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Febuxostat (Adenuric): increased risk of cardiovascular death and all-cause mortality in clinical trial in patients with a history of major cardiovascular disease

Avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate. Findings from a phase 4 clinical study (the CARES study) in patients with gout and a history of major cardiovascular disease show a higher risk for cardiovascular-related death and for all-cause mortality in patients assigned to febuxostat than in those assigned to allopurinol.

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Advice for healthcare professionals:

- avoid treatment with febuxostat in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke, or unstable angina), unless no other therapy options are appropriate
- note the clinical guidelines for gout (see below), which recommend treatment with febuxostat only when allopurinol is not tolerated or contraindicated
- report suspected adverse drug reactions to febuxostat on a Yellow Card (https://yellowcard.mhra.gov.uk/)

The CARES study

Design of the CARES study

The CARES study (ClinicalTrials.gov NCT01101035 (https://clinicaltrials.gov/ct2/show/NCT01101035)) was a phase 4, randomised, double-blind, non-inferiority trial that recruited patients with gout and a history of major cardiovascular disease from the USA, Canada and Mexico.[1]

The primary endpoint was time to first occurrence of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, and unstable angina with urgent coronary revascularisation. Outcomes analysis was for patients who had received at least 1 dose of the randomly allocated treatment.

Findings of the CARES study

Overall 57% of patients prematurely discontinued trial treatment and 45% of patients did not complete all trial visits; 6,190 patients were followed for a median of 32 months. The median duration of exposure was 728 days for patients in febuxostat group (n=3,098) and 719 days in allopurinol group (n=3,092).

The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% versus 10.4% of patients, respectively; hazard ratio 1.03, 95% confidence interval [CI] 0.87–1.23).

In secondary analysis, the incidence of cardiovascular deaths was higher in the group assigned to febuxostat than in the group assigned to allopurinol (4.3% versus 3.2%, respectively; hazard ratio 1.34, 95% CI 1.03–1.73). The incidence of all-cause mortality was also higher in patients assigned to febuxostat than in those assigned to allopurinol (7.8% versus 6.4% respectively; hazard ratio 1.22, 95% CI 1.01–1.47), which was mainly driven by the higher rate of cardiovascular deaths in the febuxostat group. For other findings of the trial, see published findings (https://www.nejm.org/doi/full/10.1056/NEJMoa1710895).[1]

EU review of risk following CARES study

An EU review of the findings of the CARES study and their impact on the safety of febuxostat has recommended avoiding febuxostat in patients with a history of major cardiovascular disease. A letter (https://assets.publishing.service.gov.uk/media/5d2dbdcded915d2feaf5f832/DHPC_FINAL_Adenuric_120619.pdf) has been sent to relevant healthcare professionals. The Summary of Product Characteristics and Patient Information Leaflet is being updated to reflect the CARES study results.

The European phase 4 FAST study is evaluating the cardiovascular safety of febuxostat and allopurinol.[2] An independent Data Monitoring Committee has regularly reviewed and assessed unblinded data from the FAST study and has the authority to discontinue the study based on evaluation of benefits and risks. The results of the FAST study are expected in 2020.

Patients taking febuxostat are advised to contact their healthcare professional if they are concerned about their medicine.

About febuxostat

Febuxostat, at doses of 80 mg and 120 mg, 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 120 mg 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.

Clinical guidelines recommend febuxostat for chronic hyperuricaemia or gout when allopurinol is not tolerated or contraindicated.[3] [4] [5] Data from the past 3 years suggest a steady increase in use of febuxostat in the UK, with usage approximately 19,000 patient-years in 2018.[6]

Report via Yellow Card

As for all medicines, MHRA will continue to monitor the benefit and risks of febuxostat. Please continue to report any suspected adverse drug reaction via the Yellow Card Scheme. Remember only a suspicion is needed to report – if in doubt, please complete a Yellow Card.

Healthcare professionals, patients, and caregivers can report suspected side effects via the Yellow Card website (https://yellowcard.mhra.gov.uk/) or via the Yellow Card app. Download the app today via iTunes Yellow Card (https://itunes.apple.com/gb/app/yellow-card-mhra/id990237487?ls=1&mt=8) for iOS devices or via PlayStore Yellow Card (https://play.google.com/store/apps/details?id=uk.org.mhra.yellowcard&hl=en_GB) for Android devices.

You can also use the app to access the latest safety information from the MHRA about medicines and medical devices on the Newsfeed. Search for medicines to see details of Yellow Card reports others have made. Medicines of interest can also be added to a Watch List to receive news and alerts about new side effects and safety advice as it emerges.

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1.

White WB, et al. CARES investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout (https://www.nejm.org/doi/full/10.1056/NEJMoa1710895). N Engl J Med 2018; 378: 1200–10. ↩ ↩[2]

2. MacDonald TM, et al. Protocol of the Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia (https://bmjopen.bmj.com/content/4/7/e005354). BMJ Open 2014; 4: e005354. ↩

3. British National Formulary. Febuxostat, National funding/access decisions (https://bnf.nice.org.uk/drug/febuxostat.html#nationalFunding). Version accessed May 2019 ↩

4. National Institute for Health and Care Excellence. Gout. Clinical Knowledge Summary (https://cks.nice.org.uk/gout#!scenario:1). Version accessed May 2019. Last revised in February 2018. ↩

5. Scottish Medicines Consortium. Febuxostat in chronic hyperuricaemia (https://www.scottishmedicines.org.uk/medicines-advice/febuxostat-adenuric-fullsubmission-63710/). Version accessed May 2019. Last revised in September 2010. Treatment with febuxostat for chronic hyperuricaemia is restricted to use in conditions when urate deposition has already occurred and when treatment with allopurinol is inadequate, not tolerated, or contraindicated. ↩

6. Data derived from IQVIA MIDAS Q1 2016 to Q4 2018, by the MHRA, February 2019. Patient-years estimated from the data by using defined daily doses (DDD) as provided by WHO. ↩

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