PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Ilaris Prior Authorization Policy
- Ilaris® (canakinumab subcutaneous injection – Novartis)

REVIEW DATE: 01/25/2023

OVERVIEW

Ilaris, an interleukin-1β (IL-1β) blocker, is indicated for the following autoinflammatory periodic fever syndromes:[1]

- **Cryopyrin-Associated Periodic Syndromes** (CAPS), including Familial Cold Autoinflammatory Syndrome and Muckle-Wells Syndrome, for treatment of patients who are ≥ 4 years of age.
- **Familial Mediterranean fever**, in adult and pediatric patients.
- **Hyperimmunoglobulin D syndrome/mevalonate kinase deficiency**, in adult and pediatric patients.
- **Still's disease**, including active **adult-onset Still's disease** and **systemic juvenile idiopathic arthritis** (SJIA), in patients ≥ 2 years of age.
- **Tumor necrosis factor receptor associated periodic syndrome** (TRAPS), in adult and pediatric patients.

In the pivotal study for period fevers, patients were required to be at least 2 years of age with a disease flare, defined as a C-reactive protein level ≥ 10 mg/L. Prior to starting Ilaris, a minimum level of disease activity at baseline was required for familial Mediterranean fever (at least one flare per month despite colchicine), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (≥ three febrile acute flares within the previous 6 month period), and TRAPS (≥ six flares per year). In this study, patients were assessed for a response following 4 months of treatment with Ilaris.

Guidelines

Ilaris is used for a variety of periodic fever syndromes and inflammatory conditions.

- **CAPS:** A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of CAPS.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval is among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease with low disease activity.
- **Familial Mediterranean Fever:** Guidelines for familial Mediterranean fever from the European League Against Rheumatism (EULAR) [2016] note that treatment goals are to prevent the clinical attacks and to suppress chronic subclinical inflammation.[6] IL-1 blockade is an option for patients with protracted febrile myalgia. In patients who develop amyloidosis, the maximal tolerated dose of colchicine and biologics (especially IL-1 blockade) are recommended.
- **Mevalonate Kinase Deficiency:** European guidelines for autoinflammatory disorders (2015) recommend consideration of short-term use of IL-1 blockers for termination of attacks and to limit or prevent steroid adverse events.[5] Maintenance therapy with an IL-1 blocker may be used in patients with mevalonate kinase deficiency and frequent attacks and/or subclinical inflammation between attacks. A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of mevalonate kinase deficiency/hyperimmunoglobulin D syndrome.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following

1 to 3 months of treatment, dose escalation or shortened dosing interval is among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease.

- **SJIA:** There are standardized treatment plans published for use of Ilaris.[7,8] At Month 3, 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 or change to Actemra. Guidelines from the American College of Rheumatology for the management of SJIA (2021) mention Ilaris as a treatment alternative, depending upon the manifestations of SJIA being treated.[9] While there are a number of other effective options for treating synovitis in patients with active SJIA, effective options for treatment of macrophage activation syndrome are much more limited and include Kineret (anakinra subcutaneous injection), calcineurin inhibitors, and systemic corticosteroids (no preferential sequencing noted). Although use of Ilaris is uncertain in some situations, macrophage activation syndrome is a potentially life-threatening situation with limited treatment options.
- **TRAPS:** European guidelines for autoinflammatory disorders (2015) note that IL-1 blockade is beneficial for the majority of patients; maintenance with IL-1 blockade, which may limit corticosteroid exposure, may be used in patients with frequent attacks and/or subclinical inflammation between attacks. A consensus protocol for hereditary autoinflammatory syndromes (2020) lists Ilaris as a treatment option across the spectrum of TRAPS.[11] Continuous therapy is recommended for severe, continuous disease. For those who do not achieve remission or minimal disease activity following 1 to 3 months of treatment, dose escalation or shortened dosing interval is among the treatment options. On-demand therapy is also a treatment option for those patients who have intermittent, mild disease.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Ilaris. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Ilaris as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Ilaris to be prescribed by or in consultation with a physician who specializes in the condition being treated.

All reviews for use of Ilaris for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Ilaris is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes (CAPS) [including Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multisystem Inflammatory Disease {NOMID} or Chronic Infantile Neurological Cutaneous and Articular {CINCA} Syndrome].** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets the following conditions (i and ii):
     - **i.** Patient is ≥ 4 years of age; AND

ii. Ilaris is prescribed by or in consultation with a rheumatologist, geneticist, allergist/immunologist, or dermatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

2. Familial Mediterranean Fever. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 2 years of age; AND

ii. Patient has tried colchicine, unless contraindicated; AND

iii. Patient will be taking Ilaris in combination with colchicine, unless colchicine is contraindicated or not tolerated; AND

iv. Prior to starting Ilaris, the patient meets both of the following (a and b):

a) C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND

b) Patient has a history of at least one flare per month despite use of colchicine, OR was hospitalized for a severe flare; AND

v. The medication is prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, gastroenterologist, oncologist, or hematologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

3. Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Prior to starting Ilaris, the patient meets both of the following (a and b):
  - **a)** C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND
  - **b)** Patient has a history of at least three febrile acute flares within the previous 6-month period OR was hospitalized for a severe flare; AND
- **iii.** The medication is prescribed by or in consultation with a rheumatologist, nephrologist, geneticist, oncologist, or hematologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on this medication for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.
  - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

4. Stills Disease, Adult Onset. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months (which is adequate for three doses) if the patient meets ALL of the following conditions (i, ii, and iii):
- **i.** Patient is ≥ 18 years of age; AND
  Note: If the patient is < 18 years of age, refer to criteria for systemic juvenile idiopathic arthritis.
- **ii.** Patient meets ONE of the following conditions (a, b, or c):
  - **a)** Patient has tried at least TWO other biologics; OR
    Note: Examples of biologics include Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection), Kineret (anakinra subcutaneous injection), Orencia (abatacept intravenous infusion, abatacept subcutaneous injection), an etanercept product, adalimumab product, or infliximab product.
  - **b)** Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient has features of poor prognosis, as determined by the prescriber; AND
      Note: Examples of features of poor prognosis include arthritis of the hip, radiographic damage, 6-month duration of significant active systemic disease, defined by: fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids.
    - **(2)** Patient has tried Actemra or Kineret; OR
  - **c)** Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND
    - **(2)** Patient has tried Kineret; AND
- **iii.** Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on this medication for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
  - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

5. Systemic Juvenile Idiopathic Arthritis (SJIA). Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months (which is adequate for three doses) if the patient meets ALL of the following conditions (i, ii, and iii):
- **i.** Patient is ≥ 2 years of age; AND
- **ii.** Patient meets ONE of the following conditions (a, b, or c):
  - **a)** Patient has tried at least TWO other biologics; OR
    Note: Examples of biologics for SJIA include Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection), Kineret (anakinra subcutaneous injection), Orencia (abatacept intravenous infusion, abatacept subcutaneous injection), an etanercept product, adalimumab product, or infliximab product.
  - **b)** Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient has features of poor prognosis, as determined by the prescriber; AND
      Note: Examples of features of poor prognosis include arthritis of the hip, radiographic damage, 6-month duration of significant active systemic disease, defined by: fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids.
    - **(2)** Patient has tried Actemra or Kineret; OR
  - **c)** Patient meets BOTH of the following [(1) and (2)]:
    - **(1)** Patient has features of SJIA with active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND
    - **(2)** Patient has tried Kineret; AND
- **iii.** Ilaris is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on this medication for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
    Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

6. **Tumor Necrosis Factor Receptor Associated Periodic Syndrome.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 2 years of age; AND
     - **ii.** Prior to starting Ilaris, the patient meets both of the following (a and b):
       - **a)** C-reactive protein level is ≥ 10 mg/L OR elevated to at least two times the upper limit of normal for the reporting laboratory; AND
       - **b)** Patient has a of at least six flares per year OR was hospitalized for a severe flare; AND
     - **iii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, nephrologist, oncologist, or hematologist.
   - **B)** Patient is Currently Receiving Ilaris. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on this medication for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):
       - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         Note: Examples of objective measures include decreased frequency of attacks, resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.
       - **b)** Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as decreased pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Ilaris is not recommended in the following situations:

1. **Concurrent Biologic Therapy.** Ilaris has not been evaluated and should not be administered in combination with another biologic agent for an inflammatory condition (see Appendix for examples). An increased incidence of serious infections has been associated with another IL-1 blocker, Kineret, when given in combination with tumor necrosis factor inhibitor in patients with rheumatoid arthritis. Concomitant administration of Ilaris and other agents that block IL-1 or its receptors is not recommended.

2. **COVID-19 (Coronavirus Disease 2019).** Forward all requests to the Medical Director.
   Note: This includes requests for cytokine release syndrome associated with COVID-19.

3. **Rheumatoid Arthritis.** Efficacy is not established. In a 12-week, Phase II, placebo-controlled, double-blind study, 277 patients who had failed methotrexate were randomized to Ilaris or placebo.[10] Although the ACR 50 at Week 12 was higher for Ilaris 150 mg (given every 4 weeks) compared with placebo (26.5% vs. 11.4%, respectively; P = not significant), there was not a statistically significant difference in ACR 50 for the other Ilaris treatment groups (Ilaris 300 mg every 2 weeks; Ilaris 600 mg loading dose followed by 300 mg every 2 weeks).

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

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4. Genetics Home Reference. US National Library of Medicine. Available at: https://ghr.nlm.nih.gov/. Accessed on January 23, 2023. Search terms: TRAPS, familial Mediterranean fever, MKD.
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Type of Revision	Summary of Changes	Review Date
Early Annual Revision	**Cryopyrin-Associated Periodic Syndromes (including Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and Neonatal Onset Multisystem Inflammatory Disease or Chronic Infantile Neurological Cutaneous and Articular Syndrome):** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Familial Mediterranean Fever:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Stills Disease, Adult Onset:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Systemic Juvenile Idiopathic Arthritis:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber. **Tumor Necrosis Factor Receptor Associated Periodic Syndrome:** Initial approval duration was changed to 6 months (previously was 3 months). For a patient currently receiving, it was clarified that this applies to a patient who is receiving for ≥ 6 months. A requirement was added for a patient who is currently receiving to have at least one objective or subjective response to therapy. Previously, response was more general and according to the prescriber.	02/16/2022
Annual Revision	No criteria changes.	01/25/2023

APPENDIX

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis.