Gout Medications Step Therapy Program

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Next Review: 7/2020

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for brand name Uloric when the following criteria are met. The brand name Uloric affected are:

- Duzallo (lesinurad and allopurinol tablets – Ironwood Pharmaceuticals/ AstraZeneca)
- Uloric® (febuxostat tablets – Takeda)
- Zurampic® (lesinurad tablets – AstraZeneca)

When Policy Topic is covered
Step therapy rules have been developed to encourage the use of allopurinol prior to Uloric and Duzallo and probenecid prior to Zurampic. If the step therapy rule is not met at the point of service, coverage will be determined by the step therapy criteria below. All approvals are provided for 1 year in duration.

Automation: Patients with a history of one Step 1 drug within the 130-day look-back period are excluded from step therapy.

Allopurinol Step Therapy Rule
Step 1A: allopurinol (Zyloprim®) tablets
Step 2A: Uloric tablets, Duzallo

Probenecid Step Therapy Rule
Step 1B: probenecid; probenecid/colchicine
Step 2B: Zurampic

CRITERIA

Allopurinol Step Therapy Rule
Exceptions for Uloric or Duzallo can be made for those who have met one of the following criteria:

1. An exception for Uloric or Duzallo can be made if the patient has tried a Step 1A agent (allopurinol) at any time in the past.

2. An Exception for Uloric can be made if the patient has renal insufficiency or decreased renal function with an estimated creatinine clearance (CrCl) less than 50 ml/min.

3. An Exception for Uloric can be made if the patient is receiving concomitant medications that have significant drug-drug interactions with the Step 1A agent (allopurinol), which are not noted with the Step 2A agent (Uloric) [e.g., cyclosporine, chlorpropamide].

Probenecid Step Therapy Rule
Exceptions for Zurampic can be made for those who have met one of the following criteria:
1. The patient has tried a Step 1B agent (probenecid; probenecid/colchicine) at any time in the past.

2. The patient is receiving concomitant medications that have significant drug-drug interactions with the Step 1B agent (probenecid; probenecid/colchicine), which are not noted with the Step 2B agent (Zurampic) [e.g., sulfonamides, sulfonlyureas, salicylates].

When Policy Topic is not covered
The use of Uloric, Duzallo and Zurampic is considered investigational for all other indications.

Considerations
Uloric, Zurampic and Duzallo require prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy Statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service
Xanthine Oxidase Inhibitors (XOIs)
Allopurinol (Zyloprim®, generics) is a xanthine oxidase inhibitor that is indicated for the management of patients with signs and symptoms of primary or secondary gout (e.g., acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy).² It is also indicated for the management of patients with leukemia, lymphoma, and malignancies who are receiving cancer therapy which causes elevations on serum and urinary uric acid levels. In addition, it is indicated for the management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day for male patients and 750 mg/day for female patients. Allopurinol is not indicated for the treatment of asymptomatic hyperuricemia. The average dose of allopurinol is 200 to 300 mg/day for patients with mild gout and 400 to 600 mg/day for patients with moderately severe tophaceous gout. The starting dosage of allopurinol should not be > 100 mg/day and the maximal recommended dosage is 800 mg daily. Patients with impaired renal function should be carefully observed during the early stages of administration of allopurinol. Since allopurinol and its metabolites are primarily eliminated by the kidney, accumulation of the agent can occur in renal failure, and the dose of allopurinol should consequently be reduced. With a creatinine clearance (CrCl) of 10 to 20 mL/min, a daily dosage of 200 mg of allopurinol is suitable. When the CrCl < 10 mL/min, the daily dosage should not exceed 100 mg. With extreme renal impairment (CrCl < 3 mL/min) the interval between doses may also need to be lengthened.

Uloric is a xanthine oxidase inhibitor indicated for the chronic management of hyperuricemia in patients with gout.¹ The agent is not recommended for the treatment of asymptomatic hyperuricemia. Uloric achieves its therapeutic effect by decreasing serum uric acid. The recommended starting dose of Uloric is 40 mg once daily (QD). For patients who do not achieve a serum uric acid < 6.0 mg/dL after 2 weeks with 40 mg, Uloric 80 mg QD is recommended. No dosage adjustment is needed when administering Uloric to patients with mild to moderate renal or hepatic impairment. There are insufficient data in patients with severe renal impairment; use caution when administering to such patients. The prescribing information for Uloric notes that no studies have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome or malignant disease, or in organ transplant patients); use of Uloric in these patients is not recommended.¹ In November 2017, the FDA informed the public of an increased risk of heart-related death with Uloric compared with allopurinol. Final results will be forthcoming.

Uricosuric Agents
Probenecid is a uricosuric agent. It is a uricosuric and renal tubular transport blocking agent indicated for treatment of hyperuricemia associated with gout and gouty arthritis. Probenecid does not have Boxed Warnings for renal events, but it should not be used in patients with known uric acid kidney
stones. Dosage requirements may be increased in patients with renal impairment, and probenecid may not be effective when glomerular filtration rate is < 30 mL/min.

Lesinurad (an active ingredient in Zurampic and Duzallo) is another uric acid transporter 1 (URAT1) inhibitor indicated in combination with a xanthine oxidase inhibitor (i.e., allopurinol or Uloric) for hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with XOI monotherapy. Agents that contain lesinurad (i.e., Zurampic, Duzallo) should not be used as monotherapy and are not recommended for treatment of asymptomatic hyperuricemia. Lesinurad reduces serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. It also causes an increase in renal uric acid excretion which may lead to renal events (e.g., transient increases in serum creatinine, renal-related AEs, and kidney stones). There are Boxed Warning regarding renal events and a Warning concerning cardiovascular (CV) events (CV death, nonfatal myocardial infarction, and non-fatal stroke). Both Zurampic and Duzallo are contraindicated in severe renal impairment, end-stage renal disease, kidney transplant recipients, dialysis, tumor lysis syndrome, and Lesch-Nyhan syndrome.

**Rationale**

**Guidelines**

The American College of Rheumatology (ACR) guidelines (2012) for the management of gout (published prior to the approval of Zurampic) recommend xanthine oxidase inhibitors, either allopurinol or Uloric (without preference), as first-line pharmacologic urate-lowering therapies (ULT).\(^1\)\(^2\) Serum urate level should be lowered sufficiently to improve the signs and symptoms of gout, with the target level < 6 mg/dL at a minimum. Probenacid is recommended as an alternative first-line pharmacologic therapy if the patient had intolerance or contraindications to either allopurinol or Uloric; however, it is not recommended as first-line monotherapy in patients with CrCl < 50 mL/min. Combination therapy with one xanthine oxidase inhibitor and one uricosuric agent is appropriate when the target serum urate levels have not been achieved by a xanthine oxidase inhibitor alone. Krystexxa\(^\circledR\) (pegloticase injection, for intravenous infusion) is appropriate in patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULTs.

The European League Against Rheumatism (EULAR) has recommendations for gout (2016). In patients with normal renal function, allopurinol is recommended as first-line ULT.\(^1\)\(^1\) The allopurinol dose should be adapted to the patient’s renal function and slowly titrated to the maximum allowed dosage. If the target SUA is not achieved, the guidelines recommend switching to a uricosuric ± allopurinol or Uloric. In patients who do not achieve target SUA, combined therapy with a uricosuric + XOI is recommended. Krystexxa is recommended only in patients with crystal-proven severe, debilitating gout, in patients with poor quality of life, when the target SUA cannot be reached with any other available drug (including combinations) at the maximal dose. Of note, the EULAR guidelines only mention Zurampic as an emerging uricosuric with positive results when used in combination with allopurinol.

**References**

1. Uloric\(^\circledR\) tablets [prescribing information]. Deerfield, IL: Takeda; November 2012.

Other References Utilized

Billing Coding/Physician Documentation Information

| Policy Number: 5.01.584 |

Policy Implementation/Update Information

| 07/2014 | New Policy titled Uloric Step Therapy Program |
| 07/2015 | Annual review – no changes made |
| 07/2016 | Annual review—no changes made to policy statement |
| 07/2017 | Annual review—no changes made to policy statement |
| 07/2018 | Added Durzallo and Zurampic to policy |
| 07/2019 | Annual review – no changes made |
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