**URAT1 Inhibitor Prior Authorization with Quantity Limit Program Summary**

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace, FocusRx and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

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**FDA APPROVED INDICATIONS AND DOSAGE**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage</th>
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</table>
| **Duzallo®**       | 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. Limitations of Use:  
• Duzallo is not recommended for the treatment of asymptomatic hyperuricemia. | One tablet once daily by mouth                                                               |
| (lesinurad/allopurinol) tablets |                                                                                                                                                                                                              |                                                                                               |
| **Zurampic®**      | 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. Limitations of Use:  
• Zurampic is not recommended for the treatment of asymptomatic hyperuricemia.  
• Zurampic should not be used as monotherapy. | 200 mg once daily in combination with a xanthine oxidase inhibitor, including allopurinol or febuxostat.  
The maximum daily dose of Zurampic is 200 mg.                                          |
| (lesinurad) tablets |                                                                                                                                                                                                              |                                                                                               |
Gout is one of the most common forms of inflammatory arthritis and is caused by accumulation of excess urate crystals (monosodium urate) in joint fluid, cartilage, bones, tendons, bursas, and other sites. In absence of hyperuricemia, defined as serum urate levels >6.8 mg/dL (405 micromol/L) and of urate crystal deposition and inflammatory responses to crystal deposition, the signs and symptoms of gout do not occur. Typically, gout initially presents as acute episodic arthritis and can also manifest as chronic arthritis of 1 or more joints. Tophi, mainly found in articular, periarticular, bursal, bone, auricular, and cutaneous tissues, are pathognomonic features of gout. Risk factors for gout include hypertension, obesity, metabolic syndromes, chronic kidney disease, consuming alcoholic drinks, consuming red meats and some seafood, and diuretic use.3-6

Goals of therapy are to treat acute gout episodes, prevent the recurrence of gout flares, and to reverse prior signs of the disease by achieving and maintaining subsaturating serum urate concentrations.4,6 Management for the prevention of recurrent gout flares and damage to joints and other tissues from urate crystal deposition includes drug therapy as well as lifestyle modification and other strategies for risk reduction.6 The goal of urate lowering therapy is to achieve a serum urate level to <6 mg/dL. Additionally, guidelines recommend that the target serum urate level should be lowered sufficiently to durably improve the signs and symptoms of gout, including palpable and visible tophi detected, and this may involve therapeutic serum urate level lowering to below 5 mg/dL.3 Treatment includes both lifestyle modifications and pharmacological therapies. Lifestyle modifications include weight loss, reduction in high fructose corn syrup, reduction in alcohol intake, limit intake of purine rich animal proteins (e.g., organ meats, beef, lamb, pork, shellfish), control of diabetes, control of hypertension, and/or control of other comorbidities.3,4 Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine are recommended to treat patients with acute gout.3-5

Guidelines do not recommend urate lowering therapy for all patients. The main indications for pharmacologic urate-lowering therapy in patients with a diagnosis of gout are:5

- Frequent or disabling gout flares
- Clinical or radiographic signs of joint damage (e.g., gouty bone erosion or gouty arthropathy)
- Tophaceous deposits in soft tissues or subchondral bone
- Gout with renal insufficiency (creatinine clearance <60 mL/minute/1.73 m²)
- Recurrent uric acid nephrolithiasis despite treatment with hydration and urinary alkalinization, even without another primary indication (such as frequent gout flares or the development of tophi) for urate-lowering pharmacotherapy; or in the presence of either recurrent uric acid or calcium oxalate nephrolithiasis in patients with hyperuricosuria (daily uric acid >800 mg per day in a man or 750 mg per day in a woman). The benefit of urate-lowering therapy in patients with calcium stones is less well-established
- Urinary uric acid excretion exceeding 1100 mg/day (6.5 mmol) when determined in men less than 25 years of age or in premenopausal women

Although evidence supports the benefit of using urate lowering therapy for shorter duration to reduce gout flares, long term use (≥12 months) in patients with a single or infrequent gout attacks (<2 attacks per year) have not been studied. Thus, the American College of Physicians (ACP) recommends against initiating urate therapy in most patients after a first gout attack or in patients with infrequent attacks.4 Urate lowering therapies include xanthine oxidase inhibitors (allopurinol, febuxostat), uricosuric agents (probenecid, benzbromarone, and lesinurad), and uricase (pegloticase and rasburicase).3-6 There is 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.\(^7\)

The American College of Rheumatology (ACR) recommend diet and lifestyle measures for majority of patients with gout. In addition, these pharmacologic therapies are recommended:\(^3\)

- 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. The ACR recommends 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). 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."\(^3\) 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.\(^4\)

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).\(^8\) Two large observational studies (one in heart failure and one in hyperuricemic patients) have shown that allopurinol is associated with reduced total mortality.\(^5,9\) Two small randomized controlled trials showed allopurinol reduced cardiovascular events markedly in both studies.\(^10,11\)

**Efficacy\(^1\)**

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 analysis. 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.

For additional clinical information see the Prime Therapeutics Formulary Chapter 10.5: Gout.

REFERENCES
URAT1 Inhibitor Prior Authorization with Quantity Limit

OBJECTIVE
The intent of the URAT1 Inhibitor Prior Authorization criteria is to promote appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines.

Doses above the set limit will be approved if the requested quantity is below the maximum FDA limit and cannot be dose optimized or when the requested quantity is above the maximum FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose.

TARGET AGENT
Duzallo® (lesinurad/allopurinol)
Zurampic® (lesinurad)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duzallo (lesinurad/allopurinol)</td>
<td>200 mg/200 mg tablet</td>
<td>68990002500320 M, N, O, or Y</td>
<td>1 tablet</td>
</tr>
<tr>
<td></td>
<td>200 mg/300 mg tablet</td>
<td>68990002500330 M, N, O, or Y</td>
<td>1 tablet</td>
</tr>
<tr>
<td>Zurampic (lesinurad)</td>
<td>200 mg tablet</td>
<td>68000040000320 M, N, O, or Y</td>
<td>1 tablet</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
URAT1 Inhibitor will be approved when ALL of the following is met:
1. The patient has a diagnosis of gout
   AND
2. ONE of the following:
   a. The patient has a baseline serum uric acid level that is >6.0 mg/dL
   OR
   b. The patient’s current 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 allopurinol 300 mg OR at least febuxostat 80 mg
   OR
   b. BOTH of the following:
      i. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to allopurinol
      AND
      ii. The patient has a documented intolerance or expected intolerance to febuxostat 80 mg or higher
   OR
   c. BOTH of the following:
      i. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to febuxostat
      AND
      ii. The patient has a documented intolerance or expected intolerance to allopurinol 300 mg or higher
   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 febuxostat 80 mg or higher

AND

4. The patient will be taking a 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) does NOT exceed 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) does NOT exceed the maximum 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 program quantity 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 maximum FDA labeled dose

   AND

      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

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 for the requested agent through Prime Therapeutics’ Prior Authorization process

   AND

2. The patient will be taking a 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) does NOT exceed 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) does NOT exceed the maximum FDA labeled dose
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity 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 maximum FDA labeled dose
   **AND**
   iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

**Length of approval:** 12 months
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

   OR

2. The patient’s medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

   OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria