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DEPARTMENT OF VETERANS AFFAIRS
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP),
VISN PHARMACIST EXECUTIVES (VPEs), AND THE CENTER FOR MEDICATION SAFETY (VA MedSAFE)

Alerts are based on the clinical evidence available at the time of publication. Recommendations are intended to assist practitioners in providing consistent, safe, high quality, and cost effective drug therapy. They are not intended to interfere with clinical judgment. When using dated material, the clinician should consider new clinical information, as available and applicable.

FEBUXOSTAT (ULORIC®): FDA EVALUTES RISK OF CARDIOVASCULAR DEATH

I. ISSUE

Preliminary results from a safety clinical trial show greater risk of cardiovascular death with febuxostat (Uloric) compared to allopurinol.

II. BACKGROUND

Febuxostat (Uloric) is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. Its drug label documents a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with febuxostat (Uloric) (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]) in randomized controlled studies conducted before approval. As such, febuxostat (Uloric) currently bears a *Warning and Precaution* about cardiovascular events although a causal relationship has not been established.

III. DISCUSSION

FDA required the manufacturer to conduct an additional safety study after approval to understand cardiovascular findings. The safety trial involved over 6,000 patients receiving either febuxostat (Uloric) or allopurinol for the treatment of gout and looked at combined outcomes of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and urgent cardiovascular revascularization. Early results show no increase in risk of these combined events with febuxostat (Uloric) compared to allopurinol. However, upon evaluation of the outcomes separately, a greater risk of cardiovascular death and death from all causes was found with febuxostat (Uloric) compared to allopurinol. FDA awaits final results from the manufacturer and will report any new information after a comprehensive review.

IV. PROVIDER RECOMMENDATIONS

FDA recommends that health care professionals:

- Consider cardiovascular safety findings when prescribing or continuing patients on febuxostat (Uloric).
- Inform patients of the risk of adverse cardiovascular events after initiation of febuxostat (Uloric) therapy due to reports of heart attacks, strokes and cardiovascular deaths seen in clinical studies, but that it is not certain that febuxostat (Uloric) caused these events.

V. REFERENCES

1. FDA Drug Safety Communication: FDA to evaluate increased risk of heart-related death and death from all causes with the gout medicine febuxostat (Uloric). https://www.fda.gov/downloads/Drugs/DrugSafety/UCM584803.pdf . Accessed 11/15/2017.
2. ULORIC® (febuxostat) [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; August 2017.

ACTIONS

- ***Facility Director*** *(or physician designee): Forward this document to the Facility Chief of Staff (COS).*
- ***Facility COS and Chief Nurse Executives:*** *Forward this document to all appropriate providers and health care staff (e.g.,* ***primary care providers and rheumatology providers, including contract providers, etc****.). In addition, forward to the Associate Chief of Staff (ACOS) for Research and Development (R&D). Forward to other VA employees as deemed appropriate.*
- ***ACOS for R&D:*** *Forward this document to Principal Investigators (PIs) who have authority to practice at the facility and to your respective Institutional Review Board (IRB).*