From the Chief Medical Officer
Professor Sir Michael McBride

Department of Health
An Roinn Sláinte
Männystrie O Poustie
www.health-ni.gov.uk

HSS(MD29/2023

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Castle Buildings
Stormont Estate
BELFAST
BT4 3SQ

Tel: 028 9052 0563
Email: Michael.McBride@health-ni.gov.uk

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Dear Colleague

FEBUXOSTAT: UPDATED ADVICE FOR THE TREATMENT OF PATIENTS WITH A HISTORY OF MAJOR CARDIOVASCULAR DISEASE

Caution is required if prescribing febuxostat in patients with pre-existing major cardiovascular disease, particularly, in those with evidence of high urate crystal and tophi burden or those initiating urate-lowering therapy.

This May 2023 Drug Safety Update replaces advice issued in Drug Safety Update published in July 2019.

Advice for healthcare professionals:

- in patients with pre-existing major cardiovascular diseases, febuxostat therapy should be used cautiously, particularly in those with evidence of high urate crystal and tophi burden or those initiating urate-lowering therapy
- following initiation of febuxostat, prescribers should titrate the febuxostat dose to minimise gout flares and inflammation
- note that clinical guidelines for gout (see, for example, NICE guideline 219 – Gout: diagnosis and management) recommend that allopurinol should be offered as first-line treatment for people with gout who have major cardiovascular disease
- report suspected adverse drug reactions associated with febuxostat to the Yellow Card scheme

Advice for healthcare professionals to give to patients:

- febuxostat is used to treat gout by reducing an excess of a chemical called uric acid (urate) in the body, which prevents attacks of gout in the long term; it can also be used to treat and prevent high blood levels of uric acid that may occur when you start to receive chemotherapy for blood cancer
- there are new recommendations to healthcare professionals about use of febuxostat in patients with previous heart problems
- if you currently have or have previously had heart failure, heart problems or stroke, it is recommended to talk to your doctor before taking febuxostat
- no action is needed from patients already on febuxostat, but talk to a healthcare professional if you are concerned.

About febuxostat and treatment of gout

Febuxostat, at doses of 80 milligrams (mg) and 120mg, is indicated for treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence, of tophus or gouty arthritis). Febuxostat at a dose of 120mg is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome. The advice in this article relates to treatment of chronic hyperuricaemia (gout).

Gout is a type of inflammatory arthritis caused by monosodium urate crystals forming inside and around joints, causing sudden flares of severe pain, heat, and swelling. Gout has been associated with an increased risk of cardiovascular disease and cardiovascular mortality. Gout flares may occur during initiation of urate-lowering treatment due to changing serum uric acid levels resulting in mobilisation of urate from tissue deposits. Management of gout flares may require use of non-steroidal anti-inflammatory drugs, colchicine, or oral corticosteroids.

Warnings regarding cardiovascular disease

In July 2019, the Medicines and Healthcare products Regulatory Agency (MHRA) advised healthcare professionals to avoid febuxostat treatment in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options were appropriate. This followed a review of the findings from a phase 4 clinical trial (the CARES study[1]) in patients with gout and a history of major cardiovascular disease. The CARES study showed a higher risk for cardiovascular-related death and for all-cause mortality in patients assigned to febuxostat than in those assigned to allopurinol.

[1] White WB and others. Cardiovascular safety of febuxostat or allopurinol in patients with gout. New England Journal of Medicine 2018: volume 378, pages 1200 to 1210.

A further trial has now been concluded on the cardiovascular safety of febuxostat, the FAST study.[2] The FAST study was conducted in patients in the UK, Denmark, and Sweden who had at least one cardiovascular risk factor and had already been treated with allopurinol for a median duration of 6 years; additionally, serum urate levels were controlled with dose-optimised allopurinol before randomisation. The FAST study concluded that febuxostat was non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and, unlike the CARES study results, that long-term use was not associated with an increased risk of death or cardiovascular death compared to allopurinol.

Following a review of the FAST study findings and advice from the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines, the product information for febuxostat has been updated to include the results. The product information retains the warning for cardiovascular disorders and now advises that treatment of patients with pre-existing major cardiovascular diseases with febuxostat should be exercised cautiously.

In particular, treatment should be exercised cautiously in patients with pre-existing major cardiovascular diseases with evidence of high urate crystal and tophi burden or those initiating urate lowering therapy. Prescribing clinicians should titrate febuxostat appropriately to minimise gout flares following initiation, thus minimising additional inflammation.

The MHRA also note that clinical guidelines for gout (for example, NICE guideline 219 – Gout: diagnosis and management which has been updated since the time of the FAST study publication), state that allopurinol should be offered as first-line treatment to people with gout who have major cardiovascular disease (for example, previous myocardial infarction or stroke, or unstable angina).

Detailed study findings

Further detailed study findings on the CARES study and the FAST study are available within the MHRA Drug Safety Update-Febuxostat: updated advice for the treatment of patients with a history of major cardiovascular disease.

Report via Yellow Card

Healthcare professionals, patients, and caregivers are asked to submit reports using the Yellow Card scheme electronically using:

- the Yellow Card website
- the Yellow Card app; download from the Apple App Store or Google Play Store
- some clinical IT systems for healthcare professionals (EMIS, SystmOne, Vision, MiDatabank, and Ulysses)

[2] Mackenzie IS and others. Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial. Lancet 2020: volume 396: pages 1745 to 1757.

When reporting suspected adverse drug reactions, please provide as much information as possible, including information about medical history, any concomitant medication, onset timing, and treatment dates. When reporting for a biological medicine or vaccine, please ensure that you provide the brand name (or product licence number and manufacturer), and the specific batch number.

Yellow Card biobank launch

The MHRA has recently launched the Yellow Card biobank in a joint venture with Genomics England. The pilot phase will start with allopurinol and rare severe skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Other topics of focus for the pilot phase will be confirmed in due course.
Those interested in getting involved should visit the Yellow Card biobank page. Individuals who have previously submitted a Yellow Card report relating to the pilot topics may also be asked if they would like to participate. In instances where a healthcare professional has reported on behalf of a patient, they may be asked to help contact the affected patient to see if they wish to be involved.

The complete MHRA Drug Safety update is available at the following link MHRA Drug Safety Update-Febuxostat: updated advice for the treatment of patients with a history of major cardiovascular disease.

Yours sincerely

PP Professor Lourda Geoghegan

Professor Sir Michael McBride
Chief Medical Officer

Professor Cathy Harrison
Chief Pharmaceutical Officer

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