AmeriHealth Caritas
VIP Care Plus

Medical Policy Bulletin
Title:
Canakinumab (Ilaris®)
Policy #:
MA08.101b

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

The following indications will be addressed in this policy. Please see the specific criteria below for the Medical Necessity Criteria:

- Cryopyrin-Associated Periodic Syndromes (CAPS) including: Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)
- Tumor Necrosis Factor (TNF) receptor--Associated Periodic Syndrome (TRAPS)
- Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)
- Familial Mediterranean Fever (FMF)
- Adult-Onset Still's Disease (AOSD)
- Systemic Juvenile Idiopathic Arthritis (SJIA)

PERIODIC FEVER SYNDROMES
Canakinumab (Ilaris®) is considered medically necessary and, therefore, covered for any of the following indications when **all** of the corresponding criteria, including Dosing and Frequency Requirements, are met:

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

- Documented diagnosis of CAPS confirmed by molecular genetic testing that reveals pathogenic variation(s) in the *NLRP3* (also known as CIAS1) gene (e.g., variation of p.Leu353Pro or p.Leu305Pro for FCAS; variation of R260W or T348M for MWS).
- Documented presence of symptoms associated with CAPS (e.g., fever or chills, rash, joint or muscle pain, eye discomfort or redness, fatigue, headache)

- Individual is 4 years of age or older.
- Canakinumab (Ilaris®) will not be used in combination with tumor necrosis factor (TNF) inhibitors (e.g., adalimumab [Humira], etanercept [Enbrel], or infliximab [Remicade]) or other IL-1 blocking agents (e.g., rilonacept [Arcalyst] and anakinra [Kineret]).
- Individual does not have chronic or active infection, including HIV, Hepatitis B, Hepatitis C or tuberculosis.
- Dosing and Frequency: Administration is every 8 weeks.
    - For individuals with body weight greater than 40 kg, dose is 150 mg.
    - For individuals with body weight 15 to 40 kg, dose is 2 mg/kg. If inadequate response, the dose may be increased to 3 mg/kg.

Continuation Therapy (after at least 24 weeks of therapy)
Canakinumab (Ilaris®) is considered medically necessary and, therefore, covered for continuation therapy following at least 24 weeks of therapy when the individual meets all of the following criteria:

- Individual meets the Dosing and Frequency criteria outlined above.
- Documented reduction in total number of fever episodes and reduction in severity of other symptoms, compared to baseline.

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

- Documented diagnosis of TRAPS confirmed by molecular genetic testing that reveals pathogenic variation(s) in the *TNFRSF1A* gene (e.g., R92Q, T50M, C29F, C30R/S, C33G/Y, Y38C, C52F, C55S, C70R/Y, C88R/Y).
- Documented presence of all of the following characteristics of TRAPS:
    - Chronic or recurrent disease (i.e., more than 6 fever episodes per year)
    - C-reactive protein (CRP) level of more than 10 mg/L
    - Physician's global assessment (PGA) score of 2 or higher for fever, skin rash, musculoskeletal pain, abdominal pain, and eye manifestations
- Individual is 2 years of age or older.
- Canakinumab (Ilaris®) will not be used in combination with tumor necrosis factor (TNF) inhibitors (e.g., adalimumab [Humira], etanercept [Enbrel], or infliximab [Remicade]) or other IL-1 blocking agents (e.g., rilonacept [Arcalyst] and anakinra [Kineret]).
- Individual does not have chronic or active infection, including HIV, Hepatitis B, Hepatitis C or tuberculosis.
- Dosing and Frequency:
    - For individuals with body weight less than or equal to 40 kg, dose is 2 mg/kg administered every 4 weeks. If inadequate response, the dose can be increased to 4 mg/kg every 4 weeks.
    - For individuals with body weight greater than 40 kg, the dose is 150 mg administered every 4 weeks. If inadequate response, the dose can be increased to 300 mg every 4 weeks.

Continuation Therapy (after at least 16 weeks of therapy)
Canakinumab (Ilaris®) is considered medically necessary and, therefore, covered for continuation therapy following at least 16 weeks of therapy when the individual meets all of the following criteria:

- Individual meets the Dosing and Frequency criteria outlined above.
- Physician's global assessment (PGA) score less than 2 for fever, skin rash, musculoskeletal pain, abdominal pain, and eye manifestations.
- Documented C-reactive protein (CRP) level of 10 mg/L or less, or a reduction by 70% or more from baseline.

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

- Documented presence of all of the following characteristics of HIDS/MKD:
    - Documented history of at least three fever episodes in a six-month period when not receiving prophylactic treatment
    - C-reactive protein (CRP) level of more than 10 mg/L
    - Physician's global assessment (PGA) score of 2 or higher for fever, abdominal pain, lymphadenopathy, aphthous ulcers
- Individual is 2 years of age or older.

- Canakinumab (Ilaris®) will not be used in combination with tumor necrosis factor (TNF) inhibitors (e.g., adalimumab [Humira], etanercept [Enbrel], or infliximab [Remicade]) or other IL-1 blocking agents (e.g., rilonacept [Arcalyst] and anakinra [Kineret]).
- Individual does not have chronic or active infection, including HIV, Hepatitis B, Hepatitis C or tuberculosis.
- Dosing and Frequency:
    - For individuals with body weight less than or equal to 40 kg, dose is 2 mg/kg administered every 4 weeks. If inadequate response, the dose can be increased to 4 mg/kg every 4 weeks.
    - For individuals with body weight greater than 40 kg, the dose is 150 mg administered every 4 weeks. If inadequate response, the dose can be increased to 300 mg every 4 weeks.

*If genetic variation(s) in the *MVK* gene is noted in documentation, the above clinical criteria must also be met.

Continuation Therapy (after at least 16 weeks of therapy)
Canakinumab (Ilaris®) is considered medically necessary and, therefore, covered for continuation therapy following at least 16 weeks of therapy when the individual meets all of the following criteria:

- Individual meets the Dosing and Frequency criteria outlined above.
- Physician's global assessment (PGA) score less than 2 for fever, skin rash, musculoskeletal pain, abdominal pain, and eye manifestations.
- Documented C-reactive protein (CRP) level of 10 mg/L or less, or a reduction by 70% or more from baseline.

Familial Mediterranean Fever (FMF)**

- Documented presence of all of the following characteristics of FMF:
    - Documented history of at least one fever episode per month
    - C-reactive protein (CRP) level of more than 10 mg/L
    - Physician's global assessment (PGA) score of 2 or higher for fever, abdominal pain, skin rash, chest pain, arthralgia, arthritis
    - Fulfillment of Tel-Hashomer Diagnostic Criteria for FMF as follows: two or more major symptoms, or one major plus two minor symptoms, as listed below:
        - Major Symptoms
            - Recurrent febrile episodes with serositis (peritonitis, synovitis or pleuritis)
            - Amyloidosis of AA type without a predisposing disease
            - Favorable response to regular colchicine treatment
        - Minor Symptoms
            - Recurrent febrile episodes
            - Erysipelas-like erythema
            - FMF in a first-degree relative
- Documented contraindication, failure, or intolerance to colchicine.
- Individual is 2 years of age or older.
- Canakinumab (Ilaris®) will not be used in combination with tumor necrosis factor (TNF) inhibitors (e.g., adalimumab [Humira], etanercept [Enbrel], or infliximab [Remicade]) or other IL-1 blocking agents (e.g., rilonacept [Arcalyst] and anakinra [Kineret]).
- Individual does not have chronic or active infection, including HIV, Hepatitis B, Hepatitis C or tuberculosis.
- Dosing and Frequency:
    - For individuals with body weight less than or equal to 40 kg, dose is 2 mg/kg administered every 4 weeks. If inadequate response, the dose can be increased to 4 mg/kg every 4 weeks.
    - For individuals with body weight greater than 40 kg, the dose is 150 mg administered every 4 weeks. If inadequate response, the dose can be increased to 300 mg every 4 weeks.

**If genetic variation(s) in the *MEFV* gene is noted in documentation, the above clinical criteria must also be met.

Continuation Therapy (after at least 16 weeks of therapy)
Canakinumab (Ilaris®) is considered medically necessary and, therefore, covered for continuation therapy following at least 16 weeks of therapy when the individual meets all of the following criteria:

- Individual meets the Dosing and Frequency criteria outlined above.
- Physician's global assessment (PGA) score less than 2 for fever, skin rash, musculoskeletal pain, abdominal pain, and eye manifestations.

- Documented C-reactive protein (CRP) level of 10 mg/L or less, or a reduction by 70% or more from baseline.

STILL'S DISEASE (ADULT-ONSET STILL'S DISEASE [AOSD], SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS [SJIA])

Canakinumab (Ilaris®) is considered medically necessary and, therefore, covered for the treatment of active Still's disease, including AOSD or SJIA when the following criteria are met:

- Documented diagnosis of moderate to severely active AOSD or SJIA characterized by all of the following symptoms:
  - chronic arthritis with two or more active joints involved (for SJIA) or four or more active joints involved (for AOSD)
  - daily, but intermittently, high spiking fever
  - additionally, accompanied by one or more of the following: rash, hepatosplenomegaly, lymphadenopathy, serositis
- Individual is 2 years of age or older.
- There is documentation of inadequate response, intolerance, or contraindication to at least one of the following: nonsteroidal anti-inflammatory drugs (NSAIDS), corticosteroids, other disease-modifying anti-rheumatic drugs (DMARDs) (e.g. anakinra, methotrexate, tocilizumab, tumor necrosis factor [TNF] inhibitors).
- Canakinumab (Ilaris®) will not be used in combination with tumor necrosis factor (TNF) inhibitors (e.g., adalimumab [Humira], etanercept [Enbrel], or infliximab [Remicade]) or other IL-1 blocking agents (e.g., rilonacept [Arcalyst] and anakinra [Kineret]).
- Individual does not have chronic or active infection, including HIV, Hepatitis B, Hepatitis C or tuberculosis.
- Dosing and Frequency: Individuals with body weight 7.5 kg or above, dose is 4 mg/kg (maximum of 300 mg) administered every 4 weeks.

Continuation Therapy (after at least 32 weeks of therapy)

Canakinumab (Ilaris®) is considered medically necessary and, therefore, covered for continuation therapy following at least 32 weeks of therapy when the individual meets all of the following criteria:

- Individual meets the Dosing and Frequency criteria outlined above.
- Documented improvement or stability of AOSD or SJIA (e.g., reduction in the signs and symptoms [including number of active joints involved], and reduction in corticosteroid dose).

NOT MEDICALLY NECESSARY

When molecular genetic testing of the relevant genes listed above reveals established "benign variation(s)" or "wild-type genotype", canakinumab (Ilaris®) is considered not medically necessary and, therefore, not covered because the available published peer-reviewed literature does not support its use in the treatment of this disease.

EXPERIMENTAL/INVESTIGATIONAL

When molecular genetic testing of the relevant genes listed above reveals "likely pathogenic" or "variations of unknown significance (VUS)", the use of canakinumab (Ilaris®) is considered experimental/investigational and, therefore, not covered because the safety and/or effectiveness of this service cannot be established by review of the available published peer-reviewed literature.

All other uses for canakinumab (Ilaris®) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of canakinumab (Ilaris®). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published

peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of canakinumab (Ilaris®) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for canakinumab (Ilaris®).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of canakinumab (Ilaris®) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

There is no Medicare coverage determination addressing ramucirumab (Cyramza®); therefore, the Company policy is applicable.

PRESCRIBING INFORMATION

Canakinumab (Ilaris®) is administered via subcutaneous injection every 4 weeks for:

- Adult-Onset Still's Disease (AOSD)
- Familial Mediterranean Fever (FMF)
- Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)
- Systemic Juvenile Idiopathic Arthritis (SJIA)
- Tumor Necrosis Factor (TNF) receptor--Associated Periodic Syndrome (TRAPS)

Canakinumab (Ilaris®) is administered via subcutaneous injection every 8 weeks for Cryopyrin-Associated Periodic Syndromes (CAPS) including: Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

Live vaccines should not be given concurrently with canakinumab (Ilaris®).

DIAGNOSTIC TOOL

The physician's global assessment (PGA) classifies clinical signs and symptoms associated with each disease with the use of a 5-point scale with scores of 0 (none), 1 (minimal), 2 (mild), 3 (moderate), and 4 (severe).

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, canakinumab (Ilaris®) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Canakinumab (Ilaris®) was approved by the FDA on June 17, 2009 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). Supplemental approvals for canakinumab (Ilaris®) have since been issued by the FDA.

Description

The cytokine interleukin-1β (IL-1β) is a key mediator of the inflammatory response; it is hypothesized that excessive release of activated IL-1β that drives inflammation. Canakinumab (Ilaris®) is a recombinant monoclonal antibody that binds to human IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors, thus reducing the inflammatory response pathway.

CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES

Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), are rare genetic syndromes cause by variation(s) in the *NLRP3* gene (also known as CIAS1 gene) which results in hyperactive cryopyrin proteins and an inappropriate inflammatory response. FCAS is characterized by fever episodes typically lasting 1 day resulting in skin rash, fever, chills, joint pain, conjunctivitis, nausea, sweating, drowsiness, headache, thirst, or headaches after exposure to cold temperatures or other environmental triggers. FCAS typically begins in infancy and occurs throughout the rest of the individual's life. MWS is characterized by fever episodes typically lasting 1-3 days resulting in skin rash, fever, chills, joint pain, conjunctivitis, or severe headaches with vomiting. MWS flare-ups may begin in infancy or early childhood. The triggers of MWS are unknown but are thought to either arise spontaneously or be triggered by cold, heat, fatigue, or other stresses. Individuals with MWS may develop hearing loss and kidney damage due to amyloidosis.

Lachmann 2009 evaluated the safety and effectiveness of canakinumab (Ilaris®) in the treatment of CAPS with a three-part, 48-week, double-blind, placebo-controlled, randomized withdrawal study. Part 1 was an 8-week open label trial where 35 individuals with MWS received a single dose of 150 mg of canakinumab (Ilaris®) subcutaneously. A complete response was defined as a global assessment of no or minimal disease activity by a physician, an assessment of no or minimal rash, and a value for both serum C-reactive protein (CRP) and serum amyloid A protein (SAA) that was within the normal range (<10 mg per liter for both measures). At the end of 8 weeks, 34 of the 35 patients (97%) achieved a complete response to canakinumab (Ilaris®). Thirty-one of those who achieved a complete response entered Part 2, a randomized, double-blind, placebo controlled withdrawal period where participants received either 150 mg of canakinumab (Ilaris®) or placebo every 8 weeks for up to 24 weeks. The primary outcome measure was the proportion of individuals with a relapse of CAPS during canakinumab (Ilaris®) treatment, as compared with placebo, in part 2. Relapse was defined as a value for either CRP or SAA of more than 30 mg per liter, accompanied by a physician’s assessment of global disease activity that was greater than minimal or that was minimal and accompanied by a rash that was assessed as more than minimal. None of those who received canakinumab (Ilaris®) had disease flares, compared to 81% of those who received placebo (P<0.001). At the end of part 2, median C-reactive protein (CRP) and serum amyloid A protein (SAA) values were normal (<10 mg per liter for both measures) in patients receiving canakinumab but were elevated in those receiving placebo (P<0.001 and P = 0.002, respectively). Part 3 was a 16-week open-label active treatment period. Clinical and biochemical remission of CAPS was sustained in 28 of the 29 patients (97%) who completed part 3.

An open-label trial was performed in individuals ages 4 to 74 years old with either MWS or FCAS phenotypes of CAPS. Results showed a clinically significant improvemTUMent of signs and symptoms and in normalization of high CRP and SAA in a majority of the individuals within one week of treatment with canakinumab (Ilaris®).

TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME

Tumor necrosis factor (TNF) receptor--associated periodic syndrome (TRAPS) is a rare genetic disorder characterized by chronic or recurrent disease (i.e., more than 6 fever episodes per year), fever, chills, abdominal pain, skin rash, periorbital edema, conjunctivitis, musculoskeletal pain, high C-reactive protein (CRP), arthralgia, and myalgia**.** TRAPS may cause inflammation in various areas of the body including the heart muscle, certain joints,

throat, or mucous membranes, amyloidosis, and kidney failure. TRAPS is caused by pathogenic variations in the *TNFRSF1A* gene that causes the tumor necrosis factor receptor 1 (TNFR1) protein to misfold which prevents its binding and subsequent signaling to the tumor necrosis factor (TNF) protein. The misfolded proteins forms clumps and cause the production of cytokines through the inflammation pathway.

DeBenedetti 2018 evaluated the safety and effectiveness of canakinumab (Ilaris®) in the treatment of genetically confirmed TRAPS, HIDS/MKD, or colchicine-resistant FMF in a randomized, Phase 3 cohort study called CLUSTER. Participants received either 150 mg of canakinumab (Ilaris®) or placebo every 4 weeks. The primary outcome was complete response, defined as resolution of baseline flare at day 15 (Physician's global assessment [PGA] score less than 2, plus CRP level of ≤10 mg/L or a reduction by ≥70% from baseline) and no new flare (PGA score of ≥2 and CRP level of ≥30 mg per liter) until week 16. At week 16, a statistically significant percentage of participants receiving canakinumab (Ilaris®) had a complete response than those receiving placebo: 61% vs. 6% of those with FMF (P<0.001), 35% versus 6% of those with HIDS/MKD (P = 0.003), and 45% versus 8% of those with TRAPS (P = 0.006).

HYPERIMMUNOGLOBULIN D SYNDROME/MEVALONATE KINASE DEFICIENCY

Hyperimmunoglobulin D (Hyper-IgD) syndrome (HIDS) is the less severe form of a metabolic disorder known as mevalonate kinase deficiency (MKD). It is characterized by periodic episodes of fever, abdominal pain, lymphadenopathy, and aphthous ulcers. HIDS/MKD usually begins during infancy. Most episodes last several days and occur periodically throughout life. The frequency of episodes and their severity vary greatly from person to person. Some individuals have no symptoms between attacks, while others have persistent symptoms from frequent attacks. Episodes can occur spontaneously or be triggered by vaccinations, infections, and/or emotional or physical stress. Amyloidosis, abdominal adhesions, and very rarely joint contractures may occur. HIDS/MKD is caused by variations in the *MVK* gene which provides instructions for making the mevalonate kinase enzyme, thus the variations result in a partial enzyme deficiency.

See DeBenedetti 2018 Study (above) for study summary.

FAMILIAL MEDITERRANEAN FEVER
Familial Mediterranean fever (FMF) is an inherited condition characterized by recurrent episodes of painful inflammation in the abdomen, lungs, or joints. FMF is characterized by periodic episodes of fever, abdominal pain, skin rash, chest pain, arthralgia, and arthritis that last one to three days and vary in severity. FMF usually begins in childhood or the teenage years, but in some cases, the initial attack occurs much later in life. The length of time between attacks is also variable and can range from days to years. During these periods, affected individuals usually have no signs or symptoms related to the condition. Colchicine is usually the first-line agent for treatment. Without treatment, amyloidosis and kidney failure may occur. FMF is caused by variations in the *MEFV* gene which provides instructions for making a protein called pyrin (also known as marenostrin), which is found in white blood cells, thus the variations result in reduced pyrin activity, which disrupts control of the inflammation process.

See DeBenedetti 2018 Study (above) for study summary.

STILL'S DISEASE

ADULT-ONSET STILL'S DISEASE
Adult-Onset Still's Disease (AOSD) is a rare inflammatory disorder characterized by episodes of high, spiking daily fevers, rash, joint or muscle pain, sore throat, hepatosplenomegaly, lymphadenopathy, and serositis. It is considered a continuum of systemic juvenile idiopathic arthritis (SJIA). AOSD primarily affects individuals 16-35 years of age and is considered a rare disease, unlike SJIA. The severity and frequency of episodes will vary between individuals. The treatment of AOSD may include nonsteroidal anti-inflammatory drugs (NSAIDS), glucocorticoids, or disease-modifying anti-rheumatic drugs (DMARDs) (e.g. anakinra, canakinumab, methotrexate, tocilizumab, tumor necrosis factor [TNF] inhibitors).

The approval of canakinumab (Ilaris) in adults with AOSD is based on the pharmacokinetic exposure and extrapolation of the established efficacy of canakinumab (Ilaris) in those with SJIA. The efficacy of canakinumab (Ilaris) was also assessed in a randomized, double-blind, placebo-controlled, Phase 2 study that enrolled 36 individuals (22 to 70 years old) diagnosed with AOSD. Individuals with active joint involvement were eligible for enrolment if they fulfilled the AOSD Yamaguchi classification criteria, had a disease activity based on DAS28(ESR) of ≥3.2 at screening, and had ≥4 tender and swollen (28-joint count) joint counts at screening and baseline; half of the

participants experienced fever, with lesser occurrences of rash and lymphadenopathy. Prior or concurrent therapies included, nonsteroidal anti-inflammatory drugs (NSAIDS), corticosteroids, other disease-modifying anti-rheumatic drugs (DMARDs) (e.g. anakinra, tocilizumab, tumor necrosis factor [TNF] inhibitors). Participants received either 4 mg/kg canakinumab (Ilaris®) or placebo every 4 weeks for at least 12 weeks. Placebo non-responders at week 12 received canakinumab (Ilaris®) from weeks 12 to 24. Participants who responded to treatment at week 24 were able to enter the open-label, long-term extension phase being treated with canakinumab (Ilaris®). The primary outcome was defined as the proportion of individuals with a clinically relevant reduction of the articular manifestation measured by change in disease activity score (ΔDAS28(ESR)>1.2) at week 12. Twelve individuals in the canakinumab (Ilaris®) and seven individuals in the placebo group showed a reduction of the DAS28(ESR) of more than 1.2 at week 12 (66.7% vs 41.2%, respectively). The difference in the DAS28(ESR) response rate of 25.5% (95% CI −10.3% to 55.9%) was not statistically significant (p=0.18, Fisher's test) and the primary outcome was not met. Canakinumab (Ilaris) led to an improvement of several other outcome measures in AOSD. The authors determined that the efficacy data (reduction in disease activity) were generally consistent with the results of a pooled efficacy analysis of individuals with SJIA.

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS
Systemic juvenile idiopathic arthritis (SJIA), also known as Still's disease, is a rare subtype of juvenile idiopathic arthritis where the individual exhibits systemic effects, such as fever spikes, rash, hepatosplenomegaly, lymphadenopathy, serositis. SJIA is thought to be driven by proinflammatory cytokines such as IL-1β. Treatment of SJIA may include nonsteroidal anti-inflammatory drugs (NSAIDS), glucocorticoids, or disease-modifying anti-rheumatic drugs (DMARDs) (e.g. anakinra, methotrexate).

Ruperto (2012) evaluated the safety and effectiveness of canakinumab (Ilaris®) in the treatment of individuals 2 to 19 years of age with SJIA and active systemic features of fever, two or more active joints involved, C-reactive protein greater than 30 mg/L, and glucocorticoid dose of less than 1 mg/kg/day.

Trial 1 was a randomized, double-blind, single-dose, 29-day study, where 84 individuals received 4 mg/kg canakinumab (Ilaris®) or placebo. The primary outcome, JIA ACR 30 response (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.) At day 15 in trial 1, 36 individuals (84%) in the canakinumab (Ilaris®) group had an adapted JIA ACR 30 response, as compared to 4 individuals (10%) in the placebo group; P<0.001). Those who had a response in Trial 1 were enrolled in Trial 2 on day 29.

Trial 2 was a two-part withdrawal design. During Part 1, 177 individuals received 4 mg/kg canakinumab (Ilaris®) every 4 weeks for 12 to 32 weeks. Those receiving glucocorticoids at enrollment, were permitted to undergo glucocorticoid tapering from week 9 through week 28, if there was at least an adapted JIA ACR 50 response (indicating the absence of fever and an improvement of ≥50% in at least three of the six core criteria for JIA, with a worsening of >30% in no more than one of the criteria). Part 2 was the withdrawal phase where individuals who had at least an adapted JIA ACR 30 response that was sustained and who were not receiving glucocorticoids or who had undergone successful glucocorticoid tapering and were receiving a stable dose of glucocorticoids were randomly assigned in a 1:1 ratio, in a double-blind fashion, to continued treatment with canakinumab (Ilaris®) or to placebo. In this withdrawal phase, individuals who had a disease flare were treated again with canakinumab (Ilaris®) in an open-label fashion. All patients who did not undergo glucocorticoid tapering, who had no response during the open-label phase, or who had a flare during the withdrawal phase could enter the ongoing long-term, open-label extension phase of the trial. The primary outcome was time to flare of systemic JIA. 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 individuals who continued to receive canakinumab (Ilaris®) than among those who were switched to placebo (74% of individuals in the canakinumab group had no flare, vs. 25% in the placebo group, P = 0.003). The average glucocorticoid dose was reduced from 0.34 to 0.05 mg/kg/day, and glucocorticoids were discontinued in 42 of 128 individuals (33%).

OFF-LABEL INDICATION
There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

References

American College of Rheumatology. Patient/Caregiver: Cryopyrin-Associated Autoinflammatory Syndromes. 03/2019. Available at: https://www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Cryopyrin-Associated-Autoinflammatory-Syndrome-CAPS-Juvenile. Accessed June 24, 2020.

American Hospital Formulary Service (AHFS). Drug Information 2020. canakinumab (Ilaris®). [Lexicomp Online Web site]. 12/09/11. Available at: http://online.lexi.com/lco/action/home [via subscription only]. Accessed June 24, 2020.

Beukelman T, Patkar N, Saag K. 2011 American College of Rheumatology Recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res.* 2011;63(4):465-482.

Canakinumab (Ilaris®). [prescribing information]. East Hanover, NJ; Novartis Pharmaceuticals Corp; 09/2020. Available at: http://www.ilaris.com/index.jsp. Accessed December 17, 2020.

De Benedetti F, Gattorno M, Anton J, et al. Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. [Study and Supplementary Appendix]. *N Engl J Med*. 2018;378(20):1908-1919.

Elsevier's Clinical Pharmacology Compendium. Canakinumab (Ilaris®). 06/17/2020. [Clinical Key Web site]. Available at: https://www.clinicalkey.com/pharmacology/ [via subscription only]. Accessed June 24, 2020.

Feist E, Quartier P, Fautrel B, et al. Efficacy and safety of canakinumab in patients with Still's disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups. *Clin Exp Rheumatol.* 2018 Jul-Aug;36(4):668-675.

Frosch M, Roth J. New insights in systemic juvenile idiopathic arthritis--from pathophysiology to treatment. *Rheumatology (Oxford).* 2008 Feb;47(2):121-5.

Greco E, Aita A, Galozzi P, et al. The novel S59P mutation in the TNFRSF1A gene identified in an adult onset TNF receptor associated periodic syndrome (TRAPS) constitutively activates NF-êB pathway. *Arthritis Res Ther.* 2015;17:93.

Hedrich CM, Günther C, Aringer M. Morbus Still im Kindes- und Erwachsenenalter [Still's disease in children and adults]. *Hautarzt*. 2017 Jun;68(6):497-511. German.

Hoffman HM, Gregory SG, Mueller JL, Tresierras M, Broide DH, Wanderer AA, et al. Fine structure mapping of CIAS1: identification of an ancestral haplotype and a common FCAS mutation, L353P. *Hum Genet.* 2003;112: 209-216.

Jamilloux Y, Gerfaud-Valentin M, Martinon F, et al. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart*. Immunol Res.* 2015 Feb;61(1-2):53-62.

Kadavath S, Efthimiou P. Adult-onset Still's disease-pathogenesis, clinical manifestations, and new treatment options. *Ann Med.* 2015 Feb;47(1):6-14.

Kedor C, Listing J, Zernicke, et al. Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation (CONSIDER): Phase II, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Investigator-Initiated Trial. *Ann Rheum Dis*. 2020 May 13;annrheumdis-2020-217155.

Kimura Y. Systemic juvenile idiopathic arthritis: Clinical manifestations and diagnosis. 07/12/2018. Available at: https://www.uptodate.com/contents/systemic-juvenile-idiopathic-arthritis-clinical-manifestations-and-diagnosis?search=sjia&source=search_result&selectedTitle=1~11&usage_type=default&display_rank=1 . Accessed June 24, 2020.

Kimura Y. Systemic juvenile idiopathic arthritis: treatment. 04/02/2019. Available at: https://www.uptodate.com/contents/systemic-juvenile-idiopathic-arthritis-treatment?search=systemic jia&source=search_result&selectedTitle=4~150&usage_type=default&display_rank=4. Accessed June 24, 2020.

Kudela H, Drynda S, Lux A, et al. Comparative study of Interleukin-18 (IL-18) serum levels in adult onset Still's disease (AOSD) and systemic onset juvenile idiopathic arthritis (sJIA) and its use as a biomarker for diagnosis and evaluation of disease activity. *BMC Rheumatol.* 2019 Feb 28;3:4.

Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al; Canakinumab in CAPS Study Group. Use of canakinumab in the cryopyrin-associated periodic syndrome. *N Engl J Med*. 2009;360(23):2416-25.

Lexi-Drugs Compendium. canakinumab (Ilaris®). 06/18/2020. [Lexicomp Online Web site]. Available at: http://online.lexi.com/lco/action/home [via subscription only]. Accessed June 24, 2020.

Livneh A, Langevitz P, Zemer D, et al. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum.* 1997;40(10):1879-85.

Luthi F, Zufferey P, Hofer MF, So AK. "Adolescent-onset Still's disease": characteristics and outcome in comparison with adult-onset Still's disease. Clin Exp Rheumatol. 2002 May-Jun;20(3):427-30.

Mandl LA. Treatment of adult Still's disease. Updated 06/11/2019. Available at: https://www.uptodate.com/contents/treatment-of-adult-stills-disease?search=adult onset still disease&source=search_result&selectedTitle=2~40&usage_type=default&display_rank=2 Accessed June 24, 2020.

National Institutes of Health (NIH). Genetic and Rare Diseases Information Center. Adult-onset Still's Disease. Updated 06/30/2020. Available at: https://rarediseases.info.nih.gov/diseases/436/adult-onset-stills-disease . Accessed December 18, 2020.

National Institutes of Health (NIH). Genetics Home Reference. Familial cold autoinflammatory syndrome. Reviewed 12/2014. Available at: https://ghr.nlm.nih.gov/condition/familial-cold-autoinflammatory-syndrome. Accessed June 24, 2020.

National Institutes of Health (NIH). Genetics Home Reference. Familial Mediterranean Fever. Reviewed 06/2014. Available at: https://ghr.nlm.nih.gov/condition/familial-mediterranean-fever. Accessed June 24, 2020.

National Institutes of Health (NIH). Genetics Home Reference. Hyper-IgD syndrome. Reviewed 06/26/17. Available at: https://rarediseases.info.nih.gov/diseases/2788/hyper-igd-syndrome. Accessed June 24, 2020.

National Institutes of Health (NIH). Genetics Home Reference. Mevalonate kinase deficiency. Reviewed 11/2018. Available at: https://ghr.nlm.nih.gov/condition/mevalonate-kinase-deficiency. Accessed June 24, 2020.

National Institutes of Health (NIH). Genetics Home Reference. Muckle-Wells syndrome. Reviewed 09/2008. Available at: https://ghr.nlm.nih.gov/condition/muckle-wells-syndrome#genes. Accessed June 24, 2020.

National Institutes of Health (NIH). Genetics Home Reference. Tumor necrosis factor receptor-associated periodic syndrome. Reviewed 02/2016. Available at: https://ghr.nlm.nih.gov/condition/tumor-necrosis-factor-receptor-associated-periodic-syndrome#genes. Accessed June 24, 2020.

National Organization of Rare Diseases (NORD). Adult-onset Still's Disease. Updated 2015. Available at: https://rarediseases.org/rare-diseases/adult-onset-stills-disease/. Accessed December 18, 2020.

National Organization of Rare Diseases (NORD). Familial Mediterranean Fever. Updated 02/2017. Available at: https://rarediseases.info.nih.gov/diseases/6421/familial-mediterranean-fever. Accessed June 24, 2020.

National Organization of Rare Diseases (NORD). Hyper-IgD syndrome. Reviewed 06/26/17. Available at: https://rarediseases.info.nih.gov/diseases/2788/hyper-igd-syndrome. Accessed June 24, 2020.

National Organization of Rare Diseases (NORD). Tumor Necrosis Factor Receptor-Associated Periodic Syndrome. Updated 2019. Available at: https://rarediseases.org/rare-diseases/tumor-necrosis-factor-receptor-associated-periodic-syndrome/. Accessed June 24, 2020.

Nirmala N, Brachat A, Feist E, et al. Gene-expression analysis of adult-onset Still's disease and systemic juvenile

idiopathic arthritis is consistent with a continuum of a single disease entity. *Pediatr Rheumatol Online J.* 2015 Nov 20;13:50.

Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum.* 2013;65(10):2499-512.

Ruperto N, Brunner HI, Quartier P, et al; PRINTO; PRCSG. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med.* 2012;367(25):2396-406.

Sfriso P, Bindoli S, Doria A, et al. Canakinumab for the treatment of adult-onset Still's disease. *Expert Rev Clin Immunol.* 2020 Feb;16(2):129-138.

Shinar Y, Obici L, Aksentijevich I, Bennetts B, Austrup F, Ceccherini I, et al. Guidelines for the genetic diagnosis of hereditary recurrent fevers. *Ann Rheum Dis*. 2012;71:1599-1605.

Tran T. Muckle–Wells syndrome: clinical perspectives. *Open Access Rheumatol.* 2017;9: 123-129.

Truven Health Analytics. Micromedex® DrugDex® Compendium. canakinumab (Ilaris®). 09/28/2020. Greenwood Village, CO. [Micromedex® Solutions Web site]. Available at: http://www.micromedexsolutions.com/micromedex2/librarian [via subscription only]. Accessed December 17, 2020.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. canakinumab (Ilaris®) prescribing information and approval letter [FDA Web site]. 09/18/2020. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed December 17, 2020.

Xia X, Dai C, Zhu X, et al. Identification of a Novel NLRP12 Nonsense Mutation (Trp408X) in the Extremely Rare Disease FCAS by Exome Sequencing. *PLoS ONE.* 2016;11(6): e0156981.

Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
E85.0 Non-neuropathic heredofamilial amyloidosis
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
M08.221 Juvenile rheumatoid arthritis with systemic onset, right elbow
M08.222 Juvenile rheumatoid arthritis with systemic onset, left elbow
M08.231 Juvenile rheumatoid arthritis with systemic onset, right wrist
M08.232 Juvenile rheumatoid arthritis with systemic onset, left wrist
M08.241 Juvenile rheumatoid arthritis with systemic onset, right hand
M08.242 Juvenile rheumatoid arthritis with systemic onset, left hand
M08.251 Juvenile rheumatoid arthritis with systemic onset, right hip
M08.252 Juvenile rheumatoid arthritis with systemic onset, left hip
M08.261 Juvenile rheumatoid arthritis with systemic onset, right knee
M08.262 Juvenile rheumatoid arthritis with systemic onset, left 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
M08.28 Juvenile rheumatoid arthritis with systemic onset, vertebrae
M08.29 Juvenile rheumatoid arthritis with systemic onset, multiple sites

HCPCS Level II Code Number(s)

J0638 Injection, canakinumab, 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.101b:

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
05/08/2023	This version of the policy will become effective 05/08/2023. The following ICD-10 CM codes have been **deleted** from this policy, due to unspecified laterality: M08.219 Juvenile rheumatoid arthritis with systemic onset, unspecified shoulder M08.229 Juvenile rheumatoid arthritis with systemic onset, unspecified elbow M08.239 Juvenile rheumatoid arthritis with systemic onset, unspecified wrist M08.249 Juvenile rheumatoid arthritis with systemic onset, unspecified hand M08.259 Juvenile rheumatoid arthritis with systemic onset, unspecified hip M08.269 Juvenile rheumatoid arthritis with systemic onset, unspecified knee M08.279 Juvenile rheumatoid arthritis with systemic onset, unspecified ankle and foot

Revisions From MA08.101a:

3/22/2023	This policy has been reissued in accordance with the Company's annual review process.
03/23/2022	This policy has been reissued in accordance with the Company's annual review process.
02/15/2021	This policy was updated to communicate the Company's coverage position of canakinumab (Ilaris®) for the treatment of Adult-Onset Still's Disease (AOSD). The following ICD-10 codes were **added** to this policy: E85.0 Non-neuropathic heredofamilial amyloidosis M06.1 Adult-onset Still's disease

Revisions From MA08.101:

05/20/2020	This policy has been reissued in accordance with the Company's annual review process.
01/28/2019	This new policy has been issued to communicate the Company's coverage position.

Version Effective Date:
5/8/2023
Version Issued Date:
5/8/2023
Version Reissued Date:
05/07/2024