Policy Number	**RX501.119**
Policy Effective Date	**11/01/2025**

Canakinumab

Table of Contents

Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

Canakinumab (Ilaris®) **may be considered medically necessary** for the treatment of the following indications:

- Periodic Fever Syndromes:
  - Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:
    - Familial Cold Autoinflammatory Syndrome (FCAS); or
    - Muckle-Wells Syndrome (MWS),
  - Tumor Necrosis Factor (TNF) Receptor Associated Periodic Syndrome (TRAPS) in adults and children,
  - Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adults and children,
  - Familial Mediterranean Fever (FMF) in adults and children; OR
- Active Still's disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in individuals aged 2 years and older; OR
- Gout flares in adults in whom:
  - Non-steroidal anti-inflammatory drugs (NSAIDS) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and
  - Repeated courses of corticosteroids are not appropriate.

Canakinumab (Ilaris®) **is considered experimental, investigational, and/or unproven** for all other non-Food and Drug Administration (non-FDA) labeled uses.

Policy Guidelines

None.

Description

Canakinumab is a recombinant, human anti-human interleukin-1 beta (IL-1β) monoclonal antibody of the IgG1/kappa isotype subclass. (1) By binding to human IL-1β, canakinumab blocks the IL-1 receptor interaction and neutralizes overactive IL-1β activity which is present in disorders such as Cryopyrin-Associated Periodic Syndromes (CAPS) and Systemic Juvenile Idiopathic Arthritis (SJIA). Canakinumab does not bind IL-1 alpha or IL-1 receptor antagonist (IL-ra).

Periodic Fever Syndromes

Periodic Fever Syndromes are a very rare group of chronic autoinflammatory diseases seen in both adults and children that are caused by mutations affecting the immune system. These mutations trigger an inflammatory response causing symptoms such as fever, rash, and painful muscles and/or joints. Several different disorders fall within this group of inherited diseases.

Cryopyrin-Associated Periodic Syndromes (CAPS)

CAPS are a rare group of genetic diseases related to defects in the cryopyrin protein (also called NLRP3). (2) Cryopyrin has an important role in controlling inflammation. The two most common CAPS diseases are familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). In FCAS, exposure to cold and perhaps other environmental triggers, causes a hive-like rash, fever, chills, nausea, headaches, and joint pain, usually lasting up to one day. MWS patients exhibit episodic fever, chills, rash, red eyes, joint pain, and severe headaches lasting one to three days, often after exposure to cold. While there are no known long-term secondary consequences associated with FCAS, MWS patients often develop deafness or partial hearing loss by their teenage years, as well as amyloidosis if left untreated.

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

TRAPS is a rare disease resulting from a gene defect in a protein called tumor necrosis factor receptor which leads to an increase in the body's inflammatory response. (3) Affecting both males and females, the disease usually starts before 10 years of age. TRAPS typically causes recurrent episodes of fever lasting more than a week, along with chills and severe muscle pain in the torso and the arms. Other common symptoms include abdominal pain with nausea and vomiting, diarrhea, and red swollen eyes. Chest pain may develop as well. Stressors such as infection, trauma, strenuous exercise, or psychological stress may trigger these episodes.

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

HIDS/MKD is a rare genetic disease caused by a defect in a gene that results in abnormalities in a protein called mevalonate kinase (MVK). (4) MVK facilitates a chemical reaction in the body involved in the process of making cholesterol. Causing a decrease in the amount of certain molecules involved in the control of the inflammation process, this genetic defect results in patients experiencing recurring episodes of fever, rash, abdominal pain, diarrhea, joint pain, mouth sores, and swollen lymph glands.

Familial Mediterranean Fever (FMF)

FMF is genetic disorder caused by mutations in the MEFV gene. (5) The MEFV gene makes a protein called pyrin that plays a role in the natural control of inflammation. When the MEFV gene does not work correctly, inflammation gets out of control and causes patients to experience episodes of fever and pain in the absence of infection. FMF most often occurs in individuals of Mediterranean and Middle Eastern descent.

Adult-Onset Still's Disease (AOSD)

Adult-onset Still's disease (AOSD) is a rare type of inflammatory arthritis that begins in adulthood. (6) Symptoms may include fever, rash, and joint pain, at first only affecting a few

joints but involving more joints over time. There is no single test that can diagnoses AOSD; instead, blood tests are used to rule out other diseases with similar symptoms.

Systemic Juvenile Idiopathic Arthritis (SJIA)
Juvenile idiopathic arthritis (JIA) is the most common type of arthritis in kids and teens. (7) Approximately 10-20% of children with JIA have a rare and serious subtype called systemic juvenile idiopathic arthritis (SJIA) that not only affects the joints, but other parts of the body, including the liver, lungs and heart. SJIA is thought to be an autoinflammatory disease that causes the innate immune system to be activated, even when there is no infection to fight. Kids with SJIA have high blood levels of IL-1 and interleukin-6 (IL-6). These proteins are known to cause inflammation in other auto-inflammatory diseases and are believed to trigger inflammation in SJIA. Common symptoms during periods of inflammation include fever, rash, and joint pain.

Gout
Gout is a painful and potentially disabling form of arthritis that occurs when excess uric acid collects in the body leading to the deposit of needlelike urate crystals in and around the joints. Gout is characterized by sudden, severe attacks of pain, swelling, redness and tenderness in the joints. Severe attacks are often followed by periods of no symptoms. Although gout most commonly affects the large joint at the base of the big toe, it can occur in any joint, including the ankles, knees, elbows, wrists and fingers. (8)

Regulatory Status
The U.S. Food and Drug Administration (FDA) approved Ilaris® (canakinumab) for the following indications (1):

- Periodic Fever Syndromes:
  - Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including:
    - Familial Cold Autoinflammatory Syndrome (FCAS); or
    - Muckle-Wells Syndrome (MWS),
  - 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; AND
- Gout flares in adults in whom non-steroidal anti-inflammatory drugs (NSAIDS) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

Ilaris® is administered via a subcutaneous injection. Injections should be performed by a clinician; the drug is not intended for self-administration.

Rationale

This policy is based on the U.S. Food and Drug Administration (FDA) labeled indications for Ilaris® (canakinumab).

Ilaris® (canakinumab) (1)

Cryopyrin-Associated Periodic Syndromes (CAPS)

The efficacy and safety of Ilaris for the treatment of CAPS was demonstrated in CAPS Study (NCT00465985), a three-part trial in patients (aged 9 to 74 years) with the Muckle-Wells Syndrome (MWS) phenotype of CAPS. Throughout the trial, patients weighing more than 40 kilograms (kg) received 150 milligrams (mg) of Ilaris and patients weighing 15 to 40 kg received 2 mg/kg. Part 1 was an 8-week open-label, single-dose period where all patients received Ilaris. Patients who achieved a complete clinical response and did not relapse by Week 8 were randomized into Part 2, a 24-week randomized, double-blind, placebo-controlled withdrawal period. Patients who completed Part 2 or experienced a disease flare entered Part 3, a 16-week, open-label, active treatment phase. A complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and serum levels of C-reactive protein (CRP) and Serum Amyloid A (SAA) of less than 10 mg/liter (L). A disease flare was defined as a CRP and/or SAA values greater than 30 mg/L and either a score of mild or worse for PHY or a score of minimal or worse for PHY and SKD.

In Part 1, a complete clinical response was observed in 71% of patients one week following the initiation of treatment and in 97% of patients by Week 8 (see Table 1 and Figure 1). In the randomized withdrawal period, a total of 81% of the patients randomized to placebo flared as compared to none (0%) of patients randomized to Ilaris. The 95% confidence interval for treatment difference in proportion of flares, 53% to 96%. At the end of Part 2, all 15 patients treated with Ilaris had absent or minimal disease activity and skin disease (See Table 1).

In a second trial (NCT00465985), patients 4 to 74 years of age with both MWS and Familial Cold Autoinflammatory Syndrome (FCAS) phenotypes of CAPS were treated in an open-label manner. Treatment with Ilaris resulted in clinically significant improvement of signs and symptoms and in normalization of high CRP and SAA in the majority of patients within 1 week.

Table 1: Physician's Global Assessment of Auto Inflammatory Disease Activity and Assessment of Skin Disease: Frequency Table and Treatment Comparison in Part 2 (Using LOCF, ITT Population)

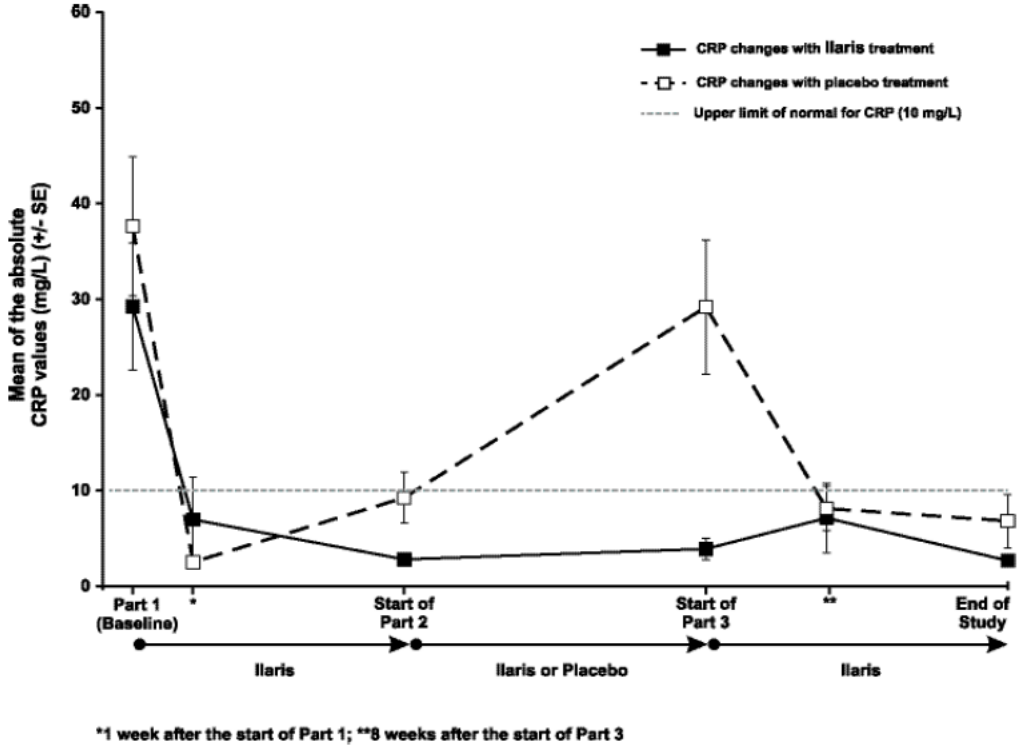
		Ilaris N = 15		**Placebo N = 16**	
	Baseline	**Start of Part 2 (Week 8)**	**End of Part 2**	**Start of Part 2 (Week 8)**	**End of Part 2**
Physician's Global Assessment of Auto Inflammatory Disease Activity – n (%)					
Absent	0/31 (0)	9/15 (60)	8/15 (53)	8/16 (50)	0/16 (0)

Minimal	1/31 (3)	4/15 (27)	7/15 (47)	8/16 (50)	4/16 (25)
Mild	7/31 (23)	2/15 (13)	0/15 (0)	0/16 (0)	8/16 (50)
Moderate	19/31 (61)	0/15 (0)	0/15 (0)	0/16 (0)	4/16 (25)
Severe	4/31 (13)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)
Assessment of skin disease – n (%)					
Absent	3/31 (10)	13/15 (87)	14/15 (93)	13/16 (81)	5/16 (31)
Minimal	6/31 (19)	2/15 (13)	1/15 (7)	3/16 (19)	3/16 (19)
Mild	9/31 (29)	0/15 (0)	0/15 (0)	0/16 (0)	5/16 (31)
Moderate	12/31 (39)	0/15 (0)	0/15 (0)	0/16 (0)	3/16 (19)
Severe	1/32 (3)	0/15 (0)	0/15 (0)	0/16 (0)	0/16 (0)

CAPS: Cryopyrin-Associated Periodic Syndromes; CRP: C-Reactive Protein; ITT: Intention to treat; SAA: Serum Amyloid A.

Markers of inflammation CRP and SAA normalized within 8 days of treatment in the majority of patients. Normal mean CRP (Figure 1) and SAA values were sustained throughout CAPS Study 1 in patients continuously treated with canakinumab. After withdrawal of canakinumab in Part 2, CRP (Figure 1) and SAA values again returned to abnormal values and subsequently normalized after reintroduction of canakinumab in Part 3. The pattern of normalization of CRP and SAA was similar.

Figure 1. Mean C-Reactive Protein Levels at the End of Parts 1, 2, and 3 of CAPS Study 1



CAPS: Cryopyrin-Associated Periodic Syndromes; CRP: C-Reactive Protein

Treatment of Periodic Fever Syndromes: TRAPS, HIDS/MKD, and FMF

The efficacy and safety of Ilaris for the treatment of tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin d syndrome (HIDS)/mevalonate kinase

deficiency (MKD), and familial Mediterranean fever (FMF) was demonstrated in a 4-Part study (TRAPS, HIDS/MKD, and FMF Study 1) (NCT02059291) consisting of three separate, disease cohorts (TRAPS, HIDS/MKD and FMF) which enrolled 185 patients aged greater than 28 days. 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 Ilaris (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks. Part 3 and Part 4 of this study are ongoing.

Randomized patients in Part 2 treated with Ilaris whose disease flare did not resolve, or who had persistent disease activity from Day 8 up to Day 14 (Physician's Global Assessment [PGA] greater than or equal to 2 or C-reactive Protein [CRP] greater than 10 mg/L and no reduction by at least 40% from baseline) received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). Patients treated with Ilaris whose disease flare did not resolve, or who had persistent disease activity from Day 15 up to Day 28 (PGA greater than or equal to 2 or CRP greater than 10 mg/L and no reduction by at least 70% from baseline), also received an additional dose of 150 mg (or 2 mg/kg for patients weighing less than or equal to 40 kg). On or after Day 29, patients treated with Ilaris in Part 2 with PGA greater than or equal to 2 and CRP greater than or equal to 30 mg/L were also up-titrated. All up-titrated patients remained at the increased dose of 300 mg (or 4 mg/kg for patients weighing less than or equal to 40 kg) every 4 weeks.

The primary efficacy endpoint of the randomized, 16-week treatment period (Part 2) was the proportion of complete responders within each cohort as defined by patients who had resolution of their index disease flare at Day 15 and did not experience a new disease flare during the remainder of the 16-week treatment period. Resolution of the index disease flare (initial flare at the time of the randomization) was defined at the Day 15 visit as a PGA Disease Activity score less than 2 ("minimal or no disease") and CRP within normal range (less than or equal to 10 mg/L) or reduction greater than or equal to 70% from baseline. The key signs and symptoms assessed in the PGA for each condition were the following: TRAPS: abdominal pain, skin rash, musculoskeletal pain, eye manifestations; HIDS/MKD: abdominal pain; lymphadenopathy, aphthous ulcers; FMF: abdominal pain, skin rash, chest pain, arthralgia/ arthritis. A new flare was defined as a PGA score greater than or equal to 2 ("mild, moderate, or severe disease") and CRP greater to or equal than 30 mg/L. In the 16-week treatment period (Part 2), patients who needed dose escalation, who crossed over from placebo to Ilaris, or who discontinued from the study due to any reason prior to Week 16 were considered as non-responders.

Patients randomized in the TRAPS cohort (N=46) were aged 2 to 76 years (median age at baseline: 15.5 years) and of this population, 57.8% did not have fever at baseline. Randomized TRAPS patients were those with chronic or recurrent disease activity defined as 6 flares per year (median number of flares per year: 9.0) with PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 112.5 mg/L). In the TRAPS cohort, 11/22 (50.0%) patients randomized to Ilaris 150 mg every 4 weeks received up-titration to 300 mg every 4

weeks during the 16-week treatment period, while 21/24 (87.5%) patients randomized to placebo crossed over to Ilaris.

Patients randomized in the HIDS/MKD cohort (N=72) were aged 2 to 47 years (median age at baseline: 11.0 years) and of this population, 41.7% did not have fever at baseline. Randomized HIDS/MKD patients were those with a confirmed diagnosis of HIDS according to known genetic MVK/enzymatic (MKD) findings, and documented prior history of greater than or equal to 3 febrile acute flares within a 6 month period (median number of flares per year: 12.0) when not receiving prophylactic treatment and during the study, had active HIDS flares defined as PGA greater than or equal to 2 and CRP greater than 10 mg/L (median CRP at baseline: 113.5 mg/L). In the HIDS/MKD cohort, 19/37 (51.4%) patients randomized to Ilaris 150 mg every 4 weeks received up-titration to 300 mg every 4 weeks during the 16-week treatment period, while 31/35 (88.6%) patients randomized to placebo crossed over to Ilaris.

Patients randomized in the FMF cohort (N=63) were aged 2 to 69 years (median age at baseline: 18.0 years) and of this population, 76.2% did not have fever at baseline. Randomized FMF patients were those with documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine. Patients had active disease defined as at least one flare per month (median number of flares per year: 18.0) and CRP greater than 10 mg/L (median CRP at baseline: 94.0 mg/L). Patients were allowed to continue their stable dose of colchicine without change. Of the 63 randomized patients, 55 (87.3%) were taking concomitant colchicine therapy on or after randomization. In the FMF cohort, 10/31 (32.3%) patients randomized to Ilaris 150 mg every 4 weeks received up-titration to 300 mg every 4 weeks during the 16-week treatment period, while 27/32 (84.4%) patients randomized to placebo crossed over to Ilaris.

For the primary efficacy endpoint, Ilaris was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment from the time of the resolution of the index flare. (see Table 2).

Table 2: Proportion of TRAPS, HIDS/MKD, and FMF Patients Who Achieved a Complete Response (Resolution of Index Flare by Day 15 and Maintained Through Week 16)

	Ilaris 150 mg	**Placebo**	**Treatment comparison**	
Cohort	**n/N (%)**	**n/N (%)**	**Odds ratio 95% CI**	**p-value**
TRAPS	10/22 (45.5%)	2/24 (8.3%)	9.17 (1.51, 94.61)	0.005
HIDS/MKD	13/37 (35.1%)	2/35 (5.7%)	8.94 (1.72, 86.41)	0.002
FMF	19/31 (61.3%)	2/32 (6.3%)	23.75 (4.38, 227.53)	<0.0001

Abbreviations: CI, confidence interval; FMF: Familial Mediterranean Fever; HIDS/MKD: Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency; TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome. n = number of patients with the response. N = number of patients evaluated for that response in each cohort.

At Day 15, a higher proportion of Ilaris-treated patients compared to placebo-treated patients experienced resolution of their index flare in all disease cohorts (see Table 3).

Table 3: Resolution of Index Flare (Full Analysis Set)

Resolution at Day 15*		
	Ilaris 150 mg every 4 weeks	**Placebo**
Variable	**n/N (%)**	**n/N (%)**
TRAPS	14/22 (63.6%)	5/24 (20.8%)
HIDS/MKD	24/37 (64.9%)	13/35 (37.1%)
FMF	25/31 (80.7%)	10/32 (31.3%)
FMF: Familial Mediterranean Fever; HIDS/MKD: Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency; TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome. n = number of patients with the response. N = number of patients evaluated for that response in each cohort. *Resolution of index disease flare (PGA less than 2 and CRP less than or equal to 10 mg/L or reduction greater than or equal to 70% from baseline).		

There was supportive evidence of efficacy for Ilaris at Day 15, as compared to placebo, for the components of the primary endpoint, CRP and PGA Disease Activity score, as well as for the secondary endpoint SAA level (see Table 4a and 4b).

Table 4a: Proportion of TRAPS, HIDS/MKD, and FMF Patients Achieving PGA Less Than 2, CRP Less Than or Equal to 10 mg/L and SAA Less Than or Equal to 10 mg/L at Day 15*

	TRAPS			**HIDS/MKD**		
Variable	**Ilaris 150 mg**	**Placebo**	**Treatment comparison**	**Ilaris 150 mg**	**Placebo**	**Treatment comparison**
	n/N (%)	**n/N (%)**	**Odds ratio 95% CI**	**n/N (%)**	**n/N (%)**	**Odds ratio 95% CI**
PGA less than 2	14/22 (63.6%)	8/24 (33.3%)	4.06 (1.12, 14.72)	26/37 (70.3%)	14/35 (40.0%)	3.42 (1.28, 9.16)
CRP less than or equal to 10 mg/L	13/22 (59.1%)	8/24 (33.3%)	3.88 (1.05, 14.26)	25/37 (67.6%)	9/35 (25.7%)	6.05 (2.14, 17.12)
SAA less than or equal to 10 mg/L	7/22 (31.8%)	2/24 (8.3%)	5.06 (0.92, 27.91)	10/37 (27.0%)	4/35 (11.4%)	2.94 (0.82, 10.53)
Abbreviations: CI: confidence interval; CRP: C-Reactive Protein; FMF: Familial Mediterranean Fever; HIDS/MKD: Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency; PGA: Physician's						

Global Assessment; SAA: Serum Amyloid A; TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome.
n = number of patients with the response.
N = number of patients evaluated for that response in each cohort. *Ilaris-treated patients who up-titrated or discontinued prior to Day 15 and placebo-treated patients who switched over to Ilaris or discontinued prior to Day 15 were classified as nonresponders.

Table 4b: Proportion of TRAPS, HIDS/MKD, and FMF Patients Achieving PGA Less Than 2, CRP Less Than or Equal to 10 mg/L and SAA Less Than or Equal to 10 mg/L at Day 15*

	FMF		
Variable	**Ilaris 150 mg**	**Placebo**	**Treatment comparison**
	n/N (%)	**n/N (%)**	**Odds ratio 95% CI**
PGA less than 2	27/31 (87.1%)	13/32 (40.6%)	10.07 (2.78, 36.49)
CRP less than or equal to 10 mg/L	28/31 (90.3%)	9/32 (28.1%)	22.51 (5.41, 93.62)
SAA less than or equal to 10 mg/L	13/31 (41.9%)	5/32 (15.6%)	3.73 (1.11, 12.52)

Abbreviations: CI: confidence interval; CRP: C-Reactive Protein; FMF: Familial Mediterranean Fever; HIDS/MKD: Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency; PGA: Physician's Global Assessment; SAA: Serum Amyloid A; TRAPS: Tumor Necrosis Factor Receptor Associated Periodic Syndrome.
n = number of patients with the response.
N = number of patients evaluated for that response in each cohort. *Ilaris-treated patients who up-titrated or discontinued prior to Day 15 and placebo-treated patients who switched over to Ilaris or discontinued prior to Day 15 were classified as nonresponders.

Treatment of Still's Disease: AOSD and SJIA

SJIA

The efficacy of Ilaris for the treatment of active SJIA was assessed in 2 Phase 3 studies (SJIA Study 1 and SJIA Study 2). Patients enrolled were aged 2 to less than 20 years (mean age at baseline: 8.5 years) with a confirmed diagnosis of SJIA at least 2 months before enrollment (mean disease duration at baseline: 3.5 years). Patients had active disease defined as greater than or equal to 2 joints with active arthritis (mean number of active joints at baseline: 15.4), documented spiking, intermittent fever (body temperature greater than 38°C) for at least 1 day within 1 week before study drug administration, and CRP greater than 30 mg/L (normal range less than 10 mg/L) (mean CRP at baseline: 200.5 mg/L). Patients were allowed to continue their stable dose of methotrexate, corticosteroids, and/or NSAIDs without change, except for tapering of the corticosteroid dose as per study design in SJIA Study 2 (see below).

SJIA Study 1 (NCT00886769) was a randomized, double-blind, placebo-controlled, single-dose 4-week study assessing the short-term efficacy of Ilaris in 84 patients randomized to receive a single subcutaneous dose of 4 mg/kg Ilaris or placebo (43 patients received Ilaris and 41 patients received placebo). The primary objective of the study was to demonstrate the superiority of Ilaris versus placebo in the proportion of patients who achieved at least 30%

improvement in an adapted pediatric American College of Rheumatology (ACR) response criterion which included both the pediatric ACR core set (ACR30 response) and absence of fever (temperature less than or equal to 38°C in the preceding 7 days) at day 15.

Pediatric ACR responses are defined by achieving levels of percentage improvement (30%, 50%, and 70%) from baseline in at least 3 of the 6 core outcome variables, with worsening of greater than or equal to 30% in no more than one of the remaining variables. Core outcome variables included a physician global assessment of disease activity, parent or patient global assessment of well-being, number of joints with active arthritis, number of joints with limited range of motion, CRP, and functional ability (Childhood Health Assessment Questionnaire-CHAQ).

Percentages of patients by pediatric ACR response are presented in Table 5.

Table 5: Pediatric ACR Response at Days 15 and 29

	Day 15			**Day 29**		
	Ilaris N = 43	**Placebo N = 41**	**Weighted Difference[1] (95% CI)[2]**	**Ilaris N = 43**	**Placebo N = 41**	**Weighted Difference[1] (95% CI)[2]**
ACR30	84%	10%	70% (56%, 84%)	81%	10%	70% (56%, 84%)
ACR50	67%	5%	65% (50%, 80%)	79%	5%	76% (63%, 88%)
ACR70	60%	2%	64% (49%, 79%)	67%	2%	67% (52%, 81%)

[1] Weighted difference is the difference between the Ilaris and placebo response rates, adjusted for the stratification factors (number of active joints, previous response to anakinra, and level of oral corticosteroid use).
[2] CI = confidence interval for the weighted difference.
N = Number of patients.
ACR: American College of Rheumatology

Results for the components of the pediatric ACR core set were consistent with the overall ACR response results, for systemic and arthritic components, including the reduction in the total number of active joints and joints with limited range of motion. Among the patients who returned for a Day 15 visit, the mean change in patient pain score (0 to 100 mm visual analogue scale) was -50.0 mm on Ilaris (N=43), as compared to +4.5 mm on placebo (N=25). The mean change in pain score among Ilaris-treated patients remained consistent through Day 29. All patients treated with Ilaris had no fever at Day 3 compared to 87% of patients in the placebo group.

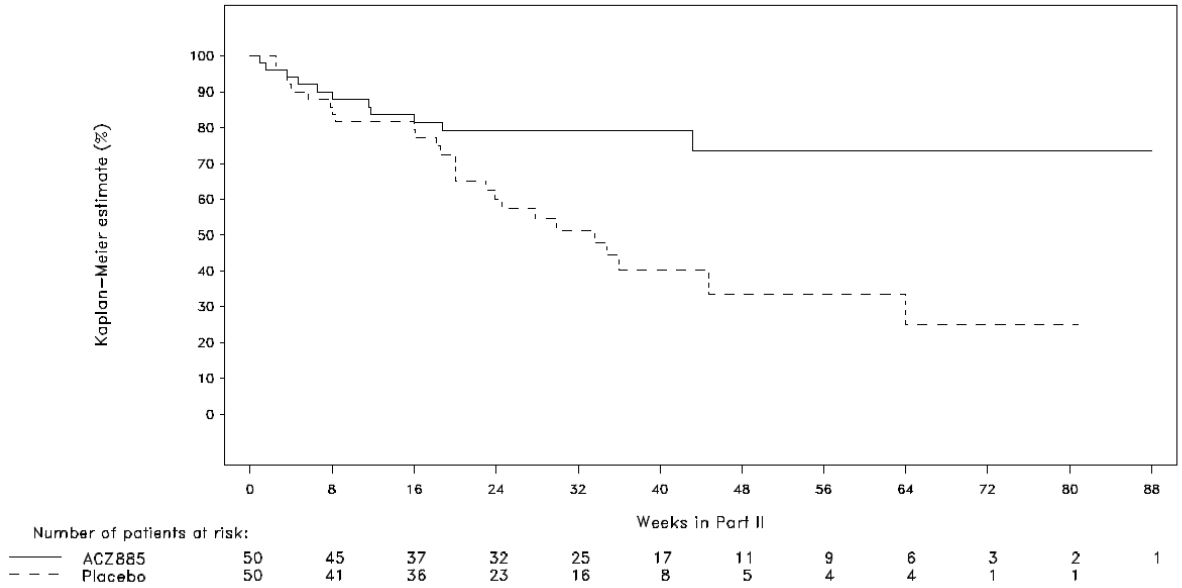
SJIA Study 2 (NCT00889863) was a randomized, double-blind, placebo-controlled, withdrawal study of flare prevention by Ilaris in patients with active SJIA. Flare was defined by worsening of ≥30% in at least 3 of the 6 core pediatric ACR response variables combined with improvement of ≥30% in no more than 1 of the 6 variables, or reappearance of fever not due to infection for

at least 2 consecutive days. The study consisted of 2 major parts: 177 patients were enrolled in the study and received 4 mg/kg Ilaris subcutaneously every 4 weeks in Part I and 100 of these patients continued into Part II to receive either Ilaris 4 mg/kg or placebo subcutaneously every 4 weeks.

Corticosteroid Dose Tapering
Of the total 128 patients taking corticosteroids who entered the open-label portion of Study 2, 92 attempted corticosteroid tapering. Fifty-seven (62%) of the 92 patients who attempted to taper were able to successfully taper their corticosteroid dose and 42 (46%) discontinued corticosteroids.

Time to Flare
Part II was a randomized withdrawal design to demonstrate that the time to flare was longer with Ilaris than with placebo. Follow-up stopped when 37 events had been observed resulting in patients being followed for different lengths of time. The probability of experiencing a flare over time in Part II was statistically lower for the Ilaris treatment group than for the placebo group (Figure 2). This corresponded to a 64% relative reduction in the risk of flare for patients in the Ilaris group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).

Figure 2. Kaplan-Meier Estimates of the Probability to Stay Flare-Free in Part II of SJIA Study 2 by Treatment (ILARIS (ACZ885) and Placebo groups)



Very few patients were followed for more than 48 weeks.

<u>Adult-Onset Still's Disease (AOSD)</u>
The efficacy of Ilaris in adults with AOSD is based on the pharmacokinetic exposure and extrapolation of the established efficacy of Ilaris in SJIA patients. Efficacy of Ilaris was also

assessed in a randomized, double-blind, placebo-controlled study that enrolled 36 patients (22 to 70 years old) diagnosed with AOSD. The efficacy data were generally consistent with the results of a pooled efficacy analysis of SJIA patients.

Treatment of 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 non-steroidal anti-inflammatory drugs (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 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: (i) 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 (ii) 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.

Efficacy on Pain

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 as shown in Table 6, and Figure 3 (Study 3). 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 (see Table 6).

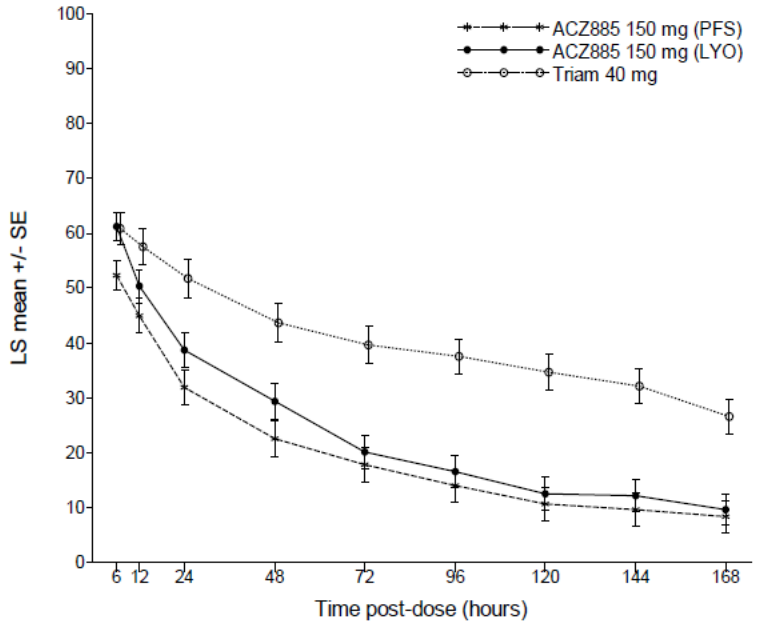
Table 6: Pain Intensity of the Most Affected Joint at 72-h post treatment

Study	**Population**	**Ilaris 150 mg**		**Triamcinolone acetonide 40 mg**		**Difference (95% CI)* in Pain Intensity 72 Hours Post-dose VAS (0-100 mm): Ilaris vs. Triamcinolone acetonide**
		N	**Mean (SE)***	**N**	**Mean (SE)***	
Study 1	Patients unable to use NSAIDs and colchicine	22	21.4 (6.05)	37	38.4 (4.65)	-17.0 mm (-32.3, -1.6)
	Patients unable to use NSAIDs and/or colchicine	113	27.9 (2.42)	115	39.7 (2.40)	-11.8 mm (-18.5, -5.1)
Study 2	Patients unable to use NSAIDs and colchicine	53	24.1 (3.32)	44	33.1 (3.65)	-9.1 mm (-18.9, 0.8)
	Patients unable to use NSAIDs and/or colchicine	112	21.9 (2.31)	114	31.7 (2.29)	-9.8 mm (-16.2, -3.4)
Study 3	Patients unable to use NSAIDs and colchicine	62	20.8 (3.11)	51	40.3 (3.42)	-19.5 mm (-28.6, -10.3)
		60[#]	18.5 (3.16)			21.8 mm (-31.0, -12.6)

	Patients unable to use NSAIDs and/or colchicine	129	19.7 (2.05)	129	32.4 (2.05)	-12.7 mm (-18.4, -7.0)
		131#	17.0 (2.04)			-15.4 mm (-21.1, -9.8)

Abbreviation: CI = confidence interval; SE=Standard Error
Prefilled Syringe (PFS) formulation.
* Adjusted mean, standard error for mean and difference between treatment groups are estimated based on analysis of covariance (ANCOVA) model with treatment, baseline VAS score and baseline BMI as covariates. For Study 3, the use of urate lowering therapy (Yes/No) at baseline is also included in the model as additional covariate.
N = number of patients randomized and received at least one dose of study treatment.

Figure 3. Pain Intensity Over Time in the Subpopulation of Patients Unable to Use NSAIDs and Colchicine (Study 3, ILARIS (ACZ885) 150mg)



Time to New Flare

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 (see Table 7). 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 (see Table 7).

Table 7: Time to New Flare Over the 12 Weeks From Randomization

Study	Population	Ilaris 150 mg	Triamcinolone acetonide 40 mg	Risk reduction for a new flare Ilaris vs.

						Triamcinolone acetonide Hazard ratio[#] (95% CI)
		N	**Flare rate*(n)**	**N**	**Flare rate*(n)**	
Study 1	Patients unable to use NSAIDs and colchicine	22	14% (3)	38	46% (17)	75% 0.25 (0.07, 0.85)
	Patients unable to use NSAIDs and/or colchicine	113	19% (21)	115	37% (40)	55 % 0.45 (0.26 to 0.76)
Study 2	Patients unable to use NSAIDs and colchicine	54	16% (8)	46	43% (19)	72% 0.28 (0.12, 0.65)
	Patients unable to use NSAIDs and/or colchicine	112	14% (15)	114	38% (42)	68% 0.32 (0.18 to 0.58)
Study 3	Patients unable to use NSAIDs and colchicine	62	10% (6)	51	32% (15)	71% 0.29 (0.11, 0.74)
		60[#]	3% (2)			91% 0.09 (0.02, 0.41)
	Patients unable to use NSAIDs and/or colchicine	129	10% (12)	129	44% (52)	82% 0.18 (0.10, 0.34)
		131[#]	9% (12)			83% 0.17 (0.09, 0.33)

Abbreviation: CI = confidence interval.
[#] Prefilled Syringe (PFS) formulation.
* Flare rates up to 12 weeks are estimated using Kaplan-Meier method; n = number of patients with new flares. The risk reduction and hazard ratio between treatment groups are estimated using Cox proportional hazard (Cox-PH) model with treatment and baseline BMI as covariates. For study 3, the use of urate lowering therapy (Yes/No) at baseline is also included in the model as additional covariate.
N = number of patients randomized and received at least one dose of study treatment.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0638

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Label:

1. Ilaris® Highlights of Prescribing Information (November 2024). Available at: <https://www.accessdata.fda.gov> (accessed August 22, 2025).

Other:

2. American College of Rheumatology. Cryopyrin-Associated Autoinflammatory Syndromes (CAPS) (March 2025). Available at: <https://www.rheumatology.org> (accessed August 22, 2025).
3. American College of Rheumatology. Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) (Juvenile) (March 2025). Available at: <https://www.rheumatology.org> (accessed August 22, 2025).
4. American College of Rheumatology. Hyperimmunoglobulin D Syndrome (HIDS) / Mevalonate Kinase Deficiency (MKD) (March 2025). Available at: <https://www.rheumatology.org> (accessed August 22, 2025).
5. American College of Rheumatology. Familial Mediterranean Fever (March 2025). Available at: <https://www.rheumatology.org> (accessed August 22, 2025).
6. Arthritis Foundation. Adult Still's Disease. Available at: <https://www.arthritis.org> (accessed August 22, 2025).
7. Arthritis Foundation. Systemic Juvenile Idiopathic Arthritis. Available at: <https://www.arthritis.org> (accessed August 31, 2025).
8. American College of Rheumatology – Gout. (February 2025). Available at: <https://www.rheumatology.org> (accessed August 31, 2025).

Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
11/01/2025	Document updated with literature review. The following change was made to Coverage: 1) Revised the experimental, investigational and/or unproven statement to: Canakinumab (Ilaris®) is considered experimental, investigational, and/or unproven for all other non-Food and Drug Administration (non-FDA) labeled uses. No new references added, others updated.
06/15/2025	Reviewed. No changes.
08/15/2024	Document updated with literature review. The following editorial changes were made to Coverage: "adult and pediatric patients" changed to "adults and children" in several areas. No change to intent. No new references added.
12/15/2023	Document updated with literature review. The following change was made to Coverage: Added "Gout flares in adults in whom: Non-steroidal anti-inflammatory drugs (NSAIDS) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and Repeated courses of corticosteroids are not appropriate" to medically necessary indications. Added/updated references 1-8.
04/01/2023	Document updated with literature review. The following change was made to Coverage: Added "concomitant use with any other biologics when treating AOSD or SJIA (e.g., infliximab, tocilizumab)" to experimental, investigational and/or unproven statement. No new references added; some updated.
06/01/2021	Document updated with literature review. The following change was made to Coverage: Modified medically necessary statement on active Systemic Juvenile Idiopathic Arthritis to: "Active Still's disease, including Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older". Added and/or updated the following references: 1 and 6.
10/01/2020	New medical document originating from RX501.051. Canakinumab (Ilaris®) may be considered medically necessary for the treatment of the following indications: 1) Periodic Fever Syndromes: Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children 4 years of age and older including Familial Cold Autoinflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS), 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, and Familial Mediterranean Fever (FMF) in adult and pediatric patients; and 2) Active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older. Canakinumab (Ilaris®) is considered experimental, investigational, and/or unproven for all other indications. The following change was made to Coverage: 1) Removed “Gouty arthritis, acute” as a covered indication.