LifeWise
Health Plan of Washington

PHARMACY / MEDICAL POLICY – 5.01.616

Pharmacologic Treatment of Gout

Effective Date:	Feb. 1, 2025	RELATED MEDICAL POLICIES:
Last Revised:	Jan. 14, 2025	None
Replaces:	N/A	

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Introduction

Gout is a type of arthritis that is caused by the buildup of uric acid that forms crystals in the joints. It leads to attacks of intense pain, redness, swelling, and tenderness. These sudden attacks often begin in the big toe, but they can occur in any joint. Chronic gout is when a person has 2 or more gout attacks in a year. Treatment for gout is meant to reduce the pain and inflammation of an attack, to prevent a future attack, and to prevent gout-related problems, such as urate crystal formation in the skin or organs, and kidney stones. This policy describes when drugs used to treat gout may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Drug	Medical Necessity
Brand colchicine **Gloperba (colchicine)** **Mitigare (colchicine)**	**Brand colchicine, Gloperba (colchicine), Mitigare (colchicine), Uloric (febuxostat), and Zyloprim (allopurinol) may be**

Drug	Medical Necessity
Uloric (febuxostat) **Zyloprim (allopurinol)**	**considered medically necessary for the treatment of gout when the following criteria are met:** • The individual has tried generic oral colchicine or generic oral allopurinol first and had an inadequate response
Ilaris (canakinumab) SC	**Ilaris (canakinumab) may be considered medically necessary for the treatment of acute gout flares when the following criteria are met:** • The individual is aged 18 years or older **AND** • Has an intolerance, contraindication, or lack of response to nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine for the treatment of acute gout flares **AND** • Has been previously treated with oral or injectable corticosteroids and is unable to be retreated with a repeat course of corticosteroids for the treatment of acute gout flares **AND** • Ilaris (canakinumab) will be used in combination with a urate lowering medication (e.g., allopurinol, febuxostat, or probenecid) unless contraindicated **AND** • The dose will be limited to 150 mg every 12 weeks **AND** • The medication is being prescribed by or in consultation with a rheumatologist

Krystexxa (pegloticase) IV	**Krystexxa (pegloticase) may be considered medically necessary for the treatment of chronic gout when the following criteria are met:**
	• The individual is aged 18 years or older
	AND
	• Tried allopurinol and has documentation of one of the following:
	  ○ Inadequate response after 3-months of treatment at the maximum tolerated dose with serum uric acid levels remaining greater than 6 mg/dL
	  OR
	  ○ Had intolerance to use of allopurinol

Drug	Medical Necessity

	OR
	• Has contraindication to use of allopurinol or tested positive for the human leukocyte antigen (HLA)-B*5801 allele**
	AND
	• Has tried one of the following urate-lowering therapies (unless a clinical reason is provided why individual is not able to take) and serum uric acid levels remain greater than 6 mg/dL:
	  ○ Febuxostat
	  ○ Probenecid
	AND
	• Documentation is provided the individual does not have a glucose-6-phosphate dehydrogenase (G6PD) deficiency (contraindication to use of Krystexxa)
	AND
	• Krystexxa is administered as an 8 mg infusion every two weeks
	AND
	• Krystexxa is co-administered with oral methotrexate 15 mg weekly unless methotrexate is contraindicated or not clinically appropriate
	AND
	• Medication is being prescribed by or in consultation with a rheumatologist
	
	Note: **Chinese, Thai, Korean, and other ethnicities with increased risk are typically screened for this allele due to higher frequency in population. Individuals who test positive are at increased risk of a severe cutaneous adverse reaction and allopurinol should be avoided.

Drug	Investigational
As listed	**All other uses of the drugs for conditions not outlined in this policy are considered investigational.** **The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.**

Length of Approval	
Approval	**Criteria**
Initial authorization	**Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.** **All other reviews for Ilaris (canakinumab) and Krystexxa (pegloticase) may be approved up to 6 months.** **All other reviews for brand colchicine, Gloperba (colchicine), Mitigare (colchicine), Uloric (febuxostat), and Zyloprim (allopurinol) may be approved up to 12 months.**
Re-authorization criteria	**Non-formulary exception reviews and all other reviews for all drugs listed in the policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes demonstrate that the individual continues to show a positive clinical response to therapy such as a documented serum uric acid level less than 6 mg/dL.**

Documentation Requirements
The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following: • Office visit notes that contain the diagnosis, relevant history, physical evaluation, G6PD status, and medication history

Coding

Code	Description
HCPCS	
J0638	Injection, canakinumab (Ilaris), 1 mg
J2507	Injection, pegloticase (Krystexxa), 1 mg

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Consideration of Age

The ages stated in this policy for which Ilaris (canakinumab) and Krystexxa (pegloticase) are considered medically necessary are based on the ages approved in the FDA labeling.

Benefit Application

Krystexxa (pegloticase) is managed through the medical benefit. Ilaris (canakinumab) is managed through the pharmacy and medical benefit. Brand colchicine, Gloperba (colchicine), Mitigare (colchicine), Uloric (febuxostat), and Zyloprim (allopurinol) are managed through the pharmacy benefit.

Evidence Review

Background

Hyperuricemia is the most significant risk factor for gout. The Framingham Heart Study found the incidence of gout per 1,000 person-years increased with increasing uric acid levels. This increase was more pronounced among men than women. Additional independent risk factors for gout include increasing age, obesity, diuretic use, hypertension, type II diabetes, and renal disease. Data from the MRFIT trial, a primary prevention trial in cardiovascular disease which followed over 12,000 men for 7 years, found individuals with severe renal dysfunction (creatinine clearance [CrCl] <30 ml/min/1.73 m^2) had a 15-fold increased risk of gout compared to those with normal renal function. Each decrease of 14 ml/min/1.73 m^2 in glomerular filtration rate (GFR) corresponded with increased risk of gout (HR 1.38, 95% CI 1.33-1.44). Several dietary factors are associated with gout. Sugar-sweetened soft-drinks, fruit juice, heavy alcohol consumption (>7 ounces/week), and purine-rich meat and seafood increase the risk of gout while low-fat dairy products and coffee decrease the risk of gout.

Gout is defined as inflammatory arthritis caused by the deposition of monosodium urate crystals. Gout is associated with hyperuricemia, typically caused by inefficient excretion (90%)

and/or over production (10%) of uric acid. Uric acid is a weak acid, the majority of which is present as the anion urate at physiologic pH. Urate can supersaturate at increased concentrations (>6.8 mg/dL) resulting in crystal formation. Crystals form via a process of nucleation as clusters aggregate, leading to crystal nuclei which continue to grow longitudinally. Nuclei can form with or without a foreign substance or other crystal present and tend to faster growth with higher serum uric acid (sUA) levels. Crystal formation is also influenced by temperature, pH, cations, articular dehydration, and presence of nucleating agents such as non-aggregated proteoglycans, insoluble collagens, and chondroitin sulfate. For these reasons, crystals are more likely to form in the first metatarsophalangeal joint as well as joints with osteoarthritis due to lower temperatures and the presence of nucleating debris, respectively.

Hyperuricemia due to over production of uric acid is linked to increased purine synthesis and/or increased dietary purine consumption. Purines are nitrogenous precursors of adenine and guanine. These components of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) are metabolized to uric acid via the enzyme xanthine oxidase; therefore, increased intake or synthesis of purines leads to increased sUA levels. Increased purine synthesis is seen as a result of increased cell turnover in hematologic cancers, psoriasis, and certain genetic disorders.

Conversely, weight loss is associated with decreased de novo purine synthesis. The most likely exogenous sources of purine which adversely affect sUA levels are meat and fish. Ethanol increases uric acid levels by increasing adenosine triphosphate (ATP) degradation to uric acid. Beer carries further risk due to its high purine content. Consumption of fructose increases uric acid as fructose metabolism depletes hepatic ATP and limits its regeneration, resulting in the degradation of ATP to uric acid.

Excretion of urate occurs via the renal system and the gut. Approximately 30% of urate excretion occurs in the gut via the ABCG2 transporter. The renal system is responsible for the remaining 70% of urate excretion. Urate is first removed from the blood via glomerular filtration. This is followed by reabsorption of 90% of urate in the proximal tubule principally via URAT1. The URAT1 transports urate in exchange for anions to maintain electrical balance in the proximal tubule. The URAT1 works in tandem with a sodium-anion co-transporter which transports sodium and anions such as lactate, pyruvate, or acetoacetate into the proximal tubule. These anions are exchanged for urate via the URAT1, resulting in urate reabsorption.

The process of renal urate excretion can be complicated by several different factors. Loss of function mutations affecting URAT1 lead to hypouricemia, as urate is no longer resorbed in the proximal tubule. Several anions have biphasic effects on the URAT1 transporter, causing anti-uricosuric effects at low concentrations and uricosuric effects via competitive inhibition at higher concentrations. Exogenous insulin increases urate reabsorption via actions at the URAT1 or the sodium dependent anion cotransporter. Insulin resistance is associated with hyperuricemia via

impaired oxidative phosphorylation which, in turn, increases adenosine, resulting in renal retention of sodium, urate, and water. Lastly, hypertension decreases glomerular filtration of urate due to decreased renal blood flow. This results in reduced urate excretion and hyperuricemia.

Hyperuricemia is associated with the formation of monosodium urate (MSU) crystals. Urate crystals can cause intense inflammatory attacks by stimulating the synthesis and the release of cellular and humoral mediators of inflammation. Crystals are phagocytized resulting in the release of inflammatory mediators such as NALP3 inflammasomes and interleukin-1β (LI-1β). Additionally, the crystals interact with lipid membranes on the phagocyte resulting in increased IL-8 levels which further stimulate inflammatory processes. Ultimately, the release of inflammatory mediators results in migration of neutrophils to the site of inflammation, leading to neutrophilic synovitis. Acute gout resolves as inflammatory mediators decrease due to several mechanisms including the coating of urate crystals with proteins, clearance of urate crystals by anti-inflammatory differentiated macrophages, apoptosis of neutrophils, and inactivation of inflammatory mediators. Over time, inflammation may persist even as acute symptoms resolve, resulting in chronic gouty arthritis.

Summary of Evidence

Efficacy – Krystexxa Co-Administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult individuals with chronic gout refractory to conventional therapy, to evaluate administration of Krystexxa 8 mg every 2 weeks co-administered with weekly administration of methotrexate 15 mg, compared to Krystexxa alone: Trial 1 (NCT03994731). In this trial, individuals were naïve to Krystexxa therapy. Individuals who were able to tolerate two weeks on oral methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating Krystexxa therapy in a 2:1 ratio. Individuals were pre-treated with a standardized infusion reaction prophylaxis regimen consisting of an oral fexofenadine, acetaminophen and intravenous methylprednisolone prior to each Krystexxa infusion. Methotrexate or placebo was continued weekly throughout the Krystexxa treatment period with daily oral folic acid in order to evaluate the immunomodulatory effect of methotrexate to attenuate development of anti-drug antibodies.

Entry criteria for individuals to be eligible for this trial were: baseline serum uric acid ≥7 mg/dL and inability to maintain serum uric acid <6 mg/dL on other urate-lowering therapy, intolerable

side effects associated with current urate-lowering therapy, and/or presence of clinically evident tophaceous deposits.

The primary endpoint was the proportion of Month 6 responders, where a responder was defined as achieving and maintaining serum uric acid less than 6 mg/dL for at least 80% of the time during Month 6. The proportion of Month 12 responders was a key secondary endpoint. A significantly greater proportion of individuals receiving Krystexxa co-administered with methotrexate compared to Krystexxa alone achieved both the primary (71% vs. 39%; $p<0.0001$) and secondary (60% vs. 31%; $p=0.0003$) endpoints.

The effect of Krystexxa co-administered with methotrexate and Krystexxa alone on tophi was assessed using standardized digital photography, image analysis and Central Readers blinded to treatment assignment. Approximately 53.3% (81/152) of randomized individuals had tophi at baseline (Week -6) that were confirmed by digital photography. Of those, 54% (28/52) in the Krystexxa co-administered with methotrexate group and 31% (9/29) in the Krystexxa alone group achieved a complete response at Month 12 (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression). The difference between the two treatment groups was statistically significant (22.8%, 95% CI: 1.2%, 44.4%).

Efficacy – Krystexxa Alone

The efficacy of Krystexxa was studied in adult individuals with chronic gout refractory to conventional therapy in two replicate, multicenter, randomized, double-blind, placebo-controlled studies of six months duration: Trial 1 and Trial 2. Individuals were randomized to receive Krystexxa 8 mg every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio.

Studies were stratified for the presence of tophi. Seventy-one percent (71%) of individuals had baseline tophi. All individuals were prophylaxed with an oral antihistamine, intravenous corticosteroid and acetaminophen. Individuals also received prophylaxis for gout flares with non-steroidal anti-inflammatory drugs (NSAIDs) or colchicine, or both, beginning at least one week before Krystexxa treatment unless medically contraindicated or not tolerated. Individuals who completed the randomized clinical trials were eligible to enroll in a 2-year open label extension study.

Entry criteria for individuals to be eligible for the trials were: baseline sUA of at least 8 mg/dL; had symptomatic gout with at least 3 gout flares in the previous 18 months or at least 1 gout tophus or gouty arthritis; and had a self-reported medical contraindication to allopurinol or

medical history of failure to normalize uric acid (to less than 6 mg/dL) with at least 3 months of allopurinol treatment at the maximum medically appropriate dose.

The mean age of study subjects was 55 years (23-89); 82% were male, mean body mass index (BMI) was 33 kg/m^2, mean duration of gout was 15 years, and mean baseline SUA was 10 mg/dL.

To assess the efficacy of Krystexxa in lowering uric acid, the primary endpoint in both trials was the proportion of individuals who achieved plasma uric acid (pUA) less than 6 mg/dL for at least 80% of the time during Month 3 and Month 6. A greater proportion of individuals treated with Krystexxa every 2 weeks achieved urate lowering to below 6 mg/dL than individuals receiving placebo. Although the 4-week regimen also demonstrated efficacy for the primary endpoint, this regimen was associated with increased frequency of anaphylaxis and infusion reactions and less efficacy with respect to tophi.

The effect of treatment on tophi was a secondary efficacy endpoint and was assessed using standardized digital photography, image analysis, and a Central Reader blinded to treatment assignment. Approximately 70% of individuals had tophi at baseline. A pooled analysis of data from Trial 1 and Trial 2 was performed as pre-specified in the protocols. At Month 6, the percentage of individuals who achieved a complete response (defined as 100% resolution of at least one target tophus, no new tophi appear and no single tophus showing progression) was 45%, 26%, and 8%, with Krystexxa 8 mg every 2 weeks, Krystexxa 8 mg every 4 weeks, and placebo, respectively. The difference between Krystexxa and placebo was statistically significant for the every 2-week dosing regimen, but not for the every 4-week dosing regimen.

Safety

The most commonly reported adverse reactions that occurred in greater than or equal to 5% of individuals treated with Krystexxa 8 mg every 2 weeks vs. placebo are gout flare (77% vs. 81%), infusion reaction (26% vs. 5%), nausea (12% vs. 2%), contusion or ecchymosis (11% vs. 5%), nasopharyngitis (7% vs. 2%), constipation (6% vs. 5%), chest pain (6% vs. 2%), anaphylaxis (5% vs. 0%), vomiting (5% vs. 2%).

Warnings and precautions on Krystexxa include the following:

- Anaphylaxis may occur with any Krystexxa infusion and patients should be pre-medicated and monitored patients.
- Infusion reactions occurred in patients treated with Krystexxa and patients should be pre-medicated and monitored.

- G6PD deficiency associated hemolysis and methemoglobinemia can occur and patients should be screened for G6PD deficiency.
- Gout flare prophylaxis is recommended for at least the first 6 months of therapy.
- Congestive heart failure exacerbation may occur and patients should be closely monitored following infusion.

Ilaris (canakinumab)

The efficacy of Ilaris was demonstrated in two 12-week, randomized, double-blind, active-controlled studies in individuals with gout flares for whom NSAIDs and/or colchicine were contraindicated, not tolerated or ineffective, and who had experienced at least three gout flares in the previous year (Studies 1 and 2). The studies continued in 1) two 12-week, double-blind, active-controlled extensions, followed by 2) two open-label extensions and continued 3) in a third open label extension (combined for both studies) up to a maximum of 36 months where all individuals were treated with Ilaris upon a new flare. In all studies (Study 1, 2, and 3), pain intensity of the most affected joint at 72 hours post-dose was consistently lower for individuals treated with Ilaris compared with triamcinolone acetonide in the subpopulation of individuals unable to use NSAIDs and colchicine. The most common infections reported in more than 2% of individuals in the Ilaris treatment groups were nasopharyngitis, upper respiratory tract infections, and urinary tract infections. Serious adverse events were reported in 1.4% of the Ilaris-treated individuals. No serious adverse events were reported in the triamcinolone acetonide-treated group.

2021 Update

Reviewed Krystexxa (pegloticase) prescribing information and conducted a literature search on the management of gout. No new information was identified that would result in changes to policy statements.

2022 Update

Reviewed Krystexxa (pegloticase) prescribing information and added a requirement that Krystexxa is being co-administered with oral methotrexate 15 mg weekly unless methotrexate is contraindicated or not clinically appropriate. Some individuals who are treated with Krystexxa

develop anti-drug antibodies which can affect the efficacy of Krystexxa. Use of Krystexxa in combination with methotrexate has been shown to help prevent anti-drug antibody production and a randomized trial documented improved efficacy when Krystexxa is co-administered with methotrexate versus use of Krystexxa alone.

2023 Update

Reviewed Krystexxa (pegloticase) prescribing information and conducted a literature search on the management of gout. No new information was identified that would result in changes to policy statements. Updated "Patient" to "individual" for the process of standardization.

2024 Update

Reviewed prescribing information for all drugs. Added coverage criteria for Ilaris (canakinumab) for the treatment of acute gout flares.

2025 Update

Reviewed prescribing information for Ilaris (canakinumab) and Krystexxa (pegloticase). A warning was added to Ilaris in November 2024 regarding hypersensitivity reactions, but no new information was identified that would result in changes to policy statements for Ilaris. Moved the gout drugs brand colchicine, Gloperba (colchicine), Mitigare (colchicine), Uloric (febuxostat), and Zyloprim (allopurinol) from Policy 5.01.605 to Policy 5.01.616 Pharmacologic Treatment of Gout with no changes to the coverage criteria. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

References

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History

Date	Comments
06/01/20	New policy, approved May 12, 2020, effective for dates of service on or after September 4, 2020, following 90-day provider notification. Add to Prescription Drug section. Krystexxa (pegloticase) may be considered medically necessary for the treatment of chronic gout when criteria are met. Coverage criteria for Krystexxa (pegloticase) (HCPCS code J2507) becomes effective for dates of service on or after September 4, 2020.
12/01/21	Annual Review, approved November 18, 2021. No changes to policy statements.
09/01/22	Annual Review, approved August 9, 2022. Updated coverage criteria to require Krystexxa is co-administered with oral methotrexate 15 mg weekly unless methotrexate is contraindicated or not clinically appropriate. Changes to coverage criteria are effective for dates of service on or after December 1, 2022, following 90-day provider notification.

Date	Comments
08/01/23	Annual Review, approved July 24, 2023. No changes to policy statements. Changed the wording from "patient" to "individual" for the process of standardization.
03/01/24	Annual Review, approved February 13, 2024. Added coverage criteria for Ilaris (canakinumab) for the treatment of acute gout flares. Added HCPCS code J0638.
02/01/25	Annual Review, approved January 14, 2025. Moved the gout drugs brand colchicine, Gloperba (colchicine), Mitigare (colchicine), Uloric (febuxostat), and Zyloprim (allopurinol) from Policy 5.01.605 Medical Necessity Criteria for Pharmacy Edits to Policy 5.01.616 Pharmacologic Treatment of Gout with no changes to the coverage criteria. Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.