Xanthine Oxidase Inhibitor Step Therapy with Quantity Limit Program Summary

This step therapy applies to Commercial and Health Insurance Marketplace formularies.

OBJECTIVE
The intent of the step therapy criteria for Xanthine Oxidase Inhibitor is to encourage the use of cost-effective generic allopurinol 300 mg before brand agents and to accommodate for use of brand agents when allopurinol cannot be used due to documented intolerance, FDA labeled contraindication, or hypersensitivity. This step therapy program will require use of the 300 mg allopurinol tablet because clinical literature shows that most patients with moderate gout require 400 mg to 600 mg/day to lower serum uric acid below 6.0 mg/dL. Requests for brand agents will be reviewed when patient-specific documentation has been provided.

TARGET AGENT
Uloric (febuxostat)

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Taget Agent will be approved when ANY ONE of the following is met:

1. The patient's medication history includes use of allopurinol 300 mg in the past 90 days
   OR
2. There is documentation that the patient is currently using the requested agent
   OR
3. The prescriber states the patient is currently using the requested agent AND is at risk if therapy is changed
   OR
4. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to allopurinol 300 mg

Length of approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.

FDA APPROVED INDICATIONS AND DOSAGE[1]

Drug	Indication[1]	Dosage
Uloric® (febuxostat) tablets 40 mg & 80 mg	• Febuxostat is indicated for the chronic management of hyperuricemia in patients with gout. • Uloric is not recommended for the treatment of asymptomatic hyperuricemia.	• Febuxostat starting dose is 40 mg once daily. • For patients who do not achieve serum uric acid (sUA) < 6 mg/dL after two weeks of treatment, 80 mg is recommended once daily. • For those who have achieved sUA < 6 mg/dL, 40 mg once daily is the recommended dosage.

CLINICAL RATIONALE

Guidelines

The goals of gout treatment are threefold: treating acute inflammation, preventing flares, and lowering serum urate levels. The goal of therapy with urate-lowering drugs is to reduce the serum urate level to <6.0 mg/dL, noting that some patients may need lowering to <5.0 mg/dL to durably improve signs and symptoms of gout.[2,10] Monitoring of serum urate is recommended every 2-5 weeks during urate lowering therapy titration, and every 6 months once serum urate target is achieved.[2]

The 2016 American College of Physicians guideline suggests that there is insufficient evidence that there is a direct causal benefit of treating to a serum urate level target which outweighs the harm of therapy. However, the guideline also notes that studies show that patients with serum urate levels <6.0 mg/dL had fewer gout flares and that additional studies are needed to compare treat to target vs. treat to avoid strategies.[15]

The 2016 European League Against Rheumatism (EULAR) guideline for the management of gout recommends that in addition to education and a non-pharmacological management approach, urate-lowering therapy (ULT) should be considered from the first presentation of the disease, and serum uric acid (SUA) levels should be maintained at<6 mg/dL (360 µmol/L) and <5 mg/dL (300 µmol/L) in those with severe gout. Allopurinol is recommended as first-line ULT and its dosage should be adjusted according to renal function. If the serum urate target cannot be achieved with allopurinol, then febuxostat, a uricosuric or combining a xanthine oxidase inhibitor with a uricosuric should be considered.[16]

The Evidence, Expertise, Exchange Initiative (3E) (2014) provided multinational evidence-based recommendations for management of gout, integrating systematic literature review and expert opinion of a broad panel of rheumatologists. There was strong consensus that allopurinol constitutes first line urate lowering therapy after consideration of its safety, efficacy and cost. Uricosurics and low to medium doses of febuxostat are considered alternatives in the presence of intolerance or nonresponsiveness to allopurinol.[14]

The American College of Rheumatology (ACR) 2012 Guidelines for the Management of Gout[2,3] recommend diet and lifestyle measures for the majority of patients with gout. In addition, these pharmacologic therapies are recommended:[2]

- Xanthine oxidase inhibitors allopurinol and febuxostat are first line agents for pharmacologic urate lowering therapy. The ACR did not preferentially recommend either xanthine oxidase inhibitor, but they did note there was a lack of published safety data for febuxostat in the setting of severe chronic kidney disease (CKD).
- Probenecid was recommended as an alternative to a xanthine oxidase inhibitor in the setting of contraindication or intolerance to ≥ 1 xanthine oxidase inhibitor. Also, probenecid is not recommended for monotherapy in those with a creatinine clearance of < 50 mL/minute.
- For refractory gout, febuxostat can be substituted for allopurinol in the event of drug intolerance or adverse events.
- Effective therapeutic options include addition of a uricosuric agent such as probenecid to a xanthine oxidase inhibitor for refractory gout.
- Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed urate lowering therapy. Pegloticase is not recommended as first line urate lowering therapy for any case scenarios.

Allopurinol is the first-line therapy for most patients and has been the mainstay of prophylactic treatment for gout and conditions associated with hyperuricemia for over 40 years. [2,4,10] Allopurinol is effective in most patients with hyperuricemia if a sufficient dose is taken, but achieving normal serum urate levels may be difficult in patients with impaired renal function or in transplant recipients.[9] Febuxostat is considered an alternative to allopurinol.[13]

Clinical data supporting the dose escalation of allopurinol from 300 mg daily to 300 mg twice daily measured the percentage of patients who achieved a serum uric acid level of ≤ 5 mg/dL. Dose escalation increased the response rate from 26% (for 300 mg daily) to 78% (for 300 mg twice daily).[4] Two large observational studies (one in heart failure and one in hyperuricemic patients) have shown that allopurinol is associated with reduced total mortality.[5,6] Two small randomized controlled trials showed allopurinol reduced cardiovascular events markedly in both studies.[7,8]

The ACR states that the recommended initial dose of allopurinol should not exceed 100 mg/day and should be less for patients with moderate to severe chronic kidney disease (50mg/day).[2] The rationale for starting the initial dose at ≤ 100 mg/day is that "a low dose could reduce early gout flares after urate lowering therapy initiation, and as a component risk management with respect to the potential for severe hypersensitivity reaction to allopurinol."[2]

Febuxostat Efficacy

Two of the pivotal trials submitted to the FDA for approval of febuxostat (FACT, APEX) studied the efficacy of different doses of febuxostat versus placebo and allopurinol in the treatment of hyperuricemia in patients with gout.[14,15]

- Patients had been randomized within these two clinical trials to receive placebo or once-daily febuxostat at a dose of 80 mg, 120 mg, or 240 mg, or once-daily allopurinol at 100 mg, 200 mg, or 300 mg. For gout flare prophylaxis during the first 8 weeks of these trials, patients received naproxen 250 mg twice daily or colchicines 0.6 mg once daily. Primary endpoints were the proportion of patients with sAU levels less than 6.0 mg/dL both at their last three visits and at their final visit.
- None of the patients in the placebo group satisfied the specified endpoints for sUA <6.0 mg/dL.

- In the allopurinol 200 mg/d treatment group, for the last three patient visits and at the final patient visit, respectively, these endpoints were satisfied for a significantly greater proportion over the placebo group, at 46% and 66% ($P \leq .01$ for both).[10]
- Febuxostat treatment satisfied the two endpoints by significantly greater proportions of patients than seen with placebo and with allopurinol at all doses (febuxostat 80 mg, 72%, 94%; febuxostat 120 mg, 78%, 89%; febuxostat 240 mg, 77%, 100%; $P \leq 0.01$ in all cases)

CONFIRMS, the largest, pivotal, phase 3 clinical trial, showed that febuxostat 80 mg was superior to febuxostat 40 mg and allopurinol 300/200 mg at achieving the main study outcome of serum uric acid less than 6.0 mg/dL at the final visit (67%, 47%, and 42%, respectively; $P < .001$ for both comparisons).[12] It should be noted that clinical trials comparing febuxostat with allopurinol included doses of allopurinol up to 300 mg/day maximum. Evidence has demonstrated that 50% of patients with hyperuricemia and gout require higher doses of allopurinol to achieve the required serum uric acid <6 mg/dL.[16]

Febuxostat Safety

Febuxostat is contraindicated in patients being treated with azathioprine, mercaptopurine or theophylline.[10] The most common adverse event leading to discontinuation from therapy with febuxostat was liver function abnormalities in 1.8% of the patients treated with the 40 mg dose and 1.2% of those treated with the 80 mg dose.[10] Unlike allopurinol, febuxostat can be administered to patients with mild to moderate renal insufficiency without need for dose reduction.[1]

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