# ADENURIC (febuxostat): increased risk of cardiovascular death and all-cause mortality in patients treated with febuxostat in the CARES study

**Dear Healthcare Professional,**

Menarini International Operations Luxembourg S.A. in agreement with the European Medicines Agency and the «SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC would like to inform you of the following:

## *Summary*


- In a phase IV clinical study (the CARES study) in patients with gout and a history of major cardiovascular (CV) disease, a significantly higher risk for all-cause mortality and for CV-related death was observed in patients treated with febuxostat compared with patients treated with allopurinol.
- Treatment with febuxostat in patients with pre-existing major CV disease (e.g. myocardial infarction, stroke or unstable angina) should be avoided, unless no other therapy options are appropriate.


## *Background on the safety concern*

Febuxostat is a non-purine selective inhibitor of xanthine oxidase that exhibits anti-hyperuricaemic activity by reducing the formation of uric acid.

Febuxostat, at dose 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 and/or gouty arthritis).

Furthermore, febuxostat 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 tumor lysis syndrome (TLS).

*The CARES study*

The Phase IV CARES (Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities) study (TMX-67_301) was a multicentre, randomized, double-blind, non-inferiority trial performed in the US, Canada and Mexico to evaluate the CV safety of febuxostat and allopurinol in subjects with gout and major cardiovascular comorbidities. More than 6,000 patients were recruited to compare CV outcomes with febuxostat versus allopurinol.

The primary endpoint in CARES was time to first occurrence of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction (MI), non-fatal stroke, CV death and unstable angina with urgent coronary revascularization. The endpoints (primary and secondary) were analysed according to the intention-to-treat (ITT) analysis including all subjects who were randomized and received at least one dose of double-blind study medication.

Overall 56.6% of patients discontinued trial treatment prematurely and 45% of patients did not complete all trial visits. In total, 6,190 patients were followed for a median of 32 months and 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% vs. 10.4% of patients, respectively; hazard ratio [HR] 1.03; two-sided repeated 95% confidence interval [CI] 0.87-1.23).

In the analysis of the individual components of MACE (secondary endpoint), the rate of CV deaths was significantly higher with febuxostat than allopurinol (4.3% vs. 3.2% of patients; HR 1.34; 95% CI 1.03-1.73). The rates of the other MACE events were similar in the febuxostat and allopurinol groups, i.e. non-fatal MI (3.6% vs. 3.8% of patients; HR 0.93; 95% CI 0.72-1.21), non-fatal stroke (2.3% vs. 2.3% of patients; HR 1.01; 95% CI 0.73-1.41) and urgent revascularization due to unstable angina (1.6% vs. 1.8% of patients; HR 0.86; 95% CI 0.59-1.26). The rate of all-cause mortality was also significantly higher with febuxostat than allopurinol (7.8% vs. 6.4% of patients; HR 1.22; 95% CI 1.01-1.47), which was mainly driven by the higher rate of CV deaths in that group.

*FAST study*

In Europe, the phase IV FAST (Febuxostat vs Allopurinol Streamlined Trial) study has been required by the EU regulatory authorities to evaluate the safety of febuxostat in comparison with allopurinol in patients with chronic symptomatic hyperuricaemia and CV risk factor.The study is currently ongoing and the results are expected by second quarter 2020.

The summary of product characteristics and patient information leaflet will be updated to reflect the CARES study results and to include specific recommendations for prescribers.

## *Call for reporting*

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

«SCIENTIFIC CENTRE OF DRUG AND MEDICAL TECHNOLOGY EXPERTISE AFTER ACADEMICIAN E. GABRIELYAN» CJSC

Address: Armenia, 0051, Yerevan, Komitas av. 49/4

Phone: (37410) 232132, 231682

Hot Line: (37410) 200505, (37496) 220505

E-mail: vigilance@pharm.am

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## *Company contact points*

| Company Name | Product name | Company contact details |
|---|---|---|
| Berlin-Chemie Armenian Representation | Adenuric(Febuxostat) 80 mg;<br>Adenuric (Febuxostat) 120 mg; | Armenia, 0070, Yerevan<br>Kajaznunu St., 4/1 Building<br>Tel +374-10-500773<br>Fax +374-10-500772 |

**References:**

[1] White WB, Saag KG, Becker MA, et al. CARES investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. NEngl J Med. 2018;378(13):1200–1210.

[2] MacDonald TM, Ford I, Nuki G, Mackenzie IS, De Caterina R, Findlay E, 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. BMJ Open 2014;4(7):e005354.