Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 10/03/2024

Ilaris® (canakinumab)

HCPCS: J0638

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Diagnosis of:
      i. Still's disease, including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA)
         1. Trial and treatment failure with one of the following: glucocorticoids or NSAIDs
         2. Trial and failure, contraindication, or intolerance to Kineret® and Actemra®
      ii. Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)
      iii. Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)
      iv. Familial Mediterranean Fever (FMF) in patients who have tried and failed colchicine
      v. Cryopyrin-Associated Periodic Syndromes (CAPS) with phenotypes: Familial Cold Auto-Inflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS)
         1. Laboratory evidence of a genetic mutation (such as in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1 – also referred to as the NLRP-3))
            OR
         2. Elevated inflammatory markers (C-reactive protein [CRP] and serum amyloid A) plus at least two of six typical CAPS manifestations:
            a) Urticaria-like rash
            b) Cold-triggered episodes
            c) Sensorineural hearing loss
            d) Musculoskeletal symptoms
            e) Chronic aseptic meningitis
            f) Skeletal abnormalities
      vi. Gout flares
         1. Member has undertaken appropriate lifestyle modifications (i.e. limiting alcohol consumption, discontinuing or changing other medications known to precipitate gout attacks when possible)
         2. Trial and treatment failure, contraindication, or intolerance to ALL of the following for the symptomatic treatment of gout flares:

a) NSAIDs
b) Colchicine
c) Corticosteroids

3. Patients requiring treatment beyond the initial quantity allowed in this policy will be required to be established on maintenance therapy with urate-lowering agents (e.g., allopurinol, febuxostat, probenecid)

c. Not to be used in combination with other biologics or targeted DMARDs for the same indication
d. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period:
      i. Still's disease (including AOSD and sJIA), TRAPS, HIDS/MKD, FMF, CAPS with FCAS or MWS phenotypes: One year at a time
      ii. Gout flares: Four months
   c. Renewal criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Bachground Information:

- Ilaris is an interleukin (IL)-1β blocker that is approved for the following indications and administered subcutaneously by a healthcare provider:
  - Periodic Fever Syndromes:
    - Cryopyrin-Associated Periodic Syndromes (CAPS) in adults and children 4 years of age and older including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).
    - Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients.
    - Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients.
    - Familial Mediterranean Fever (FMF) in adult and pediatric patients.
  - Active Still's disease, including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older.
  - Symptomatic treatment of gout flare in adults in whom NSAIDs and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

- Periodic Fever Syndromes are a group of rare autoinflammatory diseases that cause disabling and persistent fevers which may be accompanied by joint pain, swelling, muscle pain and skin rashes with complications that can be life-threatening.
    - The most common syndrome is FMF, which mainly affects people of Eastern Mediterranean ancestry. It affects 1 in 250 to 1 in 1,000 individuals in these populations, many of whom are children. FMF is characterized by episodic attacks of fever lasting one to three days and accompanied, in most cases, by abdominal pain, pleurisy, and arthralgias/arthritis.
    - TRAPS is characterized by recurrent fevers over months or years. Other clinical features include focal myalgias, conjunctivitis, and rash. Fever and associated symptoms commonly last at least five days and often continue for more than two weeks.
    - HIDS/MKD is characterized by episodic attacks of fever lasting three to seven days accompanied, in most cases, by chills, cervical lymphadenopathy, abdominal pain, vomiting, and/or diarrhea.
    - CAPS are a group of rare genetic diseases affecting approximately 200 to 300 people in the United States, attributed to a specific genetic mutation. There are two types of CAPS recognized that affect the majority of patients.
        - Familial Cold Auto-Inflammatory Syndrome (FCAS) – patients have recurrent intermittent episodes of fever and rash that primarily followed natural, artificial (e.g., air conditioning) or both types of generalized cold exposure.
        - Muckle-Wells Syndrome (MWS) – patients have chronic fever and rash that may wax and wane in intensity; sometimes exacerbated by generalized cold exposure. This syndrome may be associated with deafness or amyloidosis.
        - The diagnosis of CAPS is confirmed by genetic testing for NALP3 mutations. However in some patients the mutation is not detectable for various reasons. For these situations, diagnostic criteria include raised inflammatory markers (C-reactive protein [CRP] and serum amyloid A) plus at least two of six typical CAPS manifestations:
            - Urticaria-like rash
            - Cold-triggered episodes
            - Sensorineural hearing loss
            - Musculoskeletal symptoms
            - Chronic aseptic meningitis
            - Skeletal abnormalities
    - Clinical guidelines for management of Periodic Fever Syndromes include the following recommendations:
        - The 2016 European League Against Rheumatism (EULAR) clinical guidelines for the management of FMF recommend first-line treatment with colchicine as soon as a clinical diagnosis of FMF is established. Biological therapy with an IL-1β blocker should be considered if inflammation is not controlled with a maximally tolerated dose of colchicine.

- The 2021 EULAR/American College of Rheumatology (ACR) clinical guidelines for the management and of IL-1 mediated autoinflammatory diseases recommend IL-1β blocker therapy as standard of care for patients with TRAPS, MKD and CAPS.
    - Ilaris (cankinumab) is the preferred IL-1β blocker for TRAPS and MKD.
    - Arcalyst® (rilonacept) is another IL-1β blocker indicated for the treatment of CAPS. Both products appear to have similar efficacy. Ilaris has a more convenient dosing regimen and is indicated for a younger age population.

- Still's disease (adult onset and systemic juvenile idiopathic arthritis (sJIA))
    - sJIA is a rare and distinct subtype of juvenile idiopathic arthritis that causes body-wide inflammation. It accounts for 4-15% of JIA and is defined as arthritis in ≥ 1 joint for at least 6 weeks duration in a child age < 16 years with or preceded by a fever of at least 2 weeks duration that is documented to be daily for at least 3 days and accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis. The condition can occur in adulthood with similar features and is referred to as adult onset Still's disease (AOSD) when diagnosed in patients ages ≥16 years.
    - AOSD and sJIA may also be complicated by macrophage activation syndrome (MAS), a secondary hemophagocytic 4yndrome that can be life-threatening and requires urgent recognition and treatment. MAS presents with fevers, high ferritin levels, cytopenias, elevated liver enzyme, low fibrinogen levels, and high triglyceride levels. Regardless of MAS presence at presentation, careful monitoring is necessary as MAS can occur at anypoint during the disease course.
    - The underlying inflammatory process of AOSD and sJIA appears to be distinct from other categories of autoimmune arthritis, with interleukin (IL)-1 and IL-6 playing a central role. The goal of therapy focuses on prompt control of active inflammation and symptoms and prevention of disease- and or treatment-related morbidities like growth disturbances, joint damage and functional limitations.
    - Treatment recommendations vary depending on the presence of MAS.The 2021 ACR guideline for pharmacologic management of oligoarthritis, TMJ arthritis, and sJIA in children recommend the following for the treatment of sJIA:
        - Classes of pharmacologic interventions addressed in the recommendations include:
            - Any NSAIDs at therapeutic dosing
            - Traditional DMARDs (i.e., methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, calcineurin inhibitors (cyclosporin A, tacrolimus))
            - Biologics (i.e., tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol), abatacept, IL inhibitors (tocilizumab, anakinra, canakinumab))
            - Glucocorticoids, including any oral or intravenous agent, or intraarticular triamcinolone acetonide or triamcinolone hexacetonide.

- In the presence of MAS, an IL-1 or IL-6 inhibitor (no preferred agent) and/or systemic glucocorticoids are recommended for initial treatment. If residual arthritis is present, a traditional DMARD may be added or treatment can be switched to a different biologic agent (no preferred agent).

- In sJIA without MAS, the guidelines recommend monotherapy with an IL-1 or IL-6 inhibitor (no preferred agent) and/or a brief trial of scheduled NSAIDs. The guidelines do not provide a recommended duration of initial use for NSAIDs. Traditional DMARDs are strongly recommended against as initial monotherapy as they are minimally effective at controlling systemic features of sJIA alone. Glucocorticoids are also conditionally recommended against as initial monotherapy; however, they may be used to help control systemic and joint manifestations of sJIA until an IL-1 or IL-6 inhibitor can be started. If a patient experiences an incomplete response or intolerance to first-line treatment, switching to an alternative IL-1 or IL-6 inhibitor is recommended (no preferred agent).

- Regardless of the presence of MAS, if a patient responds to initial treatment but residual arthritis is present, a traditional DMARD or switch to a different biologic (no preferred agent) is recommended.

- Ultimately, treatment is continued and the patient monitored until the sJIA becomes inactive, at which point it is recommended that the patient taper and stop biologics and/or glucocorticoids.

- Ilaris (canakinumab; IL-1 inhibitor) and Actemra (tocilizumab; IL-6 inhibitor) are the only biologic agents FDA approved to treat sJIA, and Ilaris is the only drug approved for AOSD. There are no guidelines for treating AOSD; however, literature recommends a similar treatment approach as with sJIA. The use of Kineret (anakinra; IL-1 inhibitor) for sJIA and both Kineret and Actemra for AOSD is supported by various trials, case studies, and case series. Additionally, the efficacy of Kineret and Actemra in sJIA provides further evidence supporting the use of both agents in AOSD. The significantly lower cost of Actemra and Kineret make these agents more cost-effective alternatives to Ilaris for the treatment of sJIA and AOSD.

- Gout Flares

  - Gout is an inflammatory arthritis that results from hyperuricemia, which contributes to crystallization of monosodium urate monohydrate in the joints. It is one of the most common rheumatic diseases of adulthood with significant morbidity attributed to gout flares (i.e. severe pain, reduced quality of life, decreased physical function). Acutely, anti-inflammatory treatment (e.g., NSAIDs, colchicine, corticosteroids) is used to provide rapid pain relief and resolution of gout glares. Chronically, urate-lowering therapy (ULT; e.g., allopurinol, febuxostat, probenecid) reduce urate stores and, along with anti-inflammatory prophylaxis, reduces the risk of new flares.

  - One of the mainstays of gout treatment is patient education on diet, lifestyle modifications, and management of comorbidities with a goal of decreasing the risk and frequency of acute gout attacks and lowering serum urate levels. Dietary modifications include limiting consumption of purine-rich meat and seafood, alcohol, and beverages sweetened by high-fructose corn syrup, and encouraging the consumption of vegetables and low-/non-fat dairy products. Elimination of non-essential medications that may induce hyperuricemia should also be considered.

  - The American College of Rheumatology (ACR) guidelines for the management of gout (2020) strongly recommend the use of pharmacologic ULT in gout patients experiencing frequent gout flares, defined as $\geq$ 2 flares annually.

- Allopurinol, a xanthine oxidase inhibitor (XOI), is the preferred first-line treatment option and is strongly recommended for all patients requiring ULT based on allopurinol's efficacy, safety, tolerability, and low cost. Treatment should be initiated with a lower starting dose to mitigate safety issues, and gradually titrated to a target serum urate (SU) level of < 6 mg/dL, not to exceed a maximum of 800 mg per day.

- If SU levels are persistently above target and a patient exhibits continued gout flares (> 2 per year) or has non-resolving subcutaneous tophi despite initial treatment with a maximally tolerated or maximally dosed XOI, the guidelines conditionally recommend switching to a second XOI (i.e. febuxostat) over adding a uricosuric agent (e.g., probenecid). The conditional recommendation is due to the fact that no studies directly address the choice of switching to another XOI vs. adding a uricosuric agent when the ULT strategy requires a change.

- The 2020 ACR guidelines did not include a formal vote on the indications for uricosuric agents like probenecid; however, they do concur with the 2012 guidelines that add-on therapy with a uricosuric agent to partially responsive XOI treatment can result in improved control of SU. Additionally, literature supports the use of probenecid as monotherapy if there is a contraindication or intolerance to XOIs as it provides an alternative mechanism for the treatment of gout.

- Concomitant anti-inflammatory prophylaxis (e.g., colchicine, NSAIDs, glucocorticoids) is strongly recommended when initiating ULT for at least 3-6 months after initiation to reduce the risk of gout flares. After cessation, monitoring for flare activity and as-needed continuation of anti-inflammatory therapy if the patient continues to experience gout flares is strongly recommended.

- For patients experiencing gout flares:

    - The guidelines strongly recommend using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy over IL-1 inhibitors like Ilaris based on substantial trial data demonstrating efficacy, relative low cost, and tolerability of these agents in managing a flare. Dosing and duration should be guided by flare severity, and choice of first-line agent should be based on patient factors.

    - Those who are unable to take oral medications are strongly recommended treatment with injectable glucocorticoids over IL-1 inhibitors. The guidelines do, however, conditionally recommend use of an IL-1 inhibitor for patients experiencing gout flares for whom the preferred anti-inflammatory therapies are either ineffective, poorly tolerated, or contraindicated.

    - The guidelines do not specifically address Ilaris in these recommendations, though they acknowledge that there is high quality evidence from network meta-analyses supporting its use for gout flares; however, the ACR panel raised concerns that the comparator in clinical trials was weak and that cost would significantly favor the other lower-cost, guideline-recommended therapies.

- The approval of Ilaris for gout flares was based on two 12-week randomized, double-blind, active-controlled studies in adults with gout flares for whom NSAIDs and/or colchicine were contraindicated, not tolerated, or ineffective, and experienced at least three gout flares in the previous year (β-RELIEVED and β-RELIEVED-II). Patients were randomized to Ilaris 150 mg subcutaneous or intramuscular triamcinolone acetonide 40 mg at baseline and thereafter treated upon a new flare. A third 12-week trial was also conducted evaluating two formulations of Ilaris against intramuscular triamcinolone acetonide 40 mg. Concomitant treatment with ULT was not required and was reported by over 40% of patients at trial entry across all three trials. Findings from the studies showed that among patients unable to use NSAIDs and colchicine, pain intensity of the most affected joint at 72 hours post-dose was consistently lower for those treated with Ilaris compared with

injectable triamcinolone. Treatment was also associated with a reduction in the risk of a new flare compared to triamcinolone.

- When used to treat acute gout flares, additional doses of Ilaris if needed should be administered at least 12 weeks apart per the prescribing information.

- The safety and effectiveness of Ilaris in treating these conditions were established in multiple clinical trials. The use of Ilaris in combination with other biologic agents or targeted disease-modifying antirheumatic drugs is not recommended due to a lack of robust clinical evidence to support the safety and efficacy of concurrent use.

References:

1. Ilaris [prescribing information]. East Hanover, NJ: Novartis. August 2023.
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5. Kuemmerle-Deschner JB, Ozen S, Tyrrell PN et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). Ann Rheum Dis. 2017;76(6):942.
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7. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. Ann Rheum Dis. 2022;81(7):907-921. doi:10.1136/annrheumdis-2021-221801
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10. 2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia. Arthritis care and Research. Vol 64, No. 10, October 2012: 1431-1446.
11. Fitzgerald JD, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care and Research. Vol. 72, No. 6, June 2020:744-760.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>2.7</td><td>Effective Date:
10/03/2024</td><td>Added “for the same indication” to the not to be used in combination with other biologics or targeted DMARDs criteria</td></tr>
<tr><td>2.6</td><td>Effective Date:
10/12/2023</td><td>Updated policy to include criteria, authorization period, and supporting information for new indication for treating gout flares</td></tr>
<tr><td>2.5</td><td>Effective Date:
04/06/2023</td><td>Removed DMARDs from sJIA and AOSD step options
Background info updated to reflect 2021 ACR recommendations for sJIA</td></tr>
<tr><td>2.4</td><td>Effective Date:
12/01/2022</td><td>Annual review of medical policy – no changes to criteria</td></tr>
<tr><td>2.3</td><td>Effective Date:
12/09/2021</td><td>Removed FDA approved indications criteria</td></tr>
<tr><td>2.2</td><td>Effective Date:
02/04/2021</td><td>Added trial and failure of Actemra and Kineret to criteria for sJIA and AOSD</td></tr>
<tr><td>2.1</td><td>Effective Date:
12/03/2020</td><td>Updated step criteria for AOSD and sJIA. Added criteria bullet d – not to use in combination with biologics. Changed renewal criteria to be consistent across all diagnoses.</td></tr>
<tr><td>2.0</td><td>Effective Date;
9/28/2020</td><td>UM medical management system update for MAPPO AND BCNA
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.9</td><td>Effective Date:
08/13/2020</td><td>Updates were made to the criteria, including adding criteria for a new indication</td></tr>
<tr><td>1.8</td><td>Effective Date:
11/7/2019</td><td>Criteria updated for step therapy for SIJA</td></tr>
<tr><td>1.7</td><td>Effective Date:
08/15/2019</td><td>Annual Review of Medical Policy</td></tr>
<tr><td>1.6</td><td>Effective Date:
08/09/2018</td><td>Change in verbiage for preferred therapy</td></tr>
<tr><td>1.5</td><td>Effective Date:
05/03/2018</td><td>Annual Review of Medical Policy</td></tr>
<tr><td>1.4</td><td>Effective Date
05/04/2017</td><td>Added new criteria for TRAPS, HIDS/MKD, and FMF.</td></tr>
<tr><td>1.3</td><td>Effective Date
08/11/2016</td><td>Annual Update</td></tr>
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02/01/2015</td><td>UM medical management system update for BCN
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04/01/2014</td>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*