February 25, 2019

IMPORTANT DRUG WARNING

Subject: Important changes to the ULORIC® (febuxostat) Prescribing Information

- **Addition of a Boxed Warning on cardiovascular death**
- **Revision in the Indication and Usage to limit use to adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.**

Dear Healthcare Provider:

The purpose of this letter is to inform you of important safety changes, specifically the addition of a boxed warning and revision in the indication in the prescribing information for ULORIC (febuxostat). These changes were driven by the results obtained from CARES, a clinical study conducted in patients with gout and established cardiovascular (CV) disease to compare CV outcomes associated with ULORIC and allopurinol.[1]

- There was a higher rate of CV death in patients treated with ULORIC (134 [1.5 per 100 patient-years]) than with allopurinol (100 [1.1 per 100 patient-years]) (Hazard Ratio: 1.34, 95% Confidence Interval [CI]: 1.03, 1.73).
- ULORIC was non-inferior to allopurinol for the primary endpoint of major adverse cardiovascular events (MACE: composite of CV death, non-fatal myocardial infarction [MI], non-fatal stroke, and urgent revascularization due to unstable angina) (Hazard Ratio: 1.03, 95% CI: 0.89, 1.21).
- Sudden cardiac death was the most common cause of adjudicated CV deaths in the ULORIC group (83 of 3098; 2.7%) as compared to the allopurinol group (56 of 3092; 1.8%).

Takeda encourages prescribers to consider the risk and benefit of ULORIC prior to use.

WARNING: CARDIOVASCULAR DEATH

Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study *[see Warnings and Precautions (5.1)]*.

Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable *[see Indications and Usage (1)]*.

INDICATIONS AND USAGE

Based on the results of CARES, the Indications and Usage have changed. The previous indication for ULORIC was:

> "ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.
> ULORIC is not recommended for the treatment of asymptomatic hyperuricemia."

The **REVISED INDICATIONS AND USAGE** is as follows:

> "ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
>
> For the safe and effective use of allopurinol, see allopurinol prescribing information.
>
> Limitations of Use:
> ULORIC is not recommended for the treatment of asymptomatic hyperuricemia."

Prescriber Action

Counsel patients currently on ULORIC or those who will be prescribed ULORIC for the first time about the risks and benefits of ULORIC including:

- The higher rate of CV death in patients treated with ULORIC compared to allopurinol in a CV outcome study.
- That ULORIC should only be prescribed for chronic management of hyperuricemia to patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
- The use of prophylactic low-dose aspirin therapy by patients with a history of CV disease.
- The symptoms of heart attack or stroke, including instructions to contact a healthcare provider or get medical help right away if they have any of these symptoms.
- That effective serum urate lowering and maintaining urate levels to target is important in treatment of gout and hyperuricemia.

If you have any questions about the information contained in this letter or the safe and effective use of ULORIC, please contact our medical information department at 1-877-825-3327 or medicalinformation@takeda.com.

Reporting Adverse Events

Healthcare providers and patients are encouraged to report adverse events in patients taking ULORIC to Takeda Pharmaceuticals at 1-877-825-3327. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Indication for ULORIC 40-mg and 80-mg Tablets

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

Important Safety Information

WARNING: CARDIOVASCULAR DEATH

Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study.

Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

- ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine.

- Cardiovascular Death: In a CV outcomes study, there was a higher rate of CV death in patients treated with ULORIC compared to allopurinol; in the same study, ULORIC was non-inferior to allopurinol for the primary endpoint of major adverse cardiovascular events (MACE). Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC.
- Gout Flares: An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., NSAIDs or colchicine) upon initiation of treatment may be beneficial for up to six months.
- Hepatic Effects: Postmarketing reports of hepatic failure, sometimes fatal, have been received. Causality cannot be excluded. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.

  Obtain liver tests before starting treatment with ULORIC. Use caution in patients with liver disease. If liver injury is detected, promptly interrupt ULORIC and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart treatment if liver injury is confirmed and no alternate etiology can be found.
- Serious Skin Reactions: Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected.
- Adverse reactions occurring in at least 1% of ULORIC-treated patients, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash.

Please see enclosed Prescribing Information, including Medication Guide, for ULORIC.

This letter is not intended as a complete description of the benefits and risks related to the use of ULORIC. Please refer to the enclosed full prescribing information and medication guide.

Sincerely,

Tom Koutsavlis, MD
Senior Vice President & Head, US Medical Office
Takeda Pharmaceuticals USA, Inc.

Enclosure: ULORIC Full Prescribing Information

1. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018;378(13):1200-10.

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