UnitedHealthcare Community Plan

UnitedHealthcare® Community Plan
Medical Benefit Drug Policy

ILARIS® (CANAKINUMAB)

Policy Number: CSLA2020D0066E **Effective Date**: TBD

Instructions for Use

Table of Contents **Page**

Commercial Policy
- Ilaris® (Canakinumab)

APPLICATION

This Medical Benefit Drug Policy only applies to the state of Louisiana.

COVERAGE RATIONALE

Ilaris (canakinumab) is proven and medically necessary for: [1]

I. **The treatment of cryopyrin-associated periodic syndromes (CAPS) in patients who meet ALL of the following criteria**:
   A. For initial therapy, **all** of the following:
      1. One of the following, as diagnosed by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of the following:
         a. Familial cold autoinflammatory syndrome (FCAS)
         b. Muckle-Wells syndrome (MWS);
         and
      2. Ilaris dosing for FCAS/MWS is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 3mg/kg up to 150 mg every 8 weeks; **and**
      3. Initial authorization will be for no more than 12 months.
   B. For continuation of therapy, **all** of the following:
      1. Patient is currently on Ilaris therapy for one of the following:
         a. FCAS
         b. MWS;
         and
      2. Ilaris dosing for FCAS/MWS is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 3mg/kg up to 150 mg every 8 weeks; **and**
      3. Documentation of positive clinical response to Ilaris therapy; **and**
      4. Reauthorization will be for no more than 12 months.

II. **The treatment of tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) in patients who meet ALL of the following criteria**:
   A. For initial therapy, **all** of the following:
      1. Diagnosis of TRAPS by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of TRAPS; **and**
      2. Ilaris dosing for TRAPS is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
      3. Initial authorization will be for no more than 12 months.
   B. For continuation of therapy, **all** of the following:
      1. Patient is currently receiving Ilaris therapy for TRAPS; **and**
      2. Documentation of a positive clinical response to therapy, defined as a decrease in frequency or severity of attacks; **and**
      3. Ilaris dosing for TRAPS is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
      4. Reauthorization will be for no more than 12 months.

III. **The treatment of hyperimmunoglobulin D (Hyper-IgD) syndrome (HIDS) / mevalonate kinase deficiency (MKD) in patients who meet ALL of the following criteria**:
   A. For initial therapy, **all** of the following:
      1. One of the following, as diagnosed by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of the following:
         a. HIDS
         b. MKD;
         and
      2. Ilaris dosing for HIDS/MKD is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
      3. Initial authorization will be for no more than 12 months.
   B. For continuation of therapy, **all** of the following:
      1. Patient is currently receiving Ilaris for one of the following:
         a. HIDS
         b. MKD;
         and
      2. Documentation of a positive clinical response to therapy, defined by a decrease in frequency or severity of attacks; **and**
      3. Ilaris dosing for HIDS/MKD is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
      4. Reauthorization will be for no more than 12 months.

IV. **The treatment of familial mediterranean fever (FMF) in patients who meet ALL of the following criteria**:
   A. For initial therapy, **all** of the following:
      1. Diagnosis of FMF by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of FMF; **and**
      2. History of failure, contraindication, or intolerance to colchicine; **and**
      3. Ilaris dosing for FMF is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
      4. Initial authorization will be for no more than 12 months.
   B. For continuation of therapy, **all** of the following:
      1. Patient is currently receiving Ilaris for FMF; **and**
      2. Documentation of a positive clinical response to therapy, defined by a decrease in index disease flare or normalization of CRP; **and**
      3. Ilaris dosing for FMF is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
      4. Reauthorization will be for no more than 12 months.

V. **The treatment of systemic juvenile idiopathic arthritis (SJIA) in patients who meet ALL of the following criteria**:
   A. For initial therapy, **all** of the following:

1. Diagnosis of SJIA by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of SJIA; **and**
2. Ilaris dosing for SJIA is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
3. Patient is not receiving Ilaris in combination with another biologic (e.g., Actemra); **and**
4. Initial authorization will be for no more than 12 months.

B. For continuation of therapy, **all** of the following:
1. Patient is currently receiving Ilaris for SJIA; **and**
2. Documentation of a positive clinical response to therapy; **and**
3. Ilaris dosing for SJIA is in accordance with the United States Food and Drug Administration approved labeling: maximum dosing of 4 mg/kg up to 300mg every 4 weeks; **and**
4. Patient is not receiving Iliaris in combination with another biologic (e.g., Actemra); **and**
5. Reauthorization will be for no more than 12 months.

Ilaris is not proven or medically necessary for the management or treatment of cardiovascular disease.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Coverage Determination Guidelines may apply.

HCPCS Code	Description
J0638	Injection, canakinumab, 1 mg

ICD-10 Diagnosis Code	Description
M04.1	Periodic fever syndromes
M04.2	Cryopyrin-associated periodic syndromes
M08.20	Juvenile rheumatoid arthritis with systemic onset, unspecified site
M08.211	Juvenile rheumatoid arthritis with systemic onset, right shoulder
M08.212	Juvenile rheumatoid arthritis with systemic onset, left shoulder
M08.219	Juvenile rheumatoid arthritis with systemic onset, unspecified shoulder
M08.221	Juvenile rheumatoid arthritis with systemic onset, right elbow
M08.222	Juvenile rheumatoid arthritis with systemic onset, left elbow
M08.229	Juvenile rheumatoid arthritis with systemic onset, unspecified elbow
M08.231	Juvenile rheumatoid arthritis with systemic onset, right wrist
M08.232	Juvenile rheumatoid arthritis with systemic onset, left wrist
M08.239	Juvenile rheumatoid arthritis with systemic onset, unspecified wrist
M08.241	Juvenile rheumatoid arthritis with systemic onset, right hand
M08.242	Juvenile rheumatoid arthritis with systemic onset, left hand
M08.249	Juvenile rheumatoid arthritis with systemic onset, unspecified hand
M08.251	Juvenile rheumatoid arthritis with systemic onset, right hip
M08.252	Juvenile rheumatoid arthritis with systemic onset, left hip
M08.259	Juvenile rheumatoid arthritis with systemic onset, unspecified hip
M08.261	Juvenile rheumatoid arthritis with systemic onset, right knee
M08.262	Juvenile rheumatoid arthritis with systemic onset, left knee
M08.269	Juvenile rheumatoid arthritis with systemic onset, unspecified knee

ICD-10 Diagnosis Code	Description
M08.271	Juvenile rheumatoid arthritis with systemic onset, right ankle and foot
M08.272	Juvenile rheumatoid arthritis with systemic onset, left ankle and foot
M08.279	Juvenile rheumatoid arthritis with systemic onset, unspecified ankle and foot
M08.28	Juvenile rheumatoid arthritis with systemic onset, vertebrae
M08.29	Juvenile rheumatoid arthritis with systemic onset, multiple sites

BACKGROUND

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene. CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis. [1]

The NLRP-3 gene encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of IL-1β. Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1β that drives inflammation. SJIA is a severe autoinflammatory disease, driven by innate immunity by means of proinflammatory cytokines such as IL-1β. [1]

Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. It is expressed in a murine Sp2/0-Ag14 cell line and comprised of two 447- (or 448-) residue heavy chains and two 214-residue light chains, with a molecular mass of 145157 Daltons when deglycosylated. Both heavy chains of canakinumab contain oligosaccharide chains linked to the protein backbone at asparagine 298. The biological activity of canakinumab is measured by comparing its inhibition of IL-1β-dependent expression of the reporter gene luciferase to that of a canakinumab internal reference standard, using a stably transfected cell line. [1]

Canakinumab binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, but it does not bind IL-1α or IL-1 receptor antagonist (IL-1ra). [1]

CLINICAL EVIDENCE

Cryopyrin-Associated Periodic Syndromes

Kuemmerle-Deschner et al (2011) assessed the long-term safety and tolerability of canakinumab in a multinational, open-label, single treatment arm study in in patients with cryopyrin-associated periodic syndrome. [2] In this study, adult and pediatric patients received canakinumab every 8 weeks for up to two years. The 166 patients included canakinumab-naïve, as well as treatment experienced patients from previous studies. C-reactive protein (CRP), serum amyloid A (SAA) levels, disease activity, and/or skin rash were used to assess response to therapy. In the study, 85 of 109 canakinumab-naive patients (78%; 79/85 patients within 8 days, and five patients between days 10 and 21) achieved complete response. In the 141 patients who were assessed for relapse, 90% did not relapse, and experienced normalization of CRP/SAA levels (<10 mg/l) by day 8, which were sustained. Treatment duration ranged from 29-687 days, with a median of 414 days. Of the population, 24.1% of patients received dose increase or frequency adjustments. The most common adverse events were infections (65.7%). In addition, 18 (10.8%) patients experienced serious adverse events, which were mostly infections that responded to standard care. Regarding injection site reactions, 92% reported no injection-site reaction, while 8% reported mild-to-moderate reactions. Normal immune response was seen in patients receiving a vaccine (15%). The investigators concluded that canakinumab 150 mg every 8 weeks was well tolerated and provided substantial disease control in children and adults across all CAPS phenotypes. Higher canakinumab doses in younger patients and more severe CAPS disease were efficacious in achieving complete responses without evidence of increased adverse events. [2]

Lachmann et al (2009) evaluated the use of use of canakinumab in the cryopyrin- associated periodic syndrome in a three-part, 48-week, double-blind, placebo-controlled, randomized withdrawal study of canakinumab in patients with CAPS. [3] In the first part 1 of the study, 35 patients received 150 mg of canakinumab subcutaneously. Patients

experiencing a complete response to therapy were enrolled in part 2, where they received either 150 mg of canakinumab or placebo every 8 weeks for up to 24 weeks, based on random group assignment. Patients were moved to part 3 upon completion of part 2 or at the time of relapse, whichever occurred first. In part 3, patients received at least two more doses of canakinumab. Therapeutic responses using disease-activity scores and analysis of levels of C-reactive protein (CRP) and serum amyloid A protein (SAA) were used for evaluation. In part 1 of the study, complete response was achieved by 34 out of 35 patients (97%). Form part 1, 31 patents moved to part 2, and all 15 patients receiving canakinumab remained in remission. For patients in the placebo group, 13 of the 16 patients (81%) (P<0.001) experienced disease flares. At the end of part 2, Median CRP and SAA values were normal (<10 mg per liter for both measures) in patients receiving canakinumab at the end of part 2. For the placebo group median CRP and SAA values were elevated (P<0.001 and P = 0.002, respectively). Of the 31 patients, 28 (90%) remained in remission at the close of part 3. Specific to adverse events, there was a higher incidence of suspected infections in the treatment group compared to the placebo group (P = 0.03), as well as two serious adverse events in the treatment group, one case of urosepsis and an episode of vertigo. [3]

Familial Mediterranean Fever, Hyperimmunoglobulin D (Hyper-IgD) Syndrome / Mevalonate Kinase Deficiency and Tumor Necrosis Factor Receptor Associated Periodic Syndrome

The efficacy and safety of Ilaris for the treatment of TRAPS, HIDS/MKD, and FMF were demonstrated in a randomized, double-blind, placebo-controlled study of canakinumab in patients with FMF, HIDS/MKD or TRAPS. [7] The study followed 3 randomized groups (FMF, HIDS/MKD, TRAPS) over 4 Epochs as follow: a 12 week lead in period, randomization at flare onset, to a blinded or open-label treatment group, a randomized withdrawal of 24 weeks, followed by an open-label treatment of 72 weeks. The proportion of patients who were responders for the primary outcome at week 16 was significantly higher with canakinumab than that with placebo for all 3 disease cohorts. The median duration of exposure to canakinumab (150 mg every 4 weeks) and placebo was 113 days (range: 110-129 days) and 113 days (range: 12-119 days), respectively, for all disease cohorts. Regarding adverse events, infections and infestations were the most frequently affected system organ class across the 3 cohorts, with the most common infection being upper respiratory tract infection. The investigators concluded that the results demonstrate canakinumab had a higher rate, compared with placebo in the proportion of patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment.

Ahmet et al conducted an open-label pilot study to investigate the efficacy of canakinumab in FMF patients. [6] Patients taking colchicine experiencing ore or more attach per month in the most recent 3 months were eligible to enter a 30-day run-in period. Patients experiencing an attack during the first run-in period moved to a second 30-day period, where they received canakinumab upon their first attack, 150mg subcutaneously every 4 weeks. The dose was increased to 300 mg, if a patient experienced an attack between the first and second doses. Patients were permitted to remain on their current dose of colchicine throughout the study. After 12 weeks of treatment, patients were followed for an additional 2 months or until the next attack happened. All the included patients, in the treatment period achieved the primary endpoint of ≥50 % reduction in frequency of attacks compared with the time-adjusted pre-treatment frequency of attacks. The time-adjusted frequency of attacks over 84 days observed both in the screening and run-in periods, including the baseline attack (median 3.29, range 2.47 to 4.2), saw a steep decrease during the treatment period (median 0, mean 0.11). 5 of the patients receiving 2 mg/day colchicine, experienced an attack within the 2-month follow up, which occurred at a range of 31 to 78 days (median 71 days) after the last canakinumab injection.

Systemic Juvenile Idiopathic Arthritis

Ruperto et al conducted an open-label active treatment extension study, which enrolled SJIA patients, previously treated with canakinumab in phase III trials as well as those who did not. [8] Patients received canakinumab (4 mg/kg) subcutaneously every 4 weeks. In the trial, the proportion of patients with inactive disease increased over time, from 32.7% at baseline to 49.0% at the last assessment. The most frequently affected system organ class was infections, with nasopharyngitis being the most common event at 32%. The investigators concluded that in patients previously treated with canakinumab in pivotal trials, response to treatment was sustained or improved during long-term treatment in the extension study.

Ruperto et al conducted 2 phase 3, randomized, double-blind, placebo controlled trials to evaluate the efficacy and safety of canakinumab for the treatment of SJIA. [4] In trial 1, patients aged 2-19 years, with systemic JIA with active systemic features (fever; ≥2 active joints; C-reactive protein, >30 mg per liter; and glucocorticoid dose, ≤1.0 mg per kilogram of body weight per day), were randomly assigned in a double-blind fashion, to a single subcutaneous dose of canakinumab (4 mg per kilogram) or placebo. The study used the adapted JIA ACR 30 response and the primary

outcome, which was defined as improvement of 30% or more in at least three of the six core criteria for JIA, worsening of more than 30% in no more than one of the criteria, and resolution of fever. In trial 2, after 32 weeks of open-label treatment with canakinumab, patients who had a response and underwent glucocorticoid tapering were randomly assigned to continued treatment with canakinumab or to placebo. The primary outcome was time to flare of SJIA. For trial 1, 36 of 43 (84%) patients had an adapted JIA ACR 30 response at day 15 compared to the placebo group, for which 4 of 41 (10%) P<0.001 patients had an adapted JIA ACR 30 response at day 15. In trial 2, among the 100 patients (of 177 in the open-label phase) who underwent randomization in the withdrawal phase, the risk of flare was lower among patients who continued to receive canakinumab than among those who were switched to placebo (74% of patients in the canakinumab group had no flare, vs. 25% in the placebo group, according to Kaplan–Meier estimates; hazard ratio, 0.36; P = 0.003). Regarding glucocorticoids, use was discontinued in 33% of patients (42 of 128) and the average dose decreased to 0.05 mg per kilogram per day from 0.34 mg per kilogram per day. Seven patients experienced macrophage activation syndrome. The patients receiving canakinumab had a higher frequency of infection than with placebo. The investigators concluded that these two phase 3 studies show efficacy of canakinumab in systemic JIA with active systemic features.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Ilaris is indicated for the treatment of 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). Ilaris is also indicated for the treatment of tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) in adult and pediatric patients, hyperimmunoglobulin D (Hyper-IgD) syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients, familial mediterranean fever (FMF) in adult and pediatric patients, and active systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older. [1]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for Ilaris® (canakinumab). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed July 26, 2019)

~~Medicare does not have a National Coverage Determination (NCD) for Ilaris® (canakinumab). Local Coverage Determinations (LCDs) do not exist at this time.~~

~~In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals.~~
~~(Accessed June 13, 2018)~~

REFERENCES

1. Ilaris [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation, December 2016.
2. Kuemmerle-Deschner JB, Hachulla E, Cartwright R. Two-year results from an open-label, multicentre, phase III study evaluating the safety and effi cacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes. Ann Rheum Dis 2011;70:2095–2102.
3. Lachmann JH, Kone-Paut I, Kuemmerle-Deschner JB. Use of canakinumab in the Cryopyrin-Associated Periodic Syndrome. N Engl J Med. 2009; 360(23):2416-25.
4. Ruperto N, Brunner H I, Quartier P, Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. NEngl J Med 2012; 367:2396-406.
5. Novartis Pharmaceuticals. A Study of Canakinumab in Patients With Systemic Juvenile Idiopathic Arthritis or Hereditary Periodic Fevers Who Participated in the CACZ885G2301E1, CACZ885G2306 or CACZ885N2301 Studies. In ClinicalTrials.gov [Internet]. Bethesda (MD): National Library o fMedicine (US). 2014- [cited 2017 July 6]. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02334748 NLM Identifier: NCT 02334748

6. Ahmet Gül, Huri Ozdogan, Burak Erer, Efficacy and safety of canakinumab in adolescents and adults with colchicine resistant familial Mediterranean fever. Arthritis Research & Therapy (2015) 17:243
7. De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. N Engl J Med. 2018 May 17;378(20):1908-1919.
8. Open label extension study. Data on File. Novartis Pharmaceuticals Corporation; East Hanover, NJ.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
TBD	• **Annual review. Updated CMS statement.**

INSTRUCTIONS FOR USE

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.