

## **FDA to evaluate increased risk of heart-related death and death from all causes with the gout medicine febuxostat (Uloric)**

### **Safety Announcement**

[11-15-2017] The U.S. Food and Drug Administration (FDA) is alerting the public that preliminary results from a safety clinical trial show an increased risk of heart-related death with febuxostat (Uloric) compared to another gout medicine called allopurinol. We required the Uloric drug manufacturer, Takeda Pharmaceuticals, to conduct this safety study when we approved the medicine in 2009. Once we receive the final results from the manufacturer, we will conduct a comprehensive review and will update the public with any new information.

Febuxostat is FDA-approved to treat a type of arthritis called gout in adults. 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. Febuxostat works by lowering uric acid levels in the blood.

**Health care professionals** should consider this safety information when deciding whether to prescribe or continue patients on febuxostat. **Patients** should talk to your health care professionals if you have any questions or concerns. Do not stop taking your medicine without first consulting with your health care professional.

The febuxostat drug labels already carry a *Warning and Precaution* about cardiovascular events because the clinical trials conducted before approval showed a higher rate of heart-related problems in patients treated with febuxostat compared to allopurinol. These problems included heart attacks, strokes, and heart-related deaths. As a result, we required an additional safety clinical trial after the drug was approved and on the market to better understand these differences, and that trial was finished recently.

The safety trial was conducted in over 6,000 patients with gout treated with either febuxostat or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring urgent surgery. The preliminary results show that overall, febuxostat did not increase the risk of these combined events compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of heart-related deaths and death from all causes.

We are continuing to evaluate this safety issue and will update the public when we have more information. We urge health care professionals and patients to report side effects involving febuxostat or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

**Related Information**

[The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)

[Think It Through: Managing the Benefits and Risks of Medicines](#)



## **FDA adds *Boxed Warning* for increased risk of death with gout medicine Uloric (febuxostat)**

This is an update to the [FDA Drug Safety Communication: FDA to evaluate increased risk of heart-related death and death from all causes with the gout medicine febuxostat \(Uloric\)](#) issued on November 15, 2017.

### **Safety Announcement**

**[2-21-2019]** The U.S. Food and Drug Administration (FDA) has concluded there is an increased risk of death with Uloric (febuxostat) compared to another gout medicine, allopurinol. This conclusion is based on our in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with Uloric.

As a result, we are updating the Uloric prescribing information to require a *Boxed Warning*, our most prominent warning, and a new patient [Medication Guide](#). We are also limiting the approved use of Uloric to certain patients who are not treated effectively or experience severe side effects with allopurinol.

Uloric was FDA-approved in 2009 to treat a type of arthritis called gout in adults. 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 works by lowering uric acid levels in the blood. Gout is a chronic disease that affects approximately 8.3 million adults in the U.S.<sup>1</sup> The number of medicines to treat gout is limited and there is an unmet need for treatments for this disease.

**Patients** should tell your health care professional if you have a history of heart problems or stroke and discuss the benefits and risks of using Uloric to treat your gout. Seek emergency medical attention right away if you experience the following symptoms while taking Uloric:

- Chest pain
- Shortness of breath
- Rapid or irregular heartbeat
- Numbness or weakness on one side of your body
- Dizziness
- Trouble talking
- Sudden severe headache

Do not stop taking Uloric without first talking to your health care professional, as doing so can worsen your gout.

**Health care professionals** should reserve Uloric for use only in patients who have failed or do not tolerate allopurinol. Counsel patients about the cardiovascular risk with Uloric and advise them to seek medical attention immediately if they experience the symptoms listed above.

When we approved Uloric in 2009, we included a *Warning and Precaution* regarding possible cardiovascular events in patients treated with Uloric in the current prescribing information and required the drug manufacturer, Takeda Pharmaceuticals, to conduct a large postmarket safety clinical trial. The trial was conducted in more than 6,000 patients with gout treated with either Uloric or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring intervention, called unstable angina.

The results showed that overall, Uloric did not increase the risk of these combined events compared to allopurinol (See Data Summary). However, when the outcomes were evaluated separately, Uloric showed an increased risk of heart-related deaths and death from all causes. In patients treated with Uloric, 15 deaths from heart-related causes were observed for every 1,000 patients treated for a year compared to 11 deaths from heart-related causes per 1,000 patients treated with allopurinol for a year. In addition, there were 26 deaths from any cause per 1,000 patients treated for a year with Uloric compared to 22 deaths per 1,000 patients treated for a year with allopurinol. This safety trial was also discussed at a public [Advisory Committee meeting](#) of outside experts on January 11, 2019.

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving Uloric or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

### **Facts about Uloric (febuxostat)**

- Uloric is approved to treat a type of arthritis called gout in adults. 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 works by lowering uric acid levels in the blood.
- Common side effects of Uloric include nausea, rash, joint pain, gout flares, and liver problems.

### **Additional Information for Patients**

- FDA’s review of a large safety clinical trial showed an increased risk of heart-related death and death from all causes with the gout medicine Uloric (febuxostat).

- Inform your health care professional if you have a history of heart problems or stroke and discuss the benefits and risks of using Uloric to treat your gout.
- Seek emergency medical attention right away if you experience the following symptoms while taking Uloric:
  - Chest pain
  - Shortness of breath
  - Rapid or irregular heartbeat
  - Numbness or weakness on one side of your body
  - Dizziness
  - Trouble talking
  - Sudden severe headache
- Do not stop taking Uloric without first talking to your health care professional, as doing so can worsen your gout.
- We created a new patient [Medication Guide](#), which you should read every time you receive a prescription for Uloric. The Medication Guide explains the heart risks with Uloric and other important things you need to know about the medicine. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- Talk to your health care professional if you have any questions or concerns about Uloric.
- In addition to recommending medicines for you to take, your health care professional may also recommend diet and lifestyle changes to manage your gout, such as losing weight and eating fewer foods that are high in purines. Purines are a natural substance found in some foods. When your body breaks down purines, uric acid is produced. For more information about gout, visit the [National Institute of Arthritis and Musculoskeletal and Skin Diseases webpage](#).
- To help FDA track safety issues with medicines, report side effects from Uloric or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

### **Additional Information for Health Care Professionals**

- FDA's review of a large safety clinical trial showed an increased risk of cardiovascular death and all-cause death with the gout medicine Uloric (febuxostat).
- Reserve Uloric for use in patients who have failed or cannot tolerate maximally titrated allopurinol doses.
- Monitor for cardiovascular signs and symptoms in patients who are taking Uloric.
- Counsel patients to seek medical attention immediately if they experience chest pain, shortness of breath, rapid or irregular heartbeat, numbness or weakness on one side of the body, dizziness, trouble talking, or a sudden severe headache while taking Uloric.
- Encourage patients to read the [Medication Guide](#) they receive with their Uloric prescriptions, which helps patients understand the cardiovascular safety risks and provides other important information.

- To help FDA track safety issues with medicines, report adverse events involving Uloric or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

## Data Summary

When FDA approved Uloric (febuxostat) in 2009, we included in the prescribing information a *Warning and Precaution* regarding possible cardiovascular events in patients treated with Uloric. We also required the drug manufacturer, Takeda Pharmaceuticals, to conduct a large postmarket clinical trial to evaluate the cardiovascular safety of Uloric. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial was a multicenter, randomized, double-blind cardiovascular outcomes trial conducted in 6,190 patients with gout treated with either Uloric or allopurinol. The trial was conducted in the U.S., Canada, and Mexico, and was initiated in April 2010 and completed in July 2017. The primary endpoint was a composite of major adverse cardiovascular events (MACE): cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and unstable angina with urgent revascularization. Secondary endpoints included the individual components of the MACE composite as well as death from any cause. The study design was a noninferiority trial with a noninferiority margin of 1.3. Results showed that although the study met the pre-specified noninferiority margin, there was a significant increase in cardiovascular death (See Table 1 below). In addition, there was a significant increase in overall mortality, which was driven by cardiovascular death.

**Table 1. CARES Study Results**

N (%)	Uloric (N=3,098)	Allopurinol (N=3,092)	Hazard Ratio (95% CI)
<b>Composite Primary Endpoint:</b>	335 (10.8)	321 (10.4)	1.03 (0.89, 1.21)
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03, 1.73)
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72, 1.21)
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73, 1.41)
Unstable angina with urgent coronary revascularization	49 (1.6)	56 (1.8)	0.86 (0.59, 1.26)
<b>Additional Endpoint:</b>			
All-cause mortality	243 (7.8)	199 (6.4)	1.22 (1.01, 1.47)

All analysis based on the full analysis set defined as all subjects who were randomized and received at least one dose of double-blind study medication.

## Reference

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum* 2011;63:3136-41.

## **Related Information**

[National Institute of Arthritis and Musculoskeletal and Skin Diseases: Gout](#)

[The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective](#)

[Think It Through: Managing the Benefits and Risks of Medicines](#)

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