781FM.2 FEBUXOSTAT
Amber recommendation guidance

This guidance provides prescribing and monitoring information for febuxostat. It should be read in conjunction with the:

- Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc, and
- BNF

BACKGROUND FOR USE

Febuxostat is licensed for the treatment of chronic hyperuricaemia in conditions where uric acid deposition has already occurred (including a history or presence of tophus and/or gouty arthritis) in adults.

In Buckinghamshire it is used 2nd line where prophylaxis with allopurinol is contraindicated or not tolerated.

SUPPORTING INFORMATION

Febuxostat is a selective xanthine oxidase inhibitor.

There is good evidence of the effectiveness of febuxostat in gout prophylaxis. Febuxostat has head-to-head comparative trials with allopurinol.

CONTRAINDICATIONS AND PRECAUTIONS

Hypersensitivity to the active substance or to any of the excipients[1] (contains lactose)	Serious hypersensitivity reactions, including Steven Johnson's syndrome and anaphylaxis, are rare but reported. Stop treatment and consider alternative.
Ischaemic heart disease or congestive cardiac failure (CCF)	A greater incidence of cardiovascular death, myocardial infarction (MI) and stroke has been reported in some but not all studies[1], in patients treated with febuxostat compared to allopurinol. Although no causal relationship has been established, the risk was higher in patients with previous history of MI or congestive cardiac failure (CCF). Consider an alternative choice of treatment.
Pregnancy	There is inadequate data on febuxostat in pregnancy to establish the effect on the foetus, so use in pregnancy is not recommended.
Breastfeeding	The drug is excreted into animal milk. The effects on the infant if this is replicated in man are not known. For this reason it is contraindicated in breastfeeding women.
Severe hepatic or renal impairment	There is a lack of experience in these conditions; the drug is partly renally and partly hepatically cleared. In moderate renal impairment there is no need to adjust doses (estimated glomerular filtration rate (eGFR) >30), but there is an increased concentration of metabolites of the drug. The recommended dose in mild hepatic impairment is 80 mg. The drug uncommonly causes renal failure/nephrolithiasis.

DOSAGE

The recommended starting dose is 80 mg daily, aiming at uric acid levels below 0.3 mmol/l after 2 - 4 weeks. The dose can be increased to 120 mg if necessary.

Treatment with febuxostat should be started 1 - 2 weeks after acute gouty attack has resolved. As reduction in uric acid level may trigger gouty attacks, prophylactic treatment with colchicine or non-steroidal anti-inflammatory drug (NSAID) is recommended in the initial phase (up to 6 months). It is important to inform the patient that the full effect of treatment may take up to 6 months to develop. Febuxostat should not be stopped during the acute attack of gout.

TIME TO RESPONSE

Uric acid lowering effect takes 2 - 4 weeks. Reduction in the incidence of acute gouty attacks can take up to 6 months.

PRE-TREATMENT ASSESSMENT BY THE SPECIALIST

Uric acid, renal function, liver function tests (LFT), full blood count (FBC) and thyroid function tests (TFTs) in patients with known thyroid dysfunction, if not done in the last 3 months.

ONGOING MONITORING SCHEDULE (usually in primary care)

Uric acid levels	At 2 - 4 weeks after initiation. Aim at uric acid level <0.3 mmol/l. If response inadequate and dose increased, repeat at 2 - 4 weeks after starting the higher dose. If target dose achieved, monitor uric acid every 6 months in the first year and annually thereafter.
LFT	Do levels at the same time as uric acid levels during the first year of treatment.
FBC	Do FBC at the same time as uric acid levels during the first year of treatment. Anaemia, thrombocytopenia or pancytopenia occur rarely - if FBC abnormal stop febuxostat and seek advice urgently.

ACTIONS TO BE TAKEN

Side Effects	Action
Rash or hypersensitivity reaction	Stop treatment and consider an alternative treatment.
Gout flares	Treat symptomatically.
Gastrointestinal (GI) symptoms (diarrhoea, less commonly nausea, abdominal pain)	Often resolved with continued treatment. If severe stop febuxostat and seek advice.
Oedema	Often mild and may resolve spontaneously. Monitor and treat symptomatically if needed.
Raised LFTs can occur in 5% of patients	If alanine transaminase (ALT) elevated >2 upper limits of normal (ULN) check for other causes, i.e. high alcohol intake. If no cause found stop the febuxostat and seek advice.
Febuxostat may affect thyroid function increasing thyroid stimulating hormone (TSH) values	Monitor TFTs in patients taking treatments for hypothyroidism or thyrotoxicosis and adjust doses if needed. Routine TFTs are only needed if patient is symptomatic.
Pancreatitis	Occurs rarely – stop treatment if severe abdominal pain and check amylase. Seek advice.
Headaches	Treat symptomatically. Stop treatment if severe.
Other side effects	For a comprehensive list see SPC[1].

NOTABLE DRUG INTERACTIONS (REFER TO BNF AND SPC)

Azathioprine or mercaptopurine should not be prescribed concurrently. Febuxostat is expected to significantly raise the levels of the immunosuppressant, on theoretical grounds, which could increase the potential for side effects relating to the immunosuppression, such as agranulocytosis.

Theophylline/aminophylline – no monitoring is required with 80 mg febuxostat. There is no data for 120 mg febuxostat so theophylline monitoring is prudent.

There is a theoretical interaction with inducers of glucuronidation, such as rifampicin, carbamazepine, which may reduce the effectiveness of febuxostat – monitor uric acid 2 weeks after initiation to assess. Conversely, consider the reverse effect when stopping inducers in patients stable on the combination.

BACK-UP INFORMATION/ADVICE

Contact Details	Wycombe and Amersham	Stoke Mandeville
Rheumatology	01296 315960 (specialist nurse helpline) In an emergency contact consultant rheumatologist on-call 01494 526161 bht.rheumatology@nhs.net	01296 315960 (specialist nurse helpline) In an emergency contact consultant rheumatologist on-call 01296 315000 bht.rheumatology@nhs.net
Medicines Resource Centre	01494 425355	
Switchboard	Amersham 01494 434411	Stoke Mandeville 01296 315000

REFERENCES

1. Summary of Product Characteristics for Febuxostat (Adenuric) at www.medicines.org.uk/emc last revised July 2019
2. NICE 2008. Hyperuricaemia – febuxostat: guidance (TA164). London. Available at http://www.nice.org.uk/guidance/TA164/Guidance/pdf
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 Nov 15;59(11):1540-8
4. Schumacher HR et al. Febuxostat in the treatment of gout: 5 yr findings of the FOCUS efficacy and safety study. Rheumatology (Oxford); 2009: Feb (2) 188-194
5. Becker MA et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353(23):2450-61
6. British Society of Rheumatology and British Professionals in Rheumatology, Guideline for the Management of Gout http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/m/management_of_gout.pdf

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