria indicates that “optimal treatment with allopurinol in patients with renal impairment is defined as treatment to the creatinine clearance-adjusted dose of allopurinol then, if serum urate remains greater than 0.36 mmol/L, a gradual increase of the dose of allopurinol to 600 mg or the maximum tolerated dose.” If there is a concern about increasing the dose of allopurinol, consider discussing the patient with a Rheumatologist.

- **Do not start febuxostat in acute attack.** Febuxostat should not be started during an acute attack of gout or until it has completely settled (usually approximately one month). However, if there was a flare of gout in a patient already receiving febuxostat then the medicine should be continued and the flare treated as appropriate for that individual patient.\textsuperscript{4, 5}

- **Start febuxostat at 80 mg once daily.** Febuxostat rapidly lowers serum urate levels, therefore the patient’s response to treatment can be checked after two to four weeks. If the serum urate is > 0.36 mmol/L, increase the dose of febuxostat to 120 mg* once daily, aiming for a serum urate of < 0.36 mmol/L.

- **Co-prescribe prophylaxis with low-dose colchicine or a low dose of an NSAID when starting febuxostat.** Low dose steroids can be prescribed if colchicine and NSAIDs are not tolerated or contraindicated. Prophylaxis is required to avoid breakthrough gout attacks/flare during initiation of febuxostat and should be continued for six months.

- **Monitor liver function tests (LFTs).** LFTs should be checked prior to the initiation of febuxostat, early in treatment (one and three months) and then intermittently during treatment based on clinical judgement.

**Encourage adherence to all urate lowering medicines.** Adherence affects treatment outcomes for patients taking any medicine long-term to lower serum urate.

* According to the manufacturer the 80 mg film-coated tablets, although not scored, can be halved without altering the pharmacokinetics of the medicine. This may help reduce medicine wastage if a patient who has been taking 80 mg tablets needs to have their dose increased to 120 mg – the patient could use up their 80 mg tablets by taking one and a half.

**Other treatment options**

Benzbromarone is a uricosuric agent that works by increasing urate excretion via the kidney. There is some evidence that benzbromarone may be a more effective urate-lowering medicine than allopurinol for people with Polynesian ancestry based on a number of factors, including genetic variations in urate transporters.\textsuperscript{23, 24} Benzbromarone 100 – 200 mg daily has been shown in clinical trials to be more effective than 1000 mg probenecid daily and has similar efficacy to allopurinol 300 – 600 mg daily.\textsuperscript{25} However, there are concerns about the rare but serious adverse effect of hepatotoxicity, which has lead to withdrawal of benzbromarone in the United States and some European countries.\textsuperscript{7, 20} In New Zealand benzbromarone is available fully subsidised under Special Authority criteria similar to febuxostat, i.e. as a third-line treatment after allopurinol and probenecid. Benzbromarone is not approved by Medsafe and is available under Section 29 of the Medicine Act. Patient consent for its use must be documented.


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References: