

## Important Safety Information on ULORIC® (febuxostat) – Increased Risk of Cardiovascular Fatal Outcomes



2019/11/04

### Audience

Healthcare professionals including cardiologists, internists, hematologists, rheumatologists, family physicians, general practitioners, nurses, and pharmacists

### Key messages

- **Results from a post-market clinical study (the CARES trial)<sup>1</sup> found an increased risk of cardiovascular (CV) fatal outcomes in patients with gout and known cardiovascular disease treated with ULORIC, when compared to those treated with allopurinol (see Background section for more details).**
- **Healthcare professionals are advised to:**
  - **Use ULORIC only in adult patients with gout who have an inadequate response or intolerance to allopurinol, or for whom treatment with allopurinol is inappropriate (second line therapy).**
  - **Not recommend ULORIC treatment in patients with ischemic heart disease or congestive heart failure.**
  - **Monitor for signs and symptoms of myocardial infarction, stroke and cardiac failure in patients who are taking ULORIC.**
- **The Canadian Product Monograph (CPM) for ULORIC has been updated to include a revised indication for use and safety information, including a new *Serious Warnings and Precautions Box* with regards to increased risk of cardiovascular death.**

### What is the issue?

In a post-market CV outcome study (the CARES trial),<sup>1</sup> a higher rate of CV fatal outcomes has been reported in patients with gout and established cardiovascular disease treated with ULORIC, when compared to those treated with allopurinol (see Background section for more details). In order to mitigate the risk identified in the CARES trial,<sup>1</sup> the ULORIC CPM has been updated to include the revised indication for use and additional safety information.

### Products affected

ULORIC (febuxostat), 80 mg tablet (DIN 02357380)

## Background information

Previously, ULORIC was indicated to lower serum uric acid levels in patients with gout (a first-line therapy). Based on the results of the CARES study,<sup>1</sup> ULORIC is now indicated to lower serum uric acid levels in patients with gout who have an inadequate response or intolerance to allopurinol, or for whom treatment with allopurinol is inappropriate (a second-line therapy).

The ULORIC indication was revised to enhance the safe use of ULORIC based on evidence identified in a recently completed, randomized, double-blind, allopurinol-controlled CARES study.<sup>1</sup> This study was conducted to evaluate the CV risk of ULORIC in patients with gout who had a history of major CV disease, cerebrovascular disease, or diabetes mellitus with micro- and/or macrovascular disease. The study compared the risk of major adverse CV events between patients treated with ULORIC (N=3098) and allopurinol-treated patients (N=3092). There was a higher rate of CV death in patients treated with ULORIC (134 CV deaths of 3098) compared to patients treated with allopurinol (100 CV deaths of 3092). All-cause mortality was higher in the ULORIC group (243 deaths of 3098) than the allopurinol group (199 deaths of 3092) due to a higher rate of CV deaths (see Table 1 for details). 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%).

**Table 1: Patients with MACE\* in CARES (Cardiovascular Outcomes Study in Patients with Gout)<sup>1</sup>**

	ULORIC N=3098		Allopurinol N=3092		Hazard Ratio
	Number of Patients with Event (%)	Rate per 100 PY**	Number of Patients with Event (%)	Rate per 100 PY**	95% CI
Cardiovascular Death	134 (4.3%)	1.5	100 (3.2%)	1.1	1.34 (1.03, 1.73)
All-cause mortality	243 (7.8%)	2.6	199 (6.4%)	2.2	1.22 (1.01, 1.47)

\*Major adverse cardiovascular events (MACE)

\*\*Patient Years (PY)

Further to narrowing the ULORIC indication for use, additional changes were made to the ULORIC CPM to further mitigate the risk identified in the CARES study.<sup>1</sup> The increased risk of CV fatal outcomes has been included in the *Serious Warnings and Precautions Box* of the ULORIC CPM. The *Warnings and Precautions, Adverse Reactions, Clinical Trials* and *Consumer Information* sections in the CPM have also

been updated in relation to this issue.

### **Information for consumers**

ULORIC is used to treat a type of arthritis called gout in adults when allopurinol has not worked well enough or when allopurinol is not suitable for the patient. Gout happens when a naturally occurring substance in the body called uric acid builds up and causes sudden attacks of redness, swelling, and pain in one or more joints. ULORIC lowers uric acid levels in the blood.

Heart attacks, strokes and heart-related deaths have been reported in patients taking ULORIC. Before taking ULORIC, patients should tell their healthcare professional if they have a history of heart problems or stroke.

Patients taking ULORIC who experience signs or symptoms of cardiovascular disease such as chest pain, dizziness, fainting or feeling light-headed, rapid or irregular heartbeat, trouble talking, sudden blurry vision, or severe headache should stop taking the medication and tell their healthcare professional immediately.

Patients could contact their healthcare professional for more details about this new safety information.

### **Information for health care professionals**

Healthcare professionals are advised to:

- Use ULORIC only in adult patients with gout who have an inadequate response or intolerance to allopurinol, or for whom treatment with allopurinol is inappropriate.
- Not recommend ULORIC treatment in patients with ischemic heart disease or congestive heart failure.
- Monitor for signs and symptoms of myocardial infarction, stroke and cardiac failure in patients that are taking ULORIC.
- Inform patients about the cardiovascular risk with ULORIC and advise them to seek medical attention immediately if they experience the symptoms listed above.

### **Action taken by Health Canada**

Health Canada has worked with Takeda Canada Inc. to update the CPM for ULORIC. Health Canada is communicating this important safety information to healthcare professionals and Canadians via the [Recalls and Safety Alerts Database on the Healthy Canadians Web Site](https://healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php) (<https://healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php>). This communication update will be further distributed through the MedEffect™ e-Notice email notification system, as well as through social media

channels, including LinkedIn and Twitter.

**Report health or safety concerns**

Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of cardiovascular events or other serious or unexpected side effects in patients receiving ULORIC should be reported to Takeda or Health Canada.

Takeda Canada Inc.  
2201 Bristol Circle, suite 700  
Oakville, Ontario  
L6H 0J8  
Phone: 1-866-295-4636

**To correct your mailing address or fax number, contact Takeda Canada Inc.**

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect Canada's Web page on [Adverse Reaction Reporting](https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Products Directorate  
E-mail: [hc.mhpd-dpsc.sc@canada.ca](mailto:hc.mhpd-dpsc.sc@canada.ca)  
Telephone: 613-954-6522  
Fax: 613-952-7738

Sincerely,  
Original signed by



Dr. Jefferson Tea  
Vice President, Medical & Scientific Affairs  
Takeda Canada Inc.

**References**

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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