Ilaris (canakinumab)
Policy Number: C2435-A

CRITERIA EFFECTIVE DATES:

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<th>LAST REVIEWED DATE</th>
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<td>8/26/2020</td>
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<td>RxPA</td>
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PRODUCTS AFFECTED:
Ilaris (canakinumab)

DRUG CLASS:
Interleukin-1beta Blockers

ROUTE OF ADMINISTRATION:
Subcutaneous

PLACE OF SERVICE:
Specialty Pharmacy or Buy and Bill
The recommendation is that medications in this policy will be for pharmacy benefit coverage and the IV infusion products administered in a place of service that is a non-hospital facility-based location (i.e., home infusion provider, provider’s office, free-standing ambulatory infusion center) and the Pre-Filled Syringe product for self-administered

AVAILABLE DOSAGE FORMS:
Ilaris SOLN 150MG/ML (1.2ml)

FDA-APPROVED USES:
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), Muckle-Wells Syndrome (MWS) AND Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients AND Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients AND Familial Mediterranean Fever (FMF) in adult and pediatric patients AND Active Systemic Juvenile Idiopathic Arthritis (sJIA) in patients aged 2 years and older, Active Still’s disease, including Adult-Onset Still’s Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older, Periodic fever syndromes

COMPENDIAL APPROVED OFF-LABEL USES:
None

COVERAGE CRITERIA: INITIAL AUTHORIZATION

DIAGNOSIS:
For the treatment of active systemic juvenile idiopathic arthritis (SJIA) and for Periodic fever syndromes

REQUIRED MEDICAL INFORMATION:
Prior Authorization Criteria

FOR ALL INDICATIONS:

1. (a) Negative TB test within the last 12 months for initial and continuation of therapy requests OR
   (b) If member tests positive for latent TB, there must be documentation showing member completed a treatment course for TB OR that member has been cleared by an infectious disease specialist to begin treatment with Ilaris OR
   (c) For members who have tested positive for latent TB and have been treated, a negative chest x-ray is required every 12 months
   AND
2. Member is not on concurrent treatment or will be used in combination with other TNF-inhibitor, biologic response modifier or other biologic DMARDs, Janus kinase Inhibitors, or Phosphodiesterase 4 inhibitor (i.e., apremilast, tofacitinib, baricitinib)
   AND
3. Member does not have an active infection, including clinically important localized infections
   AND
4. Prescriber to provide recent (within 3 months) member weight for dosing

A. SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)
   1. Member must have a diagnosis of moderate to severe acute systemic juvenile idiopathic arthritis (SJIA)
      AND
   2. Prescriber has assessed baseline disease severity utilizing an objective measure/tool
      AND
   3. Documentation of drug failure or serious side effects to an adequate trial (12 weeks) of TWO of the following: glucocorticoids, Kineret (anakinra), or Actemra (tocilizumab)

B. CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES
   1. Confirmed diagnosis of one Cryopyrin-Associated Periodic Syndromes disorder (CAPS): Familial Cold Auto-inflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS)
      NOTE: Arcalyst (rilonacept) and Ilaris (canakinumab) is not indicated for use in patients with neonatal-onset multisystem inflammatory disease (NOMID), another syndrome that is included in CAPS
      AND
   2. Prescriber attests to Significant functional impairment resulting in limitations of activities of daily living (ADLs)

C. FAMILIAL MEDITERRANEAN FEVER (FMF)
   1. Documented diagnosis of FMF
      AND
   2. Prescriber attests member has protracted febrile myalgia
      AND
   3. Member has tried and failed or has a gastrointestinal intolerance to colchicine

D. HYPERIMMUNOGLOBULIN D SYNDROM/MEVALONATE KINASEDEFICEINCY
   1. (a) Documented diagnosis of HIDS confirmed by a Euro fever Classification Criteria score >42 AND an elevated immunoglobulin D level
      OR
   (b) Documented diagnosis of MVK confirmed by a Euro fever Classification Criteria score >42 AND a MVK gene mutation associated with HIDS (see Appendix)

E. TUMOR NECROIS FACTOR RECEPTOR ASSOCIATED PERIODIC SYNDROME (TRAPS)
   1. Documented Diagnosis of TRAPS confirmed by genetic testing for disease-associated
mutations (pathogenic variants) in the tumor necrosis factor receptor-1 (TNFR1) gene (TNFRSF1A)

F. ACTIVE STILL’S DISEASE:

1. Documented diagnosis of adult still’s disease
   AND
2. Documentation that member did not improvement in symptoms or has a labeled contraindication to: (i) TWO formulary non-steroidal anti-inflammatory drugs (after 14 days of treatment) AND (ii) methotrexate (after 2 months of treatment at maximally tolerated dose)

DURATION OF APPROVAL:
Initial authorization: 6 months, Continuation of treatment: up to 12 months

QUANTITY:
CAPS: >40 kg: 150 mg/dose subcutaneously every 8 weeks, 40 kg or less: 3 mg/kg/dose subcutaneously every 8 weeks,

TRAPS, HIDS/MKD, FMF: > 40 kg: 150 mg subcutaneously every 4 weeks (max 300 mg). 40 kg or less: 2 mg/kg/dose subcutaneously every 4 weeks (max 4 mg/kg/dose).

SJIA:
7.5 kg or more: 4 mg/kg/dose (Max: 300 mg/dose) subcutaneously every 4 weeks.

ACTIVE STILL’S DISEASE (AOSD and SJIA):
4 mg/kg (with a maximum of 300 mg) for patients with a body weight greater than or equal to 7.5 kg. Administer subcutaneously every 4 weeks.

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified rheumatologist, pediatric rheumatologist or physician experienced in the management of systemic juvenile idiopathic arthritis (SJIA). Submit consultation notes if applicable.

AGE RESTRICTIONS:
TRAPS, HIDS/MKD, FMF, SJIA-2 years of age or older, CAPSs-4 years of age and older
Adult-Onset Still’s Disease (AOSD)- 18 years of age and older

CONTINUATION OF THERAPY:
A. FOR ALL INDICATIONS:
   1. Adherence to therapy at least 85% of the time as verified by the prescriber or member’s medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation (documentation required) AND
   2. Documentation of no intolerable adverse effects or drug toxicity AND
   3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition’s signs and symptoms.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Ilaris (canakinumab) are considered experimental/investigational and therefore, will follow Molina’s Off-Label policy. Ilaris (canakinumab) is contraindicated in patients that are pregnant unless being used for advanced breast cancer.
BACKGROUND:
Iloris is indicated for the treatment of MWS or FCAS in patients ≥ 4 years of age.1 CAPS is a rare inherited inflammatory disease associated with overproduction of IL-1. CAPS encompass three rare genetic syndromes. FCAS, MWS, and NOMID are thought to be one condition along a spectrum of disease severity. NOMID was previously known as CINCA. FCAS is the mildest phenotype and NOMID is the most severe. The inflammatory symptoms in these patients include atypical urticaria, rash that is worse in the evening, fever, chills, severe fatigue, arthralgia, and conjunctival erythema. Exacerbations or flares can be triggered by exposure to cold, stress, exercise, or other stimuli.

Patients with NOMID may have sensorineural hearing impairment, increased intracranial pressure, and joint abnormalities. One-fourth of patients with MWS may develop systemic amyloid A (AA) amyloidosis which usually presents with renal impairment and nephrotic syndrome; amyloidosis is less common in the other forms of CAPS. In the published pivotal trial, only patients with a sustained complete response during the initial 8 weeks of the study were eligible for continuation in the trial. A complete clinical response was observed in 71% of patients 1 week after starting therapy and in 97% of patients (n = 34/35) by Week 8. A single-center observational study found that 9 out of 10 patients with CAPS (n = 8 [MWS]; n = 2 [CINCA]) improved following one dose of Ilaris; results were sustained at median follow-up of 21 months.8 NOMID is the most severe form of the CAPS. Two patients in the published pivotal CAPS trial had both MWS and NOMID. An open-label, multicenter, Phase III study evaluated the use of Ilaris in patients with all phenotypes of CAPS (n = 166) and included 32 patients with NOMID. Of the Ilaris-naïve patients, 78% of patients (n = 85/109) achieved a complete response by Day 21 and an additional 23 patients achieved a partial response (e.g., decrease in C-reactive protein [CRP], serum amyloid A [SAA] levels, disease activity, and/or skin rash). For the entire study population, CRP and SAA normalized while on Ilaris, and by Week 8, 79% of patients had absent/mild disease and 21% of patients had mild to moderate disease. At baseline, four NOMID/CINCA patients reported abnormal neurological findings; following 2 years of treatment with Ilaris, one member showed normalization of these findings. Resolution of macular edema was noted in one eye of a NOMID/CINCA patient, and improvement in blepharitis was recorded in another patient. It is notable that higher doses of Ilaris were required for NOMID/CINCA patients and patients ≤ 40 kg compared with other patients in the cohort. In an open-label Phase I/II study evaluating Ilaris in patients with NOMID (n = 7), no patients had full remission at Month 6 (primary endpoint), but four patients achieved inflammatory remission based on disease activity diary scores and normal CRP. At Month 12 and 18, 100% of patients (n = 4/4 at Month 12 and n = 3/3 for Month 18) were in inflammatory remission. Median duration in the trial was 615 days (range, 232 to 749 days). Data are available in two other patients with NOMID treated with Ilaris with long-term moderate efficacy (per the physician’s global assessment [PGA]) [exposure of 120 to 463 days].

Iloris is indicated for treatment of adult and pediatric patients with FMF. Patients with FMF experience recurring bouts of fever, often with severe abdominal pain due to peritonitis. Typical episodes last 12 to 72 hours and the length of time between attacks can range from days to years. Without treatment, amyloidosis may occur. Guidelines from the European League Against Rheumatism (EULAR) [2016] note that treatment goals are to prevent the clinical attacks and to suppress chronic subclinical inflammation. Colchicine is recommended as soon as a diagnosis is made. IL-1 blockade is mentioned as a treatment option for patients with protracted febrile myalgia. In patients who develop AA amyloidosis, the maximal tolerated dose of colchicine and biologics (especially IL-1 blockade) are recommended. A Phase III study enrolled patients with FMF (n = 63) between the ages of 2 and 69 years with documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine; 76% of patients did not have a fever at baseline. Active disease was defined as at least one flare per month; the median number of flares per year was 18. CRP was required to be at least 10 mg/mL (median, 94 mg/mL). Patients were allowed to continue on stable colchicine dose. Of the patients treated with Ilaris, 32% had the dose increased from 150 mg every 4 weeks to 300 mg every 4 weeks. In all, 84% of patients assigned to placebo (n = 27/32) crossed over to receive Ilaris. At Day 15, 81% of patients treated with Ilaris (n = 25/31) had resolution of flare vs. 31% of patients (n = 10/32) treated with placebo. Complete
response, defined as resolution of index flare by Day 15 which was maintained through Week 16, was achieved in 61% of patients (n = 19/31) treated with Ilaris vs. 6% of patients (n = 2/32) treated with placebo (P < 0.0001).

Ilaris is indicated in adult and pediatric patients with HIDS/MKD. MKD typically begins during infancy. Fevers last from 3 to 6 days and occur as often as 25 times per year. During episodes of fever, patients usually experience lymphadenopathy, abdominal pain, joint pain, diarrhea, skin rashes, and headache; amyloidosis may develop. Fever episodes may be triggered by vaccinations, surgery, injury, or stress. Of note, HIDS is considered a less severe type of MKD. Patients with a severe phenotype of MKD may experience growth retardation, ataxia, and cognitive impairment.

European guidelines for autoinflammatory disorders (2015) note that colchicine is not effective. Short-term use of IL-1 blockers should be considered for termination of attacks and should be considered to limit or prevent steroid adverse events. Maintenance therapy with an IL-1 blocker may be used in patients with frequent attacks and/or subclinical inflammation between attacks. A Phase III study enrolled patients (n = 72) with HIDS/MKD who were between the ages of 2 and 47 years. At baseline, 58% of patients did not have a fever. Patients had confirmed diagnosis according to known genetic MVK/enzymatic (MKD) findings and had a history of more than three febrile acute flares within a 6-month period (median of 12 flares per year). CRP was required to be at least 10 mg/mL (median, 113.5 mg/mL). In all, 51% of patients randomized to Ilaris had the dose titrated from 150 mg every 4 weeks to 300 mg every 4 weeks; 87% of patients (n = 31/35) who were randomized to placebo crossed over to receive Ilaris. At Day 15, 65% of patients (n = 24/37) experienced resolution of the index flare. Complete response, defined as resolution of index flare by Day 15 which was maintained through Week 16, was achieved in 35% of patients treated with Ilaris vs. 6% of patients who received placebo.

Ilaris is indicated in adult and pediatric patients with TRAPS. TRAPS is a rare condition with an estimated prevalence of one case per million individuals. It is categorized by recurrent episodes of fever which can last from days to months. The frequency of the fevers varies and may occur anywhere between every 6 weeks to every few years. Fever may be spontaneous but may also be triggered by events such as a minor injury, infection, stress, exercise, or hormonal changes. Additional signs and symptoms that may accompany fever include abdominal and muscle pain, spreading skin rash (typically on the limbs), periorbital edema, joint pain, and inflammation in various areas of the body. Amyloidosis is estimated to occur in 15% to 20% of patients with TRAPS. European recommendations for treatment of autoinflammatory disorders (2015) note that IL-1 blockade is beneficial for the majority of patients with TRAPS. Maintenance therapy with IL-1 blockade, which may limit corticosteroid exposure, is recommended for patients with frequent attacks and/or subclinical inflammation between attacks. A Phase III study enrolled patients (n = 46) between the ages of 2 and 76 years with chronic or recurrent disease activity, defined as six flares per year (median, 9 flares/year); 58% of patients did not have fever at baseline. Baseline CRP was required to be at least 10 mg/mL (median, 112.5 mg/mL). In patients treated with Ilaris, 50% of patients (n = 11/22) had their dose increased from 150 mg every 4 weeks to 300 mg every 4 weeks during the 16-week treatment period; 87.5% of patients randomized to placebo (n = 21/24) crossed over to receive Ilaris. By Day 15, 63% of patients treated with Ilaris vs. 21% of patients treated with placebo had resolution of the index flare. The proportion of patients who achieved a complete response, defined as resolution of index flare by Day 15 that was maintained through Week 16, was 46% with Ilaris vs. 8% with placebo (P = 0.005).

Ilaris is indicated for the treatment of active SJIA in patients ≥ 2 years of age. There are standardized treatment plans published for use of biologic disease-modifying antirheumatic drugs

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(DMARDs), including Actemra, Kineret, and Ilaris, for use in patients with SJIA. For Ilaris, the recommendation is to assess at Week 1 or 2 and Month 1, and adjust other therapies (e.g., corticosteroids) if disease is unchanged or worsening. Patients should be reassessed at Month 3, when patients with unchanged or worsening disease or patients whose steroid dose is > 50% of the starting dose should have an increase in prednisone plus either addition of methotrexate (MTX) OR change to Actemra. Note that when discontinuing Ilaris, patients should wait between 1 and 2 months after discontinuation before switching to a different biologic DMARD. Guidelines from the American College of Rheumatology (ACR) for the management of SJIA (2013) mention Ilaris as a treatment alternative, depending upon the manifestations of SJIA being treated.

While there are a number of other effective options for treating synovitis in patients with active SJIA, effective options for treatment of MAS are much more limited. Recommended options for treatment of MAS are limited and include Kineret, calcineurin inhibitors, and systemic corticosteroids (no preferential sequencing noted). The SJIA guidelines note that use of Ilaris is uncertain in MAS in some situations, such as for initial therapy in patients with a poor physician’s assessment; however, MAS is a potentially life-threatening situation with limited treatment options. In Phase III studies evaluating Ilaris in patients with SJIA, 56% to 66% of patients had previously tried a biologic therapy. At Day 15, 84% of patients receiving Ilaris (n = 36/43) had an adapted JIA ACR 30 response compared with 10% of patients receiving placebo (n = 4/41) [P < 0.001]. In SJIA, Ilaris is administered every 4 weeks.

Adult Onset Stills Disease (AOSD)
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.

APPENDIX:

Molina Healthcare, Inc. covers injectable/infused treatment in a hospital outpatient setting or at a hospital-affiliated infusion suite* when the level of care is determined to be medically necessary. Considerations used to determine if an alternative level of care is not suitable may include the following findings:

1. The member is clinically unstable based on documented medical history and susceptible to complication with drug administration (e.g., cardiopulmonary or renal dysfunction, risk for fluid overload)
2. The requested medication is administered as part of a chemotherapy regimen (e.g., anti-neoplastic agent, colony stimulating factor, erythropoiesis-stimulating agent, anti-emetic) for treatment of cancer or with dialysis
3. The member exhibits physical or cognitive impairment and a capable caregiver is not available to assist with safe administration of prescribed medication in the home
4. It is the patient’s first dose of the medication or it is being re-initiated after at least 12 months*
5. The member has experienced adverse events with past administration of the drug and cannot be managed by premedication or resources available at an non-hospital facility based location (NHFBL)
6. Documented history of difficulty establishing and maintaining patent vascular access, or is not a candidate for a mode of long-term vascular access during the duration of
prescribed treatment

Note: a hospital outpatient setting, or a hospital-affiliated infusion suite is expected to have immediate access to specific services of a medical center/hospital setting, including having emergency resuscitation equipment and personnel (ACLS protocol), emergency services, and inpatient admission or intensive care, if necessary

REFERENCES:

1. Ilaris® for subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2020


