Effective Date **12/15/2023**
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Coverage Policy Number **IP0235**

Canakinumab

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for canakinumab (**Ilaris®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Canakinumab (Ilaris) is considered medically necessary when ONE of the following is met:

1. **Cryopyrin-Associated Periodic Syndromes (CAPS).** Individual meets **BOTH** of the following criteria:
   A. The medication is being used for treatment of **ONE** of the following:
      i. Chronic infantile neurological cutaneous and articular (CINCA) syndrome
      ii. Familial Cold Autoinflammatory Syndrome (FCAS)
      iii. Muckle-Wells Syndrome (MWS)

iv. Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

B. Medication is prescribed by, or in consultation with, a rheumatologist, geneticist, allergist/immunologist, or dermatologist

2. **Familial Mediterranean Fever (FMF).** Individual meets **ALL** of the following criteria:
   A. Individual is 2 years of age or older
   B. Prior to starting Ilaris, **BOTH** of the following:
      i. C-reactive protein level is greater than or equal to 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory
      ii. **EITHER** of the following:
         a. History of at least one flare per month despite use of colchicine
         b. Individual was hospitalized for a severe flare despite use of colchicine
   C. **EITHER** of the following:
      i. Individual will take canakinumab (Ilaris) in combination with colchicine
      ii. Documented failure, contraindication, or intolerance to colchicine
   D. Medication is prescribed by, or in consultation with, a rheumatologist, nephrologist, geneticist, gastroenterologist, oncologist, or hematologist.

3. **Gout, Acute Flare.** Individual meets **ALL** of the following criteria:
   A. Age 18 years or older
   B. Documentation of **EITHER** of the following:
      i. **BOTH** of the following:
         a. Failure, contraindication, or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of acute gout flares
         b. Failure, contraindication, or intolerance to colchicine for the treatment of acute gout flares
      ii. **BOTH** of the following:
         a. Has been previously treated with corticosteroids (oral or injectable) for an acute gout flare
         b. Is unable to be retreated with a repeat course of corticosteroids (oral or injectable) for acute gout flares
   C. Is receiving or will be taking concomitant urate lowering medication (for example, allopurinol, febuxostat, or probenecid) for the prevention of gout unless contraindicated
   D. Medication is prescribed by or in consultation with a rheumatologist

4. **Hyperimmunoglobulin D Syndrome (HIDS) /Mevalonate Kinase Deficiency (MKD).** Individual meets **ALL** of the following criteria:
   A. Individual is 2 years of age or older
   B. Prior to starting Ilaris, the patient meets **BOTH** of the following:
      i. C-reactive protein level is greater than or equal to 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory
      ii. **EITHER** of the following:
         a. History of at least three febrile acute flares within the previous 6-month period
         b. Individual was hospitalized for a severe flare
   C. Medication is prescribed by, or in consultation with, a rheumatologist, nephrologist, geneticist, oncologist, or hematologist

5. **Stills Disease, Adult Onset.** Individual meets **BOTH** of the following:
   A. Individual is 18 years of age or older

      If the patient is less than 18 years of age, refer to criteria for systemic juvenile idiopathic arthritis (SJIA).

   B. Medication is prescribed by, or in consultation with, a rheumatologist

6. **Systemic Juvenile Idiopathic Arthritis (SJIA).** Individual meets **BOTH** of the following criteria:

A. Individual is 2 years of age or older
B. Medication is prescribed by, or in consultation with, a rheumatologist

7. **Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS).** Individual meets **ALL** of the following criteria:
   A. Individual is 2 years of age or older
   B. Individual meets **BOTH** of the following:
      i. C-reactive protein level is greater than or equal to 10 mg/L, OR elevated to at least two times the upper limit of normal for the reporting laboratory
      ii. **EITHER** of the following:
         a. Individual has a history of at least six flares per year
         b. Individual was hospitalized for a severe flare
   C. Medication is prescribed by, or in consultation with, a rheumatologist, geneticist, nephrologist, oncologist, or hematologist

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of canakinumab (Ilaris) is considered medically necessary for **ALL** covered diagnoses when the above medical necessity criteria are met AND there is documentation of beneficial response.

Examples of beneficial response include:

1. **Cryopyrin-Associated Periodic Syndromes (CAPS) [including Familial Cold Autoinflammatory Syndrome {FCAS}, Muckle-Wells Syndrome {MWS}, and Neonatal Onset Multisystem Inflammatory Disease {NOMID} or Chronic Infantile Neurological Cutaneous and Articular {CINCA} Syndrome]:** resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, stabilization of serum creatinine, fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

2. **Familial Mediterranean Fever**: decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, stabilization of serum creatinine, decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living

3. **Gout, Acute Flare**: decreased pain, resolution/improvement in gout symptoms

4. **Hyperimmunoglobulin D Syndrome (HIDS) /Mevalonate Kinase Deficiency (MKD):** decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, stabilization of serum creatinine, decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living

5. **Stills Disease, Adult Onset**: resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), reduced dosage of corticosteroids, less joint pain/tenderness, stiffness, or swelling, decreased fatigue, or improved function or activities of daily living.

6. **Systemic Juvenile Idiopathic Arthritis (SJIA)**: resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum mar less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living kers (e.g., C-reactive protein, erythrocyte sedimentation rate), or reduced dosage of corticosteroids.

7. **Tumor Necrosis Factor Receptor Associated Periodic Syndrome**: decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, stabilization of serum creatinine, decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living

Authorization Duration

Initial approval duration is up to 12 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Behcet's Disease.** Canakinumab is not indicated for use in the treatment of Behcet's disease.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[13]

2. **Cardiovascular risk reduction and disorder prevention.** The CANTOS trial (Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease) evaluated canakinumab compared with placebo among patients with a history of myocardial infarction (MI) and elevated high-sensitivity C-reactive protein (hsCRP). (Ridker, 2017) The company received a complete response letter from the FDA and based on the FDA correspondence, the CANTOS data would not support labeling for the use of Ilaris (canakinumab) as a targeted therapy for patients with cardiovascular disease who achieved a reduction of hsCRP below the target of 2mg/L. In addition, although CANTOS showed possible benefit in gout in a post hoc analysis of data, randomized controlled studies evaluating canakinumab for this use are still needed.[13]

3. **Concurrent Biologic Therapy.** Ilaris has not been evaluated and should not be administered in combination with another biologic agent for an inflammatory condition (see APPENDIX for examples). An increased incidence of serious infections has been associated with another IL-1 blocker, Kineret, when given in combination with tumor necrosis factor inhibitor in patients with rheumatoid arthritis. Concomitant administration of Ilaris and other agents that block IL-1 or its receptors is not recommended.

4. **COVID-19 (Coronavirus Disease 2019).** This includes requests for cytokine release syndrome associated with COVID-19.

5. **Majeed Syndrome.** Canakinumab is not indicated for use in the treatment of Majeed syndrome.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[16]

6. **Rheumatoid Arthritis.** Efficacy is not established. In a 12-week, Phase II, placebo-controlled, double-blind study, 277 patients who had failed methotrexate were randomized to Ilaris or placebo.[10] Although the ACR 50 at Week 12 was higher for Ilaris 150 mg (given every 4 weeks) compared with placebo (26.5% vs. 11.4%, respectively; P = not significant), there was not a statistically significant difference in ACR 50 for the other Ilaris treatment groups (Ilaris 300 mg every 2 weeks; Ilaris 600 mg loading dose followed by 300 mg every 2 weeks).

7. **Schnitzler Syndrome.** Canakinumab is not indicated for use in the treatment of Schnitzler syndrome.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[17,18]

8. **Type 1 or 2 Diabetes.** Canakinumab is not indicated for use in the treatment of Type 1 or 2 diabetes.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[19-21]

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0638	Injection, canakinumab, 1 mg

Background

OVERVIEW
Ilaris, an interleukin-1β (IL-1β) blocker, is indicated for the following uses:[1]

- **Periodic Fever Syndromes:**
    - **Cryopyrin-Associated Periodic Syndromes** (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), for treatment of patients ≥ 4 years of age.
    - **Familial Mediterranean Fever** (FMF), in adult and pediatric patients.
    - **Hyperimmunoglobulin D Syndrome** (HIDS)/**Mevalonate Kinase Deficiency** (MKD), in adult and pediatric patients.
    - **Tumor Necrosis Factor Receptor Associated Periodic Syndrome** (TRAPS), in adult and pediatric patients.
- **Still's disease**, including active **Adult-Onset Still's Disease** (AOSD) and **Systemic Juvenile Idiopathic Arthritis** (SJIA), in patients ≥ 2 years of age.
- **Gout flares** for adults in whom nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

In the pivotal study for period fevers, patients were required to be at least 2 years of age with a disease flare, defined as a C-reactive protein level ≥ 10 mg/L. Prior to starting Ilaris, a minimum level of disease activity at baseline was required for familial Mediterranean fever (at least one flare per month despite colchicine), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (≥ three febrile acute flares within the previous 6 month period), and TRAPS (≥ six flares per year). In this study, patients were assessed for a response following 4 months of treatment with Ilaris.

Guidelines
Ilaris is used for a variety of periodic fever syndromes and inflammatory conditions.

- **CAPS:** A consensus protocol for hereditary auto-inflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of CAPS.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval are among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease with low disease activity.

- **Familial Mediterranean Fever:** Guidelines for familial Mediterranean fever from the European League Against Rheumatism (2016) note that treatment goals are to prevent the clinical attacks and to suppress chronic subclinical inflammation.[6] IL-1 blockade is an option for patients with protracted febrile myalgia. In patients who develop amyloidosis, the maximal tolerated dose of colchicine and biologics (especially IL-1 blockade) are recommended.

- **Gout**: Guidelines for the management of gout flares from the American College of Rheumatology (ACR) [2020] recommend colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy.[12] If a patient is unable to tolerate or has contraindications to any of the first line conventional alternatives, IL-1 inhibitors are conditionally recommended.

- **Mevalonate Kinase Deficiency:** European guidelines for autoinflammatory disorders (2015) recommend consideration of short-term use of IL-1 blockers for termination of attacks and to limit or prevent steroid adverse events.[5] Maintenance therapy with an IL-1 blocker may be used in patients with mevalonate kinase deficiency and frequent attacks and/or subclinical inflammation between attacks. A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of mevalonate kinase deficiency/hyperimmunoglobulin D syndrome.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval are among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease.

- **SJIA:** There are standardized treatment plans published for use of Ilaris.[7,8] At Month 3, patients with unchanged or worsening disease or patients whose steroid dose is > 50% of the starting dose should have an increase in prednisone plus either addition of methotrexate or change to Actemra. Guidelines from the ACR for the management of SJIA (2021) mention Ilaris as a treatment alternative, depending upon the manifestations of SJIA being treated.[9] While there are a number of other effective options for treating synovitis in patients with active SJIA, effective options for treatment of macrophage activation syndrome are much more limited and include Kineret® (anakinra subcutaneous injection), calcineurin inhibitors, and systemic corticosteroids (no preferential sequencing noted). Although use of Ilaris is uncertain in some situations, macrophage activation syndrome is a potentially life-threatening situation with limited treatment options.

- **TRAPS:** European guidelines for autoinflammatory disorders (2015) note that IL-1 blockade is beneficial for the majority of patients; maintenance with IL-1 blockade, which may limit corticosteroid exposure, may be used in patients with frequent attacks and/or subclinical inflammation between attacks. A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of TRAPS.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval are among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease.

Dosing and Availability[1]

- Administer by subcutaneous injection

1. **CAPS**
   - 2 mg/kg for CAPS patients with body weight greater than or equal to 15 kg and less than or equal to 40 kg. For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg. Administer subcutaneously every 8 weeks
   - 150 mg for CAPS patients with body weight greater than 40 kg

2. **TRAPS, HIDS/MKD, and FMF**
   - Body weight less than or equal to 40 kg
     - The recommended starting dose is 2 mg/kg every 4 weeks
     - The dose can be increased to 4 mg/kg every 4 weeks if the clinical response is not adequate
   - Body weight greater than 40 kg
     - The recommended starting dose is 150 mg every 4 weeks
     - The dose can be increased to 300 mg every 4 weeks if the clinical response is not adequate

3. **Gout, Acute Flare**
   - Up to 150 mg administered subcutaneously no more frequently than once every 12 weeks

4. **Still's disease (AOSD)**
   - 4 mg/kg (with a maximum of 300 mg) for patients with a body weight greater than or equal to 7.5 kg
   - Administer subcutaneously every 4 weeks

5. **SJIA**
   - 4 mg/kg (with a maximum of 300 mg) for patients with a body weight greater than or equal to 7.5 kg
   - Administer subcutaneously every 4 weeks

Other Supported Uses Dosing Recommendations

- CINCA/NOMID: 2-4 mg/kg every 8 weeks[11]

Injection: 150 mg/mL solution in single-dose vials.

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APPENDIX

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	JIA	AS	nr-axSpA	PsA	PsO	CD	UC
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Adalimumab products (Humira, biosimilars)	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitors; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.[*]

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Crohn's Disease	Ulcerative Colitis
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	√	--
Skyrizi Intravenous	--	--	--	--	√[#]	--
Skyrizi Subcutaneous	--	--	√	√	√[^]	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√[^]	√[^]
Stelara Intravenous	--	--	--	--	√[#]	√[#]

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; [^] Maintenance dosing only; [#] Induction dosing only.

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
Janus Kinases Inhibitors							
Olumiant	√	--	--	--	--	--	--
Rinvoq	√	--	√	√	√	--	√
Xeljanz tablets	√	√[#]	√	--	√	--	√
Xeljanz oral solution	--	√[#]	--	--	--	--	--
Xeljanz XR	√	--	√	--	√	--	√
Phosphodiesterase Type 4 Inhibitor							
Otezla	--	--	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator							
Zeposia	--	--	--	--	--	--	√

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
Tyrosine Kinase 2 Inhibitor							
Sotyktu	--	--	--	--	--	√	--

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; * Refer to the selected standard *Prior Authorization Policies* for the specific patient population approved for each indication; # Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology		
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Psoriatic Arthritis
Interleukin-6 Blockers			
Actemra Intravenous	√	√^	--
Actemra Subcutaneous	√	√^	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√#	√
Orencia Subcutaneous	√	√#	√
CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; # Indicated in polyarticular JIA.