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Medication Policy Manual | **Policy No:** dru186

Topic: Ilaris®, canakinumab | **Date of Origin:** July 17, 2009

Committee Approval Date: September 8, 2017 | **Next Review Date:** September 2018

Effective Date: October 1, 2017

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Canakinumab (Ilaris®) is a subcutaneously administered biologic medication similar to anakinra (Kineret®) and rilonacept (Arcalyst®) that blocks the activity of interleukin-1 (IL-1), a protein involved in inflammation. It is used to treat periodic fever syndromes and systemic juvenile idiopathic arthritis (SJIA).

Policy/Criteria

I. Most contracts require prior authorization approval of canakinumab (Ilaris) prior to coverage. Canakinumab (Ilaris) may be considered medically necessary when either criterion A, B, C, D, or E below is met.

A. There is a diagnosis of cryopyrin associated periodic syndromes (CAPS) and criteria 1, 2 and 3 below are met:

1. There is laboratory evidence of a genetic mutation in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1 – sometimes referred to as the NLRP3).

AND

2. There is clinical documentation that the patient is experiencing the classic symptoms of CAPS, defined as meeting either criterion a or b below:

   a. Familial Cold Auto-Inflammatory Syndrome (FCAS) – Recurrent intermittent episodes of fever and rash that primarily followed natural, artificial (e.g., air conditioning) or both types of generalized cold exposure.

   OR

   b. Muckle-Wells Syndrome (MWS) – Syndrome of 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.

AND

3. There is clinical documentation of significant functional impairment leading to limitations in activities of daily living (ADLs).

OR

B. There is a diagnosis of familial Mediterranean fever (FMF) in adult and pediatric patients and treatment with colchicine was ineffective, not tolerated, or is contraindicated.

OR

C. There is a diagnosis of tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS) in adults and pediatric patients.

OR

D. There is a diagnosis of hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adults and pediatric patients.

OR

E. There is a diagnosis of systemic juvenile idiopathic arthritis (SJIA) and criteria 1, 2, and 3 below are met:

1. SJIA disease activity greater than 6 months confirmed by a rheumatologist

AND

2. Treatment with at least one oral systemic agent for SJIA (e.g. methotrexate or glucocorticoids) has been ineffective or not tolerated.

AND

3. Prior treatment with both tocilizumab (Actemra) and anakinra (Kineret) has been ineffective, contraindicated, or not tolerated.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider canakinumab (Ilaris) to be a self-administered medication.

B. When prior authorization is approved, canakinumab (Ilaris) may be authorized in quantities as follows:

1. **For CAPS:** up to 1 vial (150 mg) every 8 weeks (i.e. 7 vials in a 12 month period)

2. **For FMF, TRAPS, HIDS/MKD:** up to 2 vials (300 mg) every 4 weeks (i.e. 26 vials in a 12 month period)

3. **For SJIA:** up to 2 vials (300 mg) every 4 weeks (i.e. 26 vials in a 12 month period)

C. Authorization shall be reviewed as follows to confirm that current medical necessity criteria are met and that the medication is effective.

1. **Initial authorization** shall be reviewed at 1 month.

2. **Continued authorization** shall be reviewed at least annually, and documentation (including chart notes) indicating that there is disease stability or improvement must be provided.

III. Canakinumab (Ilaris) is considered investigational when used for all other conditions including, but not limited to:

A. Atherosclerotic cardiovascular disease

B. Diabetes Mellitus Type 1 or Type 2

C. Gout

D. Rheumatoid Arthritis

Position Statement

Summary

- The periodic fever syndromes are a group of rare inflammatory diseases that include CAPS, FMF, TRAPS, and HIDS, also called MKD.
- CAPS are a group of rare genetic diseases affecting approximately 200 to 300 people in the United States, attributed to a specific genetic mutation. [1]
- Two types of CAPS are recognized that affect the majority of patients
  * Familial Cold Auto-Inflammatory Syndrome (FCAS) – 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) – Syndrome of 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.
- Medications that affect interleukin-1 (IL-1) may be helpful in controlling the symptoms of CAPS.
  * Medications that affect IL-1 include anakinra (Kineret), rilonacept (Arcalyst), and canakinumab (Ilaris).
  * Rilonacept (Arcalyst) and canakinumab (Ilaris) have FDA marketing approval for this use.
- Because CAPS is so rare, it has been difficult to conduct reliable scientific studies.
- There have been no head-to-head trials comparing the efficacy of anakinra (Kineret), rilonacept (Arcalyst), or canakinumab (Ilaris) against each other or any other medication in the management of CAPS.
- The most common periodic syndrome is FMF, which mainly affects people of Eastern Mediterranean ancestry. FMF affects 1 in 250 to 1 in 1,000 individuals in these populations. [1]
  * 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.
  * Initial treatment of FMF is with colchicine. Colchicine is primarily effective as a prophylactic treatment for FMF attacks.
- 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. [1]
  * Fever may respond to use of nonsteroidal antiinflammatory drugs (NSAIDs), and glucocorticoids are required to resolve other clinical manifestations of an attack. Off-label treatment with etanercept for patients with frequent and/or severe recurrences has been reported.
- 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. [2]

    * NSAIDs and glucocorticoids are used to treat the fever and accompanying symptoms. Case reports of treatment with etanercept, anakinra, and tocilizumab have been reported in the literature.
- Canakinumab (Ilaris) received an indication for the treatment of systemic juvenile idiopathic arthritis (SJIA) in May 2013. It has been shown to improve signs and symptoms of SJIA, as measured by the adapted JIA American College of Rheumatology (ACR) 30 response.
- The majority of patients included in clinical trials of canakinumab (Ilaris) for SJIA were receiving methotrexate and prednisone at the time of study enrollment, and > 50% of patients had prior treatment with a biologic (e.g. anakinra, tocilizumab, anti-TNF agents or other biologics).
- It is unknown how the efficacy of canakinumab (Ilaris) compares to other treatments for SJIA.
    * Tocilizumab (Actemra) is an intravenously infused biologic medication that is also FDA-approved for the treatment of SJIA. It has also been shown to improve ACR 30 response in patients with SJIA.
    * Anakinra (Kineret) is another subcutaneously administered biologic medication used for the treatment of SJIA. It has also been shown to improve ACR 30 response.
    * Consensus guidelines from the Childhood Arthritis Rheumatology and Research Alliance endorse the use of both tocilizumab (Actemra) and anakinra (Kineret) in the management of SJIA. [3]
- For Regence Pharmacy Services members, tocilizumab (Actemra) and anakinra (Kineret) provide the best value among biologic medications used to treat SJIA.

Clinical Efficacy

<u>CAPS</u>

- One clinical trial evaluated the effectiveness of canakinumab (Ilaris) in 35 patients with CAPS. In phase 1, all patients received a single dose of canakinumab [4]. Those who remained relapse-free after 8 weeks and elected to continue (n=31) were then randomized to receive canakinumab (Ilaris) 150 mg SC ever 8 weeks (n=15) or placebo (n=16) for up to 24 weeks. Any patient who relapsed or completed 24 weeks of therapy was then enrolled in an open-label, follow-on trial for at least two doses and up to 52 weeks of therapy. [4]
- Of the 35 patients initially enrolled, 34 remained relapse-free for 8 weeks. [4].
- During the double-blinded, randomized phase, all subjects in the canakinumab (Ilaris) group remained relapse-free versus 29% of subjects in placebo group at 24 weeks (100% vs 29%, $p < 0.001$, NNT = 2). [4]
- Changes in laboratory markers of inflammatory disease (CRP and SAA) were supportive of clinical findings. [4]

FMF, TRAPS, HIDS/MKD

- The efficacy of canakinumab (Ilaris) for the treatment of FMF, TRAPS, HIDS/MKD was demonstrated in a 4-part study consisting of three separate disease cohorts (FMF, TRAPS, HIDS/MKD). [5]
- Patients in each cohort entered a 12-week screening period (part 1) during which they were evaluated for the onset of disease flare. Patients aged 2 to 76 years were then randomized at flare onset into a 16-week double-blind, placebo-controlled treatment period (part 2) where they received either 150 mg canakinumab (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks. Additional doses of canakinumab were permitted for patients whose disease flare did not resolve, or who had persistent disease activity. Part 3 and part 4 of the study are ongoing. [5]
- For the primary efficacy endpoint, canakinumab was more effective than placebo in the proportion of patients with FMF, TRAPS, and HIDS/MKD who resolved their disease flare at day 15 and had no new flare over the 16 weeks of treatment from the time of resolution of the index flare. [5]

SJIA

- The efficacy of canakinumab for treating SJIA was evaluated in two randomized trials.
    * Study 1 was a 29-day trial in which 84 patients were randomized to receive a single dose of canakinumab (Ilaris) or placebo. The primary endpoint evaluated was the adapted JIA ACR 30 response, defined as the absence of fever plus a ≥ 30% improvement in three or more of six variables in the JIA core set at day 15. [6]
        - There were significantly more ACR 30 responses at day 15 in the canakinumab-treated group than the placebo treated group (84% vs 10%, respectively; $p < 0.001$). These responses were sustained through day 29.
        - More than 90% of placebo-treated patients discontinued treatment due to lack of efficacy vs 14% of canakinumab-treated patients.
    * Study 2 consisted of an open-label phase in which patients were treated with canakinumab (Ilaris) every four weeks for 12 to 32 weeks, and a withdrawal phase in which patients with at least a JIA ACR 50 (absence of fever plus a ≥ 50% improvement in three or more of six variables in the JIA core set) in the open-label phase were randomized to continue canakinumab (Ilaris) or receive placebo. [6]
        - Of the 177 patients enrolled in Study 2, 71 were rolled over from Study 1 who either had a JIA ACR 30 response at day 15 or discontinued placebo treatment due to lack of efficacy. One hundred patients entered with withdrawal phase of the study.
        - The primary efficacy endpoint evaluated was time to flare of systemic JIA. The median time to flare was 236 days in the placebo group and had not yet been reached in the canakinumab group ($p = 0.003$).

- There is no evidence comparing the safety and efficacy of canakinumab to other treatments for SJIA.

Safety [5]

- The most common adverse reactions reported by patients with CAPS who were treated with canakinumab are nasopharyngitis, diarrhea, influenza, headache and nausea. [4]
- The most common adverse reactions reported in patients with FMF, TRAPS, and HIDS/MKD were injection site reactions and nasopharyngitis.
- The most commonly reported adverse reactions in patients with SJIA were infection, abdominal pain, and injection site reactions.
- Serious adverse events include an increased incidence of serious infections and vertigo. [4]

Dosing [5]

CAPS

- For the treatment of CAPS, canakinumab is administered every eight weeks as a single dose via subcutaneous injection.
    - The recommended dose of canakinumab is 150 mg for CAPS patients with body weight greater than 40 kg.
    - For CAPS patients with body weight between 15 kg and 40 kg, the recommended dose is 2 mg/kg.
    - For children 15 to 40 kg with an inadequate response, the dose can be increased to 3 mg/kg.

FMF, TRAPS, HIDS/MKD

- For the treatment of FMF, TRAPS, or HIDS/MKD, the dose of canakinumab (Ilaris) is 2 mg/kg administered every 4 weeks for patients with body weight ≤ 40 kg. The dose can be increased to 4 mg/kg every 4 weeks if the clinical response is not adequate.
- For patients with body weight > 40 kg, the recommended dose is 150 mg administered every 4 weeks. The dose can be increased to 300 mg every 4 weeks if the clinical response is not adequate.

SJIA

- For the treatment of SJIA, the dose of canakinumab (Ilaris) is 4 mg/kg administered every four weeks as a subcutaneous injection for patients with body weight ≥ 7.5 kg.
- The maximum dose of canakinumab for the treatment of SJIA is 300 mg.
- There are no dosing recommendations for patients with body weight < 7.5 mg.

Other Uses

- Several studies have evaluated the use of canakinumab (Ilaris) for treating acute gouty arthritis.
    * A Cochrane systematic review concluded that there is moderate-quality evidence that canakinumab (Ilaris) 150 mg probably results in better pain relief, joint swelling and participant-assessed global assessment of treatment response in people with an acute gout flare compared to a sub-optimal dose of intramuscular triamcinolone, It is also probably associated with an increased risk of adverse events. There are no studies comparing canakinumab with more commonly used first-line therapies for acute gout flares such as NSAIDs or colchicine. [7]
    * Canakinumab was studied in a 16-week randomized, double-blind, double-dummy, dose-ranging study against colchicine in 432 patients with acute gouty arthritis. The results suggest that canakinumab is superior to daily colchicine for prophylaxis against gouty arthritis flares. There are some flaws affecting the validity and generalizability of the results, including that < 5% of the study subjects were from North America, and the dose of colchicine studied was lower than the labeled dose for prophylaxis. [8]
    * Canakinumab was also studied in two 12-week phase III, double-blind, active-controlled studies against triamcinolone acetate in 456 patients with acute gouty arthritis for whom NSAIDs and colchicine were ineffective or not tolerated. The results suggest that canakinumab may provide significant pain and inflammation relief compared to triamcinolone. These studies assessed single doses over a short period of time, so it is unclear if the reported benefit is sustained over time. [3]
- Canakinumab (Ilaris) has been in patients with previous myocardial infarction (MI) and a high blood level of C-reactive protein. In a phase 3, randomized, placebo-controlled trial, treatment with canakinumab (Ilaris) 150 mg and 300 reduced the primary composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. While promising, additional information is needed to clarify the risk-benefit profile of the drug as the magnitude of benefit is relatively small and canakinumab (Ilaris) had a significantly higher risk of serious infection and sepsis compared to placebo. [9]
- Canakinumab (Ilaris) is also currently being studied in multiple conditions including diabetes mellitus and rheumatoid arthritis. Results from these studies are not yet available.

Cross References
Arcalyst®, rilonacept, Medication Policy Manual,dru159
Actemra®, tocilizumab, Medication Policy Manual, dru209
Kineret®, anakinra, Medication Policy Manual, dru049

Codes	Number	Description
HCPCS	J0638	Injection, canakinumab, 1 mg

References

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Revision History

Revision Date	Revision Summary
9/8/2017	• Clarified age range for FMF, TRAPS, HIDS/MKD indications • Added atherosclerotic disease as an investigational use
01/13/2017	Addition of coverage criteria for FMF, TRAPS, HIDS/MKD
10/21/2016	No criteria changes with this annual review.