Ilaris® (Canakinumab)

Policy Number: 2026D0066M
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➲ Instructions for Use

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Related Commercial Policy
- Provider Administered Drugs – Site of Care

Community Plan Policy
- Ilaris® (Canakinumab)

Application

UnitedHealthcare Commercial

This Medical Benfit Drug Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Benefit Drug Policy applies to Individual Exchange benefit plans.

Coverage Rationale

➲ See Benefit Considerations

Cryopyrin-Associated Periodic Syndromes (CAPS) Including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)

Ilaris® (canakinumab) is proven for the treatment of Cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS).

Ilaris is medically necessary for the treatment of Cryopyrin-associated periodic syndromes (CAPS) including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) when all of the following criteria are met:

- For **initial therapy**, **all** of the following:
  - One of the following, as diagnosed by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of the following:
    - FCAS; **or**
    - MWS

    and
  - Ilaris dosing for FCAS/MWS is in accordance with the U.S. Food and Drug Administration (FDA)–approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Patient is currently on Ilaris therapy for one of the following:
    - FCAS; **or**
    - MWS

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and
- Ilaris dosing for FCAS/MWS is in accordance with the FDA-approved labeling; **and**
- Documentation of positive clinical response to Ilaris therapy; **and**
- Reauthorization will be for no more than 12 months

Tumor Necrosis Factor (TNF) Receptor-Associated Periodic Syndrome (TRAPS)

Ilaris is proven for the treatment of tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS).

Ilaris is medically necessary for the treatment of tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) when all of the following criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of TRAPS by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of TRAPS; **and**
  - Ilaris dosing for TRAPS is in accordance with the FDA-approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Patient is currently receiving Ilaris therapy for TRAPS; **and**
  - Documentation of a positive clinical response to therapy; **and**
  - Ilaris dosing for TRAPS is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)

Ilaris is proven for the treatment of hyperimmunoglobulin D (Hyper-IgD) syndrome (HIDS)/mevalonate kinase deficiency (MKD).

Ilaris is medically necessary for the treatment of hyperimmunoglobulin D (Hyper-IgD) syndrome (HIDS)/mevalonate kinase deficiency (MKD) when all of the following criteria are met:

- For **initial therapy**, **all** of the following:
  - One of the following, as diagnosed by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of the following:
    - HIDS; **or**
    - MKD

    and
  - Ilaris dosing for HIDS/MKD is in accordance with the FDA-approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Patient is currently receiving Ilaris for one of the following:
    - HIDS; **or**
    - MKD

    and
  - Documentation of a positive clinical response to therapy; **and**
  - Ilaris dosing for HIDS/MKD is in accordance with the FDA-approved labeling; **and**
  - Reauthorization will be for no more than 12 months

Familial Mediterranean Fever (FMF)

Ilaris is proven for the treatment of Familial Mediterranean fever (FMF).

Ilaris is medically necessary for the treatment of Familial Mediterranean fever (FMF) when all of the following criteria are met:

- For **initial therapy**, **all** of the following:
  - Diagnosis of FMF by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of FMF; **and**
  - History of failure, contraindication, or intolerance to colchicine; **and**
  - Ilaris dosing for FMF is in accordance with the FDA-approved labeling; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Patient is currently receiving Ilaris for FMF; **and**

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- Documentation of a positive clinical response to therapy; **and**
- Ilaris dosing for FMF is in accordance with the FDA-approved labeling; **and**
- Reauthorization will be for no more than 12 months

Active Still's Disease Including Adult-Onset Stills's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA)

Ilaris is proven for the treatment of active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA).

Ilaris is medically necessary for the treatment of active Still's disease including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) when all of the following criteria are met:

- For **initial therapy**, **all** of the following:
  - One of the following, as diagnosed by, or in consultation with, a rheumatologist or immunologist with expertise in the diagnosis of the following:
    - AOSD; **or**
    - SJIA

    and
  - Ilaris dosing for AOSD/SJIA is in accordance with the FDA-approved labeling; **and**
  - Patient is not receiving Ilaris in combination with another systemic targeted immunomodulator [e.g., adalimumab, Cimzia (certolizumab), Enbrel (etanercept), Olumiant (baricitinib), Orencia (abatacept), Rinvoq (upadacitinib), Simponi (golimumab), Xeljanz (tofacitinib)] for treatment of the same indication; **and**
  - Initial authorization will be for no more than 12 months
- For **continuation of therapy**, **all** of the following:
  - Patient is currently receiving Ilaris for AOSD/SJIA; **and**
  - Documentation of a positive clinical response to therapy; **and**
  - Ilaris dosing for AOSD/SJIA is in accordance with the FDA-approved labeling; **and**
  - Patient is not receiving Ilaris in combination with another systemic targeted immunomodulator [e.g., adalimumab, Cimzia (certolizumab), Enbrel (etanercept), Olumiant (baricitinib), Orencia (abatacept), Rinvoq (upadacitinib), Simponi (golimumab), Xeljanz (tofacitinib)] for treatment of the same indication; **and**
  - Reauthorization will be for no more than 12 months

Gout Flares

Ilaris is proven for the treatment of gout flares when all of the following criteria are met:

- Diagnosis of a gout flare; **and**
- History of contraindication, intolerance, or treatment failure with **both** of the following:
  - Colchicine; **and**
  - Non-steroidal anti-inflammatory drugs (NSAIDs)

  and
- Provider attests that the patient is not an appropriate candidate for systemic corticosteroids; **and**
- Ilaris dosing is in accordance with the FDA-labeled dosing for gout flares; **and**
- Authorization will be issued for one dose for 12 weeks

Ilaris is medically necessary for the treatment of gout flares when all of the following criteria are met:

- Diagnosis of a gout flare; **and**
- History of contraindication, intolerance, or treatment failure with **both** of the following:
  - Colchicine; **or**
  - Non-steroidal anti-inflammatory drugs (NSAIDs)

  and
- Provider attests that the patient is not an appropriate candidate for systemic corticosteroids; **and**
- Prescribed by one of the following:
  - Rheumatologist; **or**
  - Nephrologist

  and
- Ilaris dosing is in accordance with the FDA-labeled dosing for gout flares; and
- Authorization will be issued for one dose for 12 weeks

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

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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 the member specific benefit plan document 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 guidelines may apply.

HCPCS Code	Description
J0638	Injection, canakinumab, 1 mg

Diagnosis Code	Description
M04.1	Periodic fever syndromes
M04.2	Cryopyrin-associated periodic syndromes
M06.1	Adult-onset Still's disease
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
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
M08.2A	Juvenile rheumatoid arthritis with systemic onset, other specified site
M10.00	Idiopathic gout, unspecified site
M10.011	Idiopathic gout, right shoulder
M10.012	Idiopathic gout, left shoulder
M10.019	Idiopathic gout, unspecified shoulder
M10.021	Idiopathic gout, right elbow
M10.022	Idiopathic gout, left elbow
M10.029	Idiopathic gout, unspecified elbow
M10.031	Idiopathic gout, right wrist

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Diagnosis Code	Description
M10.032	Idiopathic gout, left wrist
M10.039	Idiopathic gout, unspecified wrist
M10.041	Idiopathic gout, right hand
M10.042	Idiopathic gout, left hand
M10.049	Idiopathic gout, unspecified hand
M10.051	Idiopathic gout, right hip
M10.052	Idiopathic gout, left hip
M10.059	Idiopathic gout, unspecified hip
M10.061	Idiopathic gout, right knee
M10.062	Idiopathic gout, left knee
M10.069	Idiopathic gout, unspecified knee
M10.071	Idiopathic gout, right ankle and foot
M10.072	Idiopathic gout, left ankle and foot
M10.079	Idiopathic gout, unspecified ankle and foot
M10.08	Idiopathic gout, vertebrae
M10.09	Idiopathic gout, multiple sites
M10.10	Lead-induced gout, unspecified site
M10.111	Lead-induced gout, right shoulder
M10.112	Lead-induced gout, left shoulder
M10.119	Lead-induced gout, unspecified shoulder
M10.121	Lead-induced gout, right elbow
M10.122	Lead-induced gout, left elbow
M10.129	Lead-induced gout, unspecified elbow
M10.131	Lead-induced gout, right wrist
M10.132	Lead-induced gout, left wrist
M10.139	Lead-induced gout, unspecified wrist
M10.141	Lead-induced gout, right hand
M10.142	Lead-induced gout, left hand
M10.149	Lead-induced gout, unspecified hand
M10.151	Lead-induced gout, right hip
M10.152	Lead-induced gout, left hip
M10.159	Lead-induced gout, unspecified hip
M10.161	Lead-induced gout, right knee
M10.162	Lead-induced gout, left knee
M10.169	Lead-induced gout, unspecified knee
M10.171	Lead-induced gout, right ankle and foot
M10.172	Lead-induced gout, left ankle and foot
M10.179	Lead-induced gout, unspecified ankle and foot
M10.18	Lead-induced gout, vertebrae
M10.19	Lead-induced gout, multiple sites
M10.20	Drug-induced gout, unspecified site
M10.211	Drug-induced gout, right shoulder
M10.212	Drug-induced gout, left shoulder
M10.219	Drug-induced gout, unspecified shoulder
M10.221	Drug-induced gout, right elbow

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Diagnosis Code	Description
M10.222	Drug-induced gout, left elbow
M10.229	Drug-induced gout, unspecified elbow
M10.231	Drug-induced gout, right wrist
M10.232	Drug-induced gout, left wrist
M10.239	Drug-induced gout, unspecified wrist
M10.241	Drug-induced gout, right hand
M10.242	Drug-induced gout, left hand
M10.249	Drug-induced gout, unspecified hand
M10.251	Drug-induced gout, right hip
M10.252	Drug-induced gout, left hip
M10.259	Drug-induced gout, unspecified hip
M10.261	Drug-induced gout, right knee
M10.262	Drug-induced gout, left knee
M10.269	Drug-induced gout, unspecified knee
M10.271	Drug-induced gout, right ankle and foot
M10.272	Drug-induced gout, left ankle and foot
M10.279	Drug-induced gout, unspecified ankle and foot
M10.28	Drug-induced gout, vertebrae
M10.29	Drug-induced gout, multiple sites
M10.30	Gout due to renal impairment, unspecified site
M10.311	Gout due to renal impairment, right shoulder
M10.312	Gout due to renal impairment, left shoulder
M10.319	Gout due to renal impairment, unspecified shoulder
M10.321	Gout due to renal impairment, right elbow
M10.322	Gout due to renal impairment, left elbow
M10.329	Gout due to renal impairment, unspecified elbow
M10.331	Gout due to renal impairment, right wrist
M10.332	Gout due to renal impairment, left wrist
M10.339	Gout due to renal impairment, unspecified wrist
M10.341	Gout due to renal impairment, right hand
M10.342	Gout due to renal impairment, left hand
M10.349	Gout due to renal impairment, unspecified hand
M10.351	Gout due to renal impairment, right hip
M10.352	Gout due to renal impairment, left hip
M10.359	Gout due to renal impairment, unspecified hip
M10.361	Gout due to renal impairment, right knee
M10.362	Gout due to renal impairment, left knee
M10.369	Gout due to renal impairment, unspecified knee
M10.371	Gout due to renal impairment, right ankle and foot
M10.372	Gout due to renal impairment, left ankle and foot
M10.379	Gout due to renal impairment, unspecified ankle and foot
M10.38	Gout due to renal impairment, vertebrae
M10.39	Gout due to renal impairment, multiple sites
M10.40	Other secondary gout, unspecified site
M10.411	Other secondary gout, right shoulder

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Diagnosis Code	Description
M10.412	Other secondary gout, left shoulder
M10.419	Other secondary gout, unspecified shoulder
M10.421	Other secondary gout, right elbow
M10.422	Other secondary gout, left elbow
M10.429	Other secondary gout, unspecified elbow
M10.431	Other secondary gout, right wrist
M10.432	Other secondary gout, left wrist
M10.439	Other secondary gout, unspecified wrist
M10.441	Other secondary gout, right hand
M10.442	Other secondary gout, left hand
M10.449	Other secondary gout, unspecified hand
M10.451	Other secondary gout, right hip
M10.452	Other secondary gout, left hip
M10.459	Other secondary gout, unspecified hip
M10.461	Other secondary gout, right knee
M10.462	Other secondary gout, left knee
M10.469	Other secondary gout, unspecified knee
M10.471	Other secondary gout, right ankle and foot
M10.472	Other secondary gout, left ankle and foot
M10.479	Other secondary gout, unspecified ankle and foot
M10.48	Other secondary gout, vertebrae
M10.49	Other secondary gout, multiple sites
M10.9	Gout, unspecified

Background

Canakinumab is a recombinant, human anti-human-IL-1β monoclonal antibody that belongs to the IgG1/κ isotype subclass. 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).

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 [also known as Cold-Induced Autoinflammatory Syndrome-1 (CIAS1)]. 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.

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.

Gout flares are characterized by activation of resident macrophages and infiltrating neutrophils in the joint, and concomitant overproduction of IL-1β resulting in an acute painful inflammatory response. IL-1β production by macrophages is triggered by uric acid (monosodium urate monohydrate) crystals in the joint and surrounding tissue through activation of the NLRP3 inflammasome complex.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some

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diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

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 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 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%). From 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, 150 mg subcutaneously every 4 weeks. The dose was increased to 300 mg,

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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 and Adult Onset Still's Disease

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.

Kedor et al. conducted a double-blind, randomized placebo-controlled trial to evaluate the efficacy and safety of canakinumab in patients with AOSD and active joint involvement. Patients aged 22-70 years, with high active AOSD were enrolled, with 12 patients in the canakinumab group and 7 patients in the placebo group. The primary outcome was defined as the proportion of patients with a clinically relevant reduction of the articular manifestation measured by change in disease activity score. The study was terminated prematurely, due to the rarity and severity of disease and conditional approval of AOSD by the European Medicines Agency, therefore, only 36 out of the planned 68 patients could be included in the efficacy analysis. The primary endpoint did not achieve statistical significance, however, treatment of patient with AOSD and active joint involvement led to an improvement of ACR30, ACR 50% response and ACR 70% response, as well as disease activity score. The safety profile was similar to that reporting in SJIA. The authors concluded that efficacy data were generally consistent with the results of the pooled efficacy analysis of SJIA patients.[9]

Gout Flares

The efficacy of Ilaris was demonstrated in two 12-week, randomized, double-blind, active-controlled studies in patients 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 patients were treated with ILARIS upon a new flare. In Study 1 (NCT01029652), patients were randomized to receive ILARIS 150 mg subcutaneous (n = 115) or triamcinolone acetonide 40 mg intramuscular (n = 115) at baseline and thereafter treated upon a new flare. Two patients randomized to canakinumab were not included in the analysis as they did not receive any study medication. In Study 2 (NCT01080131), patients were randomized to receive Ilaris 150 mg subcutaneous (n = 112) or triamcinolone acetonide 40 mg intramuscular (n = 114) at baseline and thereafter treated upon a new flare. In Studies 1 and 2, over

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85% of patients had at least one co-morbidity, including hypertension (60%), obesity (53%), diabetes (15%), and ischemic heart disease (12%). Twenty-five percent of patients had chronic kidney disease (stage ≥ 3), based on eGFR. Concomitant treatment with allopurinol or other uric acid lowering therapies was reported by 42% of patients at entry. The majority of patients (73%) reported between 3-6 flares in the year prior to study entry and the remainder reported seven or more flares. Approximately one-third of the patients enrolled [76 in the Ilaris group (33.5%) and 84 in the triamcinolone acetonide (36.7%) group] had documented inability (intolerance, contraindication or lack of response) to use both NSAIDs and colchicine. The remainder had intolerance, contraindication or lack of response to either NSAIDs or colchicine.

In both studies, the co-primary endpoints were: (1) patient's assessment of gout flare pain intensity at the most affected joint at 72 hours post-dose measured on a 0-100 mm visual analogue scale (VAS) and (2) the time to first new gout flare. The studies aimed to determine whether Ilaris 150 mg would be superior to triamcinolone acetonide 40 mg. Study 3 (NCT01356602), an additional 12-week, randomized, double-blind, active-controlled study, enrolled 397 patients with Ilaris 150 mg subcutaneous [Pre-Filled Syringe (PFS), n = 133, Lyophilizate (LYO), n = 132] or triamcinolone acetonide 40 mg intramuscular (n = 132). Eight patients (2 Ilaris PFS, 3 Ilaris LYO, 3 triamcinolone) were not included for efficacy assessment as they did not receive study medication. Pain intensity at the most affected joint, assessed on a 0-100 mm VAS at 72-hours post-dose was the primary endpoint, and time to first new gout flare was a secondary endpoint. Approximately 44% of patients (45.9% Ilaris PFS group, 47.4%, Ilaris LYO group and 40.6% in the triamcinolone acetonide group) were unable to use NSAIDs and colchicine (due to contraindications, intolerance, or inadequate response) in this study. Analyses of both endpoints were conducted for Studies 1, 2, and 3 for the subpopulation of patients unable to use NSAIDs and colchicine (due to contraindications, intolerance, or inadequate response) and overall population of patients unable to use NSAIDs and/or colchicine. In all studies (Study 1, 2, and 3), pain intensity of the most affected joint (0-100 mm VAS) at 72 hours post-dose was consistently lower for patients treated with Ilaris compared with triamcinolone acetonide in the subpopulation of patients unable to use NSAIDs and colchicine. This benefit of Ilaris on pain intensity was comparable to the overall patient populations i.e., patients unable to use NSAIDs and/or colchicine in all three studies. In the subpopulation of patients in Studies 1, 2 and 3 unable to use NSAIDs and colchicine, time to new flare over 12 weeks from randomization showed a reduction in the risk of a new flare when treated with ILARIS compared with triamcinolone acetonide 40 mg. This risk reduction for a new flare after Ilaris treatment versus triamcinolone acetonide was comparable to the overall patient population over 12 weeks in all 3 studies.

Professional Societies

Juvenile Idiopathic Arthritis

In the 2021 American College of Rheumatology *Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis*, biologic DMARDs (IL-1 and IL-6 inhibitors) are conditionally recommended as initial monotherapy for systemic JIA without macrophage activation syndrome (MAS) and there is no preferred agent.[10] NSAIDs are also conditionally recommended as initial monotherapy for systemic JIA without MAS, though only for a small proportion of patients with mild to moderate symptoms. IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of conventional synthetic DMARDs for inadequate response to or intolerance of NSAIDs and/or glucocorticoids. For systemic JIA with MAS, IL-1 and IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS and there is no preferred agent.

Still's Disease

In the 2024 EULAR/PReS recommendations for the diagnosis and management of Still's disease, systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD) are considered the same disease and the preferred unified terminology is Still's disease. The recommendations emphasize rapid diagnosis, shared decision-making, treatment-to-target monitoring, and prompt recognition and management of macrophage activation syndrome (MAS). IL-1 or IL-6 inhibitors are recommended to be initiated as early as possible once the diagnosis is established and are prioritized to avoid prolonged systemic glucocorticoid use. Maintenance of clinically inactive disease for 3 to 6 months without glucocorticoids is recommended before initiating biologic DMARD tapering. Difficult-to-treat patients, patients with severe MAS, and patients with Still's disease-associated lung disease should be managed in collaboration with Still's disease expert centers.

Familial Mediterranean Fever

In the 2024 EULAR/PReS endorsed recommendations for the management of Familial Mediterranean fever (FMF), the treatment goal is to achieve minimal or no clinical activity and complete control of subclinical inflammation to prevent associated damage. Colchicine is recommended to start as soon as a clinical diagnosis is made and remains the cornerstone of lifetime FMF management. In adherent patients with persistent attacks or subclinical inflammation despite colchicine, dose escalation within the recommended range is advised. For adherent patients who do not respond adequately to the maximum tolerated colchicine dose, additional treatment should be considered, with the highest level of

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evidence supporting IL-1-targeting treatments. The recommendations also emphasize regular monitoring of response, toxicity, and adherence, and note that biologic doses may be optimized, with tapering or discontinuation considered if remission is achieved.

Gout

In the 2020 American College of Rheumatology *Guideline for the Management of Gout*, the following recommendations are made for gout flare management:

- For patients experiencing a gout flare, we strongly recommend using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or adrenocorticotropic hormone (ACTH) (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences). When colchicine is the chosen agent, we strongly recommend low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects.
- For patients experiencing a gout flare for whom other anti-inflammatory therapies are poorly tolerated or contraindicated, we conditionally recommend using IL-1 inhibition over no therapy (beyond supportive/analgesic treatment).
- For patients who may receive nothing by mouth (NPO), we strongly recommend glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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 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 Still's disease, including adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 years and older. Ilaris is also indicated for the symptomatic treatment of gout flares in adults in whom non-steroidal anti-inflammatory drugs and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

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Policy History/Revision Information

Date	Summary of Changes

11/01/2026	**Template Update**
	• Transferred content to shared policy template that applies to both UnitedHealthcare Commercial and Individual Exchange benefit plans
	• Added Application section to indicate this policy applies to:
	  ○ UnitedHealthcare Commercial benefit plans
	  ○ Individual Exchange benefit plans
	Coverage Rationale
	Active Still's Disease Including Adult-Onset Stills's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA)
	• Added language to clarify the patient must not be receiving Ilaris in combination with *another systemic* targeted immunomodulator *for treatment of the same indication*
	Supporting Information
	• Updated *Clinical Evidence* and *References* sections to reflect the most current information
	• Archived previous policy versions 2025D0066L and IEXD0066.09

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. 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.

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