Febuxostat (ULORIC®)
Criteria for Use
(Revised September 2018)

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. ***THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at the *PBM INTERnet* or *PBM INTRAnet* site for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive febuxostat.

- ☐ Hypersensitivity or history of intolerance to febuxostat (or inactive tablet ingredients)
- ☐ Asymptomatic hyperuricemia
- ☐ Concomitant administration of drugs that are metabolized by xanthine oxidase (e.g., theophylline, mercaptopurine, azathioprine)

Inclusion Criteria

The answers to all the following must be fulfilled to meet criteria.

- ☐ The patient is a candidate for the chronic treatment of gout, i.e. patient is hyperuricemic and has recurrent gouty attacks (≥ 2 acute attacks/year) or other manifestation of chronic gout (tophaceous disease, erosive gouty arthritis, or uric acid urolithiasis).
- ☐ There is documentation of a lack of adequate response or contraindication to or an inability to tolerate appropriately dose-maximized trials of allopurinol[a] and/or probenecid[b] (Refer to page 4 for dosing guidance).

  In patients with known cardiovascular disease, use of low dose aspirin is encouraged (if no contraindications exist) and NSAIDs should be discontinued if possible or used at the lowest dose for the shortest possible duration (see issues for consideration).

Dosage and Administration

- The initial recommended starting dose of febuxostat is 40mg daily; a dose of 80mg daily is recommended for patients who do not achieve a serum urate < 6mg/dL after 2 weeks of treatment at the lower dose.
- Doses >80 mg daily are not approved for use in the United States. However, doses of 80 mg and 120 mg are approved for use in Europe.
- In patients with severe renal impairment (CrCl 10-29 mL/min), the dose should be limited to 40 mg daily.
- No dose adjustment is needed in patients with mild to moderate hepatic impairment (Child-Pugh Class A or B). Evidence is lacking in patients with severe hepatic disease and therefore caution is advised.
- Febuxostat may be administered without regard to food or antacid use.
- Prophylaxis against acute gout flare (with colchicine or NSAIDs) is recommended during the first 6 months of urate lowering therapy.

Monitoring

- Baseline liver function testing is recommended upon initiation of febuxostat and periodically thereafter in patients with symptoms suggestive of liver toxicity including fatigue, anorexia, right upper abdominal discomfort, darkened urine or jaundice. If liver injury is confirmed with testing, febuxostat should be withheld and the cause investigated. If liver injury is confirmed and no other etiology is found, febuxostat should not be restarted.
- A serum uric acid target of < 6 mg/dL is recommended for effective gout management and has been associated with reduced frequency of acute gout flares, deceased tophus size, and decreased detection of urate crystals in synovial fluid. In selected patients with more severe disease, a serum uric acid level of < 5 mg/dL may be recommended until urate crystals and associated symptoms of gout have resolved.
- In the clinical development program for febuxostat, a higher rate of cardiovascular thromboembolic events (e.g., cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) was observed in febuxostat compared to allopurinol-treated patients, although a causal relationship with febuxostat had not been established at that time. As a condition for FDA approval, a cardiovascular safety study comparing febuxostat to allopurinol was required by the FDA. Until that study was completed, patients on febuxostat were to be monitored for signs and symptoms of myocardial infarction and stroke (Refer to the "Issues for Consideration" section for details on the CARES clinical trial).[2]
- In February 2018, the FDA updated the labeling for febuxostat regarding post-marketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) in patients taking febuxostat. Febuxostat should be discontinued if serious skin reactions are suspected (Refer to the "Issues for Consideration" section).

Issues for Consideration

The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial was conducted to determine if febuxostat was non-inferior to allopurinol in risk for major cardiovascular events in patients with known cardiovascular disease and gout.[1]

- The CARES trial was planned and completed since there was a higher incidence of cardiovascular events and death in the studies conducted for initial FDA approval of febuxostat; although a causal relationship had not been established at that time.

- The primary endpoint in the CARES trial was a composite endpoint of first occurrence of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke or urgent revascularization for unstable angina (USA). Secondary endpoints included a composite of cardiovascular death, non-fatal MI or non-fatal stroke and individual components of the primary endpoint. Additional safety outcomes included all-cause mortality, transient ischemic attack, hospitalization for heart failure, arrhythmias not associated with ischemia and venous thromboembolic events.

- Results: 6,190 patients were analyzed. Modified intention to treat analysis, as follows on the next page: (8 patients were enrolled and never received study drug and were excluded from the analysis)

Endpoint	Febuxostat (n=3098)	Allopurinol (n=3092)	Statistics
Primary Composite	335 (10.8%)	321 (10.4%)	HR 1.03 (0.87-1.23) p=0.66
Cardiovascular Death	134 (4.3%)	100 (3.2)	HR 1.34 (1.03-1.73) p=0.03
Nonfatal MI	111 (3.6%)	118 (3.8%)	HR 0.93 (0.72-1.21) p=0.61
Nonfatal Stroke	71 (2.3%)	79 (2.3%)	HR 1.01 (0.73-1.41) p=0.94
Urgent Revasc for USA	49 (1.6%)	56 (1.8%)	HR 0.86 (0.59-1.26) p=0.44
Composite of CV death, nonfatal MI or Stroke	296 (9.6%)	271 (8.8%)	HR 1.09 (0.92-1.28) P=0.33
All-Cause Death	243 (7.8%)	199 (6.4%)	HR 1.22 (1.01-1.47) p=0.04

- When the data were analyzed for events occurring while on study treatment or within 30 days of discontinuing treatment, there were no differences in the primary endpoint (HR 1, 94% CI 0.82-1.22, p=0.99) or in all-cause death (HR 1.26, 95% CI 0.93-1.72, p=0.14) but a difference in cardiovascular death remained higher in those receiving febuxostat vs. allopurinol (HR 1.49, 95% CI 1.01-2.22, p=0.047).
- Sudden cardiac death was the most prevalent cause of cardiovascular death (Febuxostat n=83 vs. Allopurinol n=56). When subgroups were examined for heterogeneity, there was an interaction for NSAID use and lack of daily low-dose aspirin use and increased cardiovascular death with febuxostat. No heterogeneity was found for other subgroups.
- Trial Limitations:
  - 56.6% of patients discontinued treatment early (rates were similar between groups)
    - Median duration of treatment: 728 days for febuxostat and 719 days for allopurinol.
  - 45% of patients did not complete all trial visits (rates were similar between groups)
    - Median duration of follow-up: 968 days for febuxostat and 942 days for allopurinol.
- Author Conclusions: Febuxostat was non-inferior to allopurinol with regard to rates of adverse cardiovascular events. However, there was a higher rate of cardiovascular deaths and all-cause mortality in the febuxostat vs. allopurinol group.
  - The explanation for the higher risk for cardiovascular death with febuxostat is unclear since preclinical cardiovascular studies did not reveal any issues related to an adverse effect on the heart. Rate of all adjudicated non-fatal events were similar between groups. The only heterogeneity observed among subgroups and taking febuxostat was a higher rate of cardiovascular death in patients receiving NSAIDs or in those who were not taking low-dose aspirin. The FDA is in the process of reviewing the data before they provide guidance.

- Provider Recommendations: For patients who are currently receiving and tolerating febuxostat or in those patients being considered for treatment with febuxostat, providers should:
    - Engage in a shared-decision making discussion with the patient regarding the findings of the CARES trial and determine the best course of therapy for individual patients considering this evidence. Options may include:

      1. Reevaluate treatment with febuxostat and consider replacing febuxostat with allopurinol 100 mg daily with appropriate dose-titration (increase by 100 mg/day at 1-4 week intervals) to reduce serum uric acid levels to <6 mg/dL (or <5 mg/dL in certain patients with severe gout until tophi are resolved) and reduce or improve associated symptoms of gout, in properly selected patients.

      OR

      2. Continue febuxostat and emphasize use of low dose aspirin in patients with known cardiovascular disease or those at high-risk, if appropriate. Additionally, discontinue nonsteroidal anti-inflammatory drugs (NSAIDs) if possible or use at the lowest possible dose for the shortest duration of time. Because of the higher risk for all-cause and CV mortality with febuxostat in patients with gout and known CV disease, consider a referral to Rheumatology (including e-consults) to determine the ongoing necessity of febuxostat and whether alternative agents can be used for managing gout.

    - Since only those patients with known major cardiovascular disease and gout were eligible for enrollment in the CARES trial, it is unknown if patients with gout and without cardiovascular disease are at a similar higher risk for adverse cardiovascular events with febuxostat versus allopurinol but caution is advised.

- In February 2018, the FDA updated the labeling for febuxostat regarding post-marketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) in patients taking febuxostat. Febuxostat should be discontinued if serious skin reactions are suspected. Many of these patients reported similar adverse skin events with allopurinol so febuxostat should be used with caution in these patients.[2]

Renewal Criteria

- Patient is tolerating febuxostat and is adherent to therapy.
- Patient has achieved a clinically significant reduction in serum urate within 6 months of initiation of febuxostat (i.e. the patient has reached a serum urate acid level of < 6 mg/dL to reduce the frequency of acute gout flares and/or to favorably alter other manifestations of chronic gout).

Dosing Guidance: (Allopurinol and Probenecid)

[a] FDA-approved dosing guidelines for allopurinol advocate upwards dose titration, starting from an initial dose of 100 mg daily, followed by dose increases of 100mg every 1-4 weeks until a serum urate level of ≤ 6mg/dl is achieved. Allopurinol 200-300mg daily is typically sufficient for patients with mild gout; however, a dose of 400 to 600mg daily may be required to control severe tophaceous disease. Allopurinol is FDA-approved for doses up to 800mg daily in the treatment of hyperuricemia in patients with gout who have normal renal function. FDA dosing guidelines advocate limiting the maximum allopurinol dose to 100mg daily when the creatinine clearance (CrCl) < 10ml/min and to 200mg daily when the CrCl is 10-20ml/min, but do not specify a scale for dosing allopurinol in moderate renal dysfunction. However, guidelines from professional societies[3-4] recognize starting at a lower dose of allopurinol (e.g., 50 mg daily) in patients with chronic kidney disease (CKD) and utilizing a more gradual titration schedule of increasing the daily dose every 2-5 weeks (based upon creatinine clearance)[4] with some patients able to reach doses of >300 mg daily with adequate patient education and close monitoring for allopurinol toxicity (e.g., pruritis, rash, elevated hepatic transaminases).[3] Maximum serum urate lowering resulting from a stable dose of allopurinol occurs within 2-3 weeks. Allopurinol may increase the frequency of attacks during the first 6-12 months of therapy even if goal urate has been obtained; prophylactic doses of a NSAID or colchicine should be given concurrently during the first 6 months of therapy. Noncompliance with allopurinol and/or under-dosing of the drug should not be misinterpreted as treatment failure. Inability to achieve a serum urate < 6mg/dl should not be considered a treatment failure if acute flares are controlled or if other manifestations of chronic gout are positively influenced (allow up to 6 months).

[b] Probenecid use should be avoided in patients who have a CrCl < 50ml/min; use should also be avoided in patients who over excrete urate (where 24-hour urinary uric acid excretion is > 800mg/day). Probenecid is initiated at 250mg twice daily and can be titrated in 500mg increments every 4 weeks to clinical response (maximum dose of 2-3 g/day). Patients on probenecid should maintain good hydration by targeting a urine output of 2-3L/day; alkalinization of the urine may be desirable early in therapy until goal urate is achieved and/or tophaceous deposits resolve.

References

1. White WB, Saag KG, Becker MA, et al. Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. N Engl J Med 2018;378:1200-1210.
2. Febuxostat (Uloric) Manufacturer Prescribing Information. February 2018. Takeda Pharmaceuticals America, Inc. Deerfield, IL 60015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021856lbl.pdf (Accessed 6-11-2018)
3. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia. Arthritis Care & Research 2012;64: 1431-1446.
4. Richette P, Doherty M, Pascual E, et al. 2016 Updated EULAR Evidence-Based Recommendations for the Management of Gout. Ann Rheum Dis 2017;76:29-42.

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