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(IN REPLY PLEASE QUOTE THIS FILE REF.)

29 May 2023

Dear Healthcare Professionals,

Febuxostat: updated advice for the treatment of patients with a history of major cardiovascular disease

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that 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.

In July 2019, the 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) 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.

A further trial has now been concluded on the cardiovascular safety of febuxostat, the FAST study. The FAST study was conducted in patients in the United Kingdom, 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.

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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 notes that clinical guidelines for gout, 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).

As such, febuxostat treatment of chronic hyperuricaemia in patients with pre-existing major cardiovascular diseases should be exercised cautiously, with particular caution in patients with evidence of high urate crystal and tophi burden or those initiating urate lowering therapy.

Healthcare professionals are advised:

- 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 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

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/febuxostat-updated-advice-for-the-treatment-of-patients-with-a-history-of-major-cardiovascular-disease

In Hong Kong, there are 10 registered pharmaceutical products containing febuxostat and all are prescription-only medicines. So far, the Department of Health (DH) has received 5 cases of adverse drug reaction with febuxostat, of which one case was related to stroke. Related news regarding the cardiovascular risk and mortality was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 16 Nov 2017, with the latest update posted on 11 Dec 2019. Letters to inform local healthcare professionals were issued by DH on 22 Feb 2019. In Jun 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter and noted that the package insert of the local products had included relevant cardiovascular risk information. The matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

pp (Terence MAN)
for Assistant Director (Drug)