VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION REVIEW MEDICAL POLICY

POLICY: Inflammatory Conditions – Ilaris Utilization Review Medical Policy
- Ilaris® (canakinumab for subcutaneous injection – Novartis)

REVIEW DATE: 04/22/2020; selected revision 06/24/2020

OVERVIEW

Ilaris, an interleukin-1β (IL-1β) blocker, is indicated for the following uses:[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.
- **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.
- **Hyperimmunoglobulin D Syndrome/mevalonate kinase deficiency**, in adult and pediatric patients.
- **Familial Mediterranean Fever**, in adult and pediatric patients.

In the pivotal study for period fevers (TRAPS, Hyperimmunoglobulin D Syndrome/mevalonate kinase deficiency, and Familial Mediterranean Fever), 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.

- **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 (2013) 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.
- **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.
- **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 AA amyloidosis, the maximal tolerated dose of colchicine and biologics (especially IL-1 blockade) are recommended.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Ilaris. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the criteria and dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). 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.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indication

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 3 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 has had a response, as determined by the prescriber.

   Dosing. Approve the following dosing (A and B):
   - **A)** Each individual dose must meet the following (i or ii):
     - **i.** *Patient is ≥ 15 kg and ≤ 40 kg*: Approve up to 3 mg/kg for each dose; OR
     - **ii.** *Patient is > 40 kg*: Approve up to 150 mg for each dose; AND
   - **B)** There must be an interval of at least 8 weeks between doses.

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 4 months if Ilaris 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 has had a response, as determined by the prescriber.

Note: The patient may not have a full response, but there should have been a recent or past response to Ilaris.

Dosing. Approve the following dosing (A and B):
A) Each individual dose must meet the following (i or ii):
- **i.** *Patient is ≤ 40 kg*: Approve up to 4 mg/kg for each dose; OR
- **ii.** *Patient is > 40 kg*: Approve up to 300 mg for each dose; AND

B) There must be an interval of at least 4 weeks between doses.

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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 4 months if Ilaris 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 has had a response, as determined by the prescriber.
Note: The patient may not have a full response, but there should have been a recent or past response to Ilaris.

Dosing. Approve the following dosing (A and B):
A) Each individual dose must meet the following (i or ii):
- **i.** *Patient is ≤ 40 kg*: Approve up to 4 mg/kg for each dose; OR
- **ii.** *Patient is > 40 kg*: Approve up to 300 mg for each dose; AND

B) There must be an interval of at least 4 weeks between doses.

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4. 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 3 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 has had a response as determined by the prescriber.
Note: Examples of responses to therapy include resolution of fevers or rash, improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue; improved function or activities of daily living, and reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Ilaris.

Dosing. Approve the following dosing (A and B):
A) The dose is up to 4 mg/kg to a maximum of 300 mg per dose; AND
B) There must be an interval of at least 4 weeks between doses.

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5. 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 3 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 has had a response as determined by the prescriber.
Note: Examples of responses to therapy include resolution of fevers or rash, improvement in limitation of motion, less joint pain or tenderness, decreased duration of morning stiffness or fatigue; improved function or activities of daily living, and reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Ilaris.

Dosing. Approve the following dosing (A and B):
A) The dose is up to 4 mg/kg to a maximum of 300 mg per dose; AND
B) There must be an interval of at least 4 weeks between doses.

5. **Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 4 months if 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 has had a response, as determined by the prescriber.
     Note: The patient may not have a full response, but there should have been a recent or past response to Ilaris.

   Dosing. Approve the following dosing (A and B):
   - **A)** Each individual dose must meet the following (i or ii):
     - **i.** *Patient is ≤ 40 kg*: Approve up to 4 mg/kg for each dose; OR
     - **ii.** *Patient is > 40 kg*: Approve up to 300 mg for each dose; AND
   - **B)** There must be an interval of at least 4 weeks between doses.

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.[11,12] In a 12-week, Phase II, placebo-controlled, double-blind study, 277 patients who had failed methotrexate were randomized to Ilaris or placebo.[11] 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 = 0.028), 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.

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HISTORY

Type of Revision	Summary of Changes	Date Reviewed
New Policy	--	04/22/2020
06/24/2020	**Systemic Juvenile Idiopathic Arthritis:** Resolution of rash was added as an example of a response to therapy. **Still's Disease, Adult Onset:** Criteria were updated to align with the new labeling. Criteria and dosing for systemic juvenile idiopathic arthritis now also apply to adult-onset Still's disease.	06/24/2020

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, PJIA, PsO, PsA, RA, SJIA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PJIA, PsO, PsA, RA, SJIA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: PJIA, PSA, RA
		IV formulation: PJIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Ilaris (canakinumab SC injection**)**	Inhibition of IL-1β	SJIA
Kineret® (anakinra SC injection)	Inhibition of IL-1	RA, SJIA^
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* 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; IV – Intravenous, TNF – Tumor necrosis factor; IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; PJIA – Polyarticular juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; SJIA – Systemic juvenile idiopathic arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of SJIA supported in guidelines; DMARD – Disease-modifying antirheumatic drug.