



URAT1 Inhibitor Prior Authorization and Quantity Limit Criteria Program Summary

This program applies to Commercial, NetResults A series, NetResults F series and Health Insurance Marketplace formularies.

OBJECTIVE

The intent of the URAT1 Inhibitor Prior Authorization criteria is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines. For initial evaluation, appropriate therapy is defined as those patients who have a diagnosis of gout. The program requires that the patient has not already achieved the goal uric acid level of <6.0 mg/dL; or the patient has achieved a uric acid level of <6.0 mg/dL and the prescriber has provided documentation supporting the further lowering of uric acid levels. The program also requires one of the following: the patient is currently taking at least 300 mg of allopurinol or 80 mg of febuxostat; the patient has a documented contraindication or hypersensitivity to allopurinol, and has a documented intolerance or expected intolerance to 80 mg or higher of febuxostat; the patient has a documented contraindication or hypersensitivity to febuxostat, and has a documented intolerance or expected intolerance to 300 mg or higher of allopurinol; or the patient has a documented intolerance or expected intolerance to 300 mg or higher of allopurinol and 80 mg or higher of febuxostat.

For renewal evaluation, the program requires the patient to have been previously approved through Prime Therapeutics' prior authorization program for the requested agent. The program also requires the concurrent use of allopurinol or febuxostat along with Zurampic. The program will not approve patients who have a contraindication to the requested agent. The program will approve for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

TARGET AGENT

Duzallo (lesinurad/allopurinol)

Zurampic (lesinurad)

Brand (generic)	GPI	Multisource Code	Quantity Limit Per Day
Duzallo (lesinurad/allopurinol)			
200 mg/200 mg tablet	68990002500320	M, N, O, or Y	1 tablet
200 mg/300 mg tablet	68990002500330	M, N, O, or Y	1 tablet
Zurampic (lesinurad)			
200 mg tablet	68000040000320	M, N, O, or Y	1 tablet

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

URAT1 Inhibitor will be approved when ALL of the following is met:

1. The patient's has a diagnosis of gout

AND

2. ONE of the following:

- a. The patient's serum uric acid level is >6.0 mg/dL (either within the past 6 months OR prior to initiating therapy with the requested agent)

OR

- b. The patient's most recent (within the past 6 months) serum uric acid level is ≤6.0 mg/dL and the prescriber has provided documentation supporting the further lowering of the serum uric acid level

- AND**
3. ONE of the following:
 - a. The patient is currently taking at least 300 mg of allopurinol or at least 80 mg of febuxostat
 - OR**
 - b. BOTH of the following:
 - i. The patient has a documented FDA labeled contraindication, or hypersensitivity to allopurinol
 - AND**
 - ii. The patient has a documented intolerance or expected intolerance to 80 mg or higher of febuxostat
 - OR**
 - c. BOTH of the following:
 - i. The patient has a documented FDA labeled contraindication, or hypersensitivity to febuxostat
 - AND**
 - ii. The patient has a documented intolerance or expected intolerance to 300 mg or higher of allopurinol
 - OR**
 - d. The patient has a documented intolerance or expected intolerance to 300 mg or higher of allopurinol **AND** has a documented intolerance or expected intolerance to 80 mg or higher of febuxostat
- AND**
4. The patient will be taking an xanthine oxidase inhibitor (e.g. allopurinol or febuxostat) concurrently with the requested agent (Duzallo requests automatically qualify)
- AND**
5. The patient does not have an FDA labeled contraindication to the requested agent
- AND**
6. ONE of the following:
 - a. The requested quantity (dose) is NOT greater than the program quantity limit
 - OR**
 - b. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
 - AND**
 - ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
 - AND**
 - iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
 - OR**
 - c. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
 - AND**
 - ii. The requested quantity (dose) is greater than the FDA labeled dose
 - AND**
 - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of approval: 12 months

Renewal Evaluation

URAT1 Inhibitor will be approved when ALL of the following are met:

1. The patient has been previously approved through Prime Therapeutics' prior authorization program for the requested agent
AND
2. The patient will be taking an xanthine oxidase inhibitor (e.g. allopurinol or febuxostat) concurrently with the requested agent (Duzallo requests automatically qualify)
AND
3. The patient does not have an FDA labeled contraindication to the requested agent
AND
4. ONE of the following:
 - a. The requested quantity (dose) is NOT greater than the program quantity limit
OR
 - b. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
AND
 - ii. The requested quantity (dose) is less than or equal to the FDA labeled dose
AND
 - iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
 - c. ALL of the following:
 - i. The requested quantity (dose) is greater than the program quantity limit
AND
 - ii. The requested quantity (dose) is greater than the FDA labeled dose
AND
 - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

Length of approval: 12 months

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The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

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FDA APPROVED INDICATIONS AND DOSAGE^{1,14}

Drug	Indication ¹	Dosage
<p>Duzallo (lesinurad/allopurinol)</p> <p>Tablets 200 mg/200 mg 200 mg/300 mg</p>	<p>Treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a medically appropriate daily dose of allopurinol alone.</p> <p>Limitations of Use:</p> <ul style="list-style-type: none"> • Duzallo is not recommended for the treatment of asymptomatic hyperuricemia. 	<p>200 mg lesinurad/300 mg allopurinol tablet per day (or one 200 mg lesinurad/200 mg allopurinol tablet per day for patients with renal impairment (45 – < 60 mL/min eCLcr) on a medically appropriate dose of 200 mg allopurinol)</p>
<p>Zurampic (lesinurad)</p> <p>tablets 200 mg</p>	<p>Indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.</p> <p>Limitations of Use:</p> <ul style="list-style-type: none"> • Zurampic is not recommended for the treatment of asymptomatic hyperuricemia. • Zurampic should not be used as monotherapy. 	<p>200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat.</p> <p>The maximum daily dose of Zurampic is 200 mg.</p>

CLINICAL RATIONALE

Guidelines

The goals of gout treatment are threefold: treating acute inflammation, preventing flares, and lowering serum urate levels.¹⁰ 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.¹²

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.¹³

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.¹¹

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.¹⁰

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

Efficacy

The efficacy of lesinurad 200 mg and 400 mg once daily was studied in 3 multicenter, randomized, double-blind, placebo-controlled clinical studies in adult patients with hyperuricemia and gout in combination with a xanthine oxidase inhibitor, allopurinol (at least 300 mg) or febuxostat (80 mg). All studies were of 12 months duration and patients received prophylaxis for gout flares with colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) during the first 5 months of Zurampic treatment. Zurampic 200 mg in combination with allopurinol was superior to allopurinol alone in lowering serum uric acid to less than 6 mg/dL at Month 6. Zurampic in combination with febuxostat was statistically superior to febuxostat alone in lowering serum uric acid levels.¹ However, there was not statistical evidence of a difference in the proportion of patients treated with Zurampic 200 mg in combination with febuxostat achieving a serum uric acid < 5 mg/dL by month 6, compared with patients receiving febuxostat alone.

There have been no phase 3 clinical trials with lesinurad/allopurinol. Bioequivalence of lesinurad/allopurinol to co-administered lesinurad and allopurinol was demonstrated.

Safety

Lesinurad is contraindicated in severe renal impairment, end stage renal disease, kidney transplant recipients, or patients on dialysis. It is also contraindicated in those with tumor lysis syndrome or Lesch-Nyhan syndrome. Lesinurad carries black box warnings that acute renal failure has occurred with lesinurad and was more common when lesinurad was given alone, and that Lesinurad should be used in combination with a xanthine oxidase inhibitor.¹

Lesinurad/allopurinol is contraindicated in severe renal impairment, end stage renal disease, kidney transplant recipients, or patients on dialysis. It is also contraindicated in those with tumor lysis syndrome or Lesch-Nyhan syndrome. A third contraindication is a known hypersensitivity to allopurinol, including previous occurrence of skin rash. Lesinurad/allopurinol carries a black box warning that acute renal failure has occurred with lesinurad.

REFERENCES

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