Medical Drug Clinical Criteria

Subject:	Interleukin-1 Inhibitors		
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Overview

This document addresses the use of interleukin-1 (IL-1) inhibitors which block IL-1β signaling, thereby reducing the effects of overactive inflammasone which is a crucial mediator of autoinflammatory conditions. Indications are drug-specific but IL-1 inhibitors are approved for the treatment of cryopyrin-associated periodic syndromes (CAPS), rheumatoid arthritis, systemic juvenile idiopathic arthritis, familial Mediterranean fever (FMF), Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), tumor necrosis factor receptor associated periodic syndrome (TRAPS), and other conditions as appropriate. Agents addressed in this clinical guideline include:

- Arcalyst (rilonacept)
- Ilaris (canakinumab)
- Kineret (anakinra)

Rheumatoid Arthritis: The American College of Rheumatology (ACR) guidelines recommend disease-modifying antirheumatic drug (DMARD) monotherapy as first-line treatment in individuals with RA with moderate to high disease activity. Methotrexate (MTX) monotherapy, titrated to a dose of at least 15 mg, is recommended over hydroxychloroquine, sulfasalazine, and leflunomide. Methotrexate monotherapy is also recommended over monotherapy with biologics (TNFi, IL-6 inhibitors, abatacept) or JAK inhibitors. For individuals taking maximally tolerated doses MTX who are not at target, the addition of a biologic or JAK inhibitor is recommended. Non-TNFi biologics or JAK inhibitors are conditionally recommended over TNFi in individuals with heart failure. Anakinra was not included in these guidelines due to infrequent use.

Juvenile Idiopathic Arthritis: The American College of Rheumatology (ACR) guidelines provide recommendations for juvenile idiopathic arthritis, including systemic disease (SJIA) and JIA with polyarthritis (PJIA). SJIA is an autoinflammatory condition marked by intermittent fever, rash, and arthritis. PJIA is marked by the presence of more than four affected joints in the first six months of illness. For SJIA, NSAIDs or glucocorticoids are conditionally recommended as initial monotherapy, depending on whether macrophage activation syndrome (MAS) is present or not. IL-1 inhibitors (anakinra or canakinumab), or tocilizumab are also conditionally recommended as initial therapy or to achieve inactive disease, with no preferred agent. For SJIA without MAS, IL-1 inhibitors (anakinra or canakinumab) and tocilizumab are strongly recommended for inadequate response to or intolerance of NSAIDs and/or glucocorticoids (ACR 2021). For children with active polyarthritis, biologic therapy including TNFi, abatacept, or tocilizumab +/- DMARD is recommended following initial DMARD therapy (preferably methotrexate) (ACR 2019). Adult-onset Still's Disease (AOSD) describes SJIA when the condition begins after the patient's 16th birthday. Though only canakinumab has been specifically FDA approved for AOSD, other agents used for SJIA may be useful in clinical practice.

CAPS and DIRA: Cryopyrin-associated periodic syndromes (CAPS) are rare, clinically overlapping, IL-1 associated, autoinflammatory conditions and include familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disorder [(NOMID), also known as chronic infantile neurologic cutaneous and articular (CINCA) syndrome]. Individuals with FCAS, when exposed to generalized cold, experience a systemic inflammatory response including fever, urticarial rash, and substantial arthralgias. MWS is characterized by progressive sensorineural hearing loss, secondary amyloidosis with nephropathy, and intermittent episodes of fever, headache, urticarial rash, and arthralgia. NOMID is the most severe CAPS with a multitude of symptoms that develop at or near the time of birth and may result in premature death or secondary amyloidosis as a result of chronic inflammation. IL-1 inhibitors play a central role in the treatment of CAPS. Deficiency of Interleukin-1 Receptor Antagonist (DIRA) is a distinct but related extremely rare autoinflammatory disease found in neonates. The most common characteristics of DIRA include sterile multifocal osteomyelitis, periostitis and neutrophilic pustulosis and may also include periarticular swelling, oral mucosal lesions and vasculitis. DIRA typically presents between birth and 2 months postpartum and is diagnosed through homozygous germline mutations in *IL1RN* gene. If untreated, DIRA can lead to multiorgan failure and death. There are currently two medications indicated for DIRA, Aracalyst (rilonacept) and Kineret (anakinra).

FMF, HIDS/MKD, and TRAPS: Familial Mediterranean fever (FMF), Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), and Tumor necrosis factor receptor associated periodic syndrome (TRAPS) are autoinflammatory conditions

characterized by recurrent fever episodes with variable skin, joint, and serosal involvement. Colchicine is the standard first-line therapy for FMF while there is no standard first-line treatment for HIDS/MKD or TRAPS. Ilaris (canakinumab) is approved for the treatment of FMF, HIDS/MKD, and TRAPS.

Recurrent Pericarditis (RP): Acute pericarditis refers to inflammation of the pericardial sac caused by infection, malignancy, or autoimmune disorder, with most cases being idiopathic. Symptoms may return after initial attack, especially in cases with an autoimmune origin, but exact recurrence rates are unknown. Treatment of Recurrent Pericarditis (RP) may include NSAIDS, colchicine, or glucocorticoid therapy. Arcalyst is FDA approved for treatment of recurrent pericarditis and for reduction in the risk of recurrence.

Gout: The 2020 American College of Rheumatology (ACR) guidelines were published prior to the approval of Ilaris for gout flares. Guidelines recommend oral colchicine, NSAIDs or glucocorticoids as appropriate first-line therapy for gout flares over IL-1 inhibitors. For individuals for whom other anti-inflammatory therapies are poorly tolerated or contraindicated, guidelines conditionally recommend using IL-1 inhibition over no therapy. Canakinumab was recently approved by the FDA for the symptomatic treatment of adult patients with gout flares in whom NSAIDs and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and in whom repeated courses of corticosteroids are not appropriate.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Arcalyst (rilonacept)

Initial requests for Arcalyst (rilonacept) may be approved for the following:

I. Cryopyrin-associated periodic syndromes (CAPS) when each of the following criteria are met:
   A. Individual is 12 years of age or older with either of the following cryopyrin-associated periodic syndromes:
      1. Familial cold autoinflammatory syndromes; **OR**
      2. Muckle-Wells syndrome;

OR

II. Deficiency of Interleukin-1 Receptor Antagonist (DIRA) when each of the following criteria are met:
   A. Individual weighs at least 10 kilograms; **AND**
   B. DIRA is verified through *IL1RN* mutations; **AND**
   C. Disease is in remission from previous anakinra (Kineret) treatment;

OR

III. Recurrent Pericarditis (RP) when each of the following criteria are met:
   A. Individual is 12 years of age or older using for treatment of RP or reduction in risk of recurrence; **AND**
   B. Individual has a history of at least two pericarditis episodes (i.e. presents with at least the third episode) (Klein 2021).

Continuation requests for Arcalyst (rilonacept) may be approved if the following criteria are met:

I. Individual has been receiving and is maintained on a stable dose of Arcalyst; **AND**
II. There is clinically significant improvement or stabilization in clinical signs and symptoms of disease.

Requests for Arcalyst (rilonacept) may not be approved for the following:

I. In combination with topical or oral JAK inhibitors, ozanimod, etrasimod, deucravacitinib, or any of the following biologic immunomodulators: TNF antagonists, IL-23 inhibitors, IL-17 inhibitors, vedolizumab, ustekinumab, abatacept, other IL-1 inhibitors, IL-6 inhibitors, rituximab, or natalizumab; **OR**
II. Tuberculosis, other active serious infections, or a history of recurrent infections [repeat TB testing is not required for ongoing therapy]; **OR**
III. If initiating therapy, individual has not had a tuberculin skin test (TST) or a Centers for Disease Control (CDC-) and Prevention -recommended equivalent to evaluate for latent tuberculosis (unless switching therapy from another targeted immune modulator and no new risk factors); **OR**
IV. When the above criteria are not met and for all other indications.

Ilaris (canakinumab)

Initial requests for Ilaris (canakinumab) may be approved for the following:

I. Cryopyrin-associated periodic syndromes (CAPS) when each of the following criteria are met:
   A. Individual is 4 years of age or older with either of the following cryopyrin-associated periodic syndromes:
      1. Familial cold autoinflammatory syndromes; **OR**
      2. Muckle-Wells syndrome;

OR

II. Familial Mediterranean fever (FMF) when each of the following criteria are met:
   A. Individual has active type 1 FMF disease with genetic verification of the diagnosis (MEFV gene exon 10 mutation) (De Benedetti 2018); **AND**
   B. Individual has recurrent, active disease (defined as at least one flare per month); **AND**
   C. Individual has failed to respond to or is intolerant of colchicine therapy;

OR

III. Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) when each of the following criteria are met:
   A. Individual has HIDS with genetic verification of the diagnosis by deoxyribonucleic acid (DNA) analysis or enzymatic studies (for example, mutations in the MVK gene or markedly reduced mevalonate kinase activity); **AND**
   B. Individual has confirmed prior history of greater than or equal to three febrile acute flares within a 6-month period when not receiving prophylactic treatment;

OR

IV. Tumor necrosis factor receptor associated periodic syndrome (TRAPS) when each of the following criteria are met:
   A. Individual has TRAPS with genetic verification of the diagnosis (TNFRSF1A gene mutation) (De Benedetti 2018); **AND**
   B. Individual has chronic or recurrent disease activity (defined as six flares in a 12-month period);

OR

V. Still's disease (Adult-onset Still's Disease [AOSD] or Systemic juvenile idiopathic arthritis [SJIA]) when the following is met:
   A. Individual is 2 years of age or older with Still's Disease as either ASOD or SJIA;

OR

VI. Gout flares when each of the following criteria are met:
   A. Individual 18 years of age or older and is using Ilaris for symptomatic treatment of a gout flare; **AND**
   B. Individual meets either of the following:
      1. Individual has had an inadequate response to *both* nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine; **OR**
      2. Individual has a contraindication to or is intolerant of *both* NSAIDs and colchicine; **AND**
   C. Repeated courses of corticosteroids are not appropriate for the individual; **AND**
   D. If individual has received a prior administration of Ilaris for a gout flare, there is a least a 12-week interval between treatments.

Approval duration for gout flares: Treatment of one flare (one 150 mg subcutaneous administration).

Continuation requests for Ilaris (canakinumab) may be approved if the following criteria are met:

I. Individual has been receiving and is maintained on a stable dose of Ilaris; **AND**
II. There is clinically significant improvement or stabilization in clinical signs and symptoms of disease.

Requests for Ilaris (canakinumab) may not be approved for the following:

I. In combination with topical or oral JAK inhibitors, ozanimod, etrasimod, deucravacitinib, or any of the following biologic immunomodulators: TNF antagonists, IL-23 inhibitors, IL-17 inhibitors, vedolizumab, ustekinumab, abatacept, other IL-1 inhibitors, IL-6 inhibitors, rituximab, or natalizumab; **OR**
II. Tuberculosis, other active serious infections, or a history of recurrent infections [repeat TB testing not required for ongoing therapy]; **OR**
III. If initiating therapy, individual has not had a tuberculin skin test (TST) or a Centers for Disease Control (CDC-) and Prevention -recommended equivalent to evaluate for latent tuberculosis (unless switching therapy from another targeted immune modulator and no new risk factors); **OR**
IV. When the above criteria are not met and for all other indications.

Kineret (anakinra)

Initial requests for Kineret (anakinra) may be approved for the following:

I. Rheumatoid Arthritis (RA) when each of the following criteria are met:
   A. Individual is 18 years of age or older with moderate to severe RA; **AND**
   B. Documentation is provided that individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR 2021); **OR**
   C. Documentation is provided that if methotrexate is not tolerated, individual has had an inadequate response to, or is intolerant of other conventional therapy (sulfasalazine, leflunomide, or hydroxychloroquine); **OR**
   D. Documentation is provided that individual has a contraindication to methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine;

OR

II. Individual has a diagnosis of deficiency of interleukin-1 receptor antagonist (DIRA), verified through *IL1RN* mutations;

OR

III. Individual has a diagnosis of treatment-naïve or refractory (DP B IIa) neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurological cutaneous and articular (CINCA) syndrome;

OR

IV. Individual has a diagnosis of multicentric Castleman's Disease (MCD) (NCCN 2A); **AND**
V. Disease has progressed following treatment of relapsed/refractory or progressive disease;

OR

VI. Individual has a diagnosis of Chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome CRS that is refractory to steroids and anti-IL-6 therapy (NCCN 2A); **OR**
VII. Individual has a diagnosis of Chimeric antigen receptor (CAR) T cell-induced neurotoxicity that is refractory to steroids (NCCN 2A);

OR

VIII. Individual has a diagnosis of Erdheim-Chester Disease (NCCN 2A); **AND**
IX. Individual is using anakinra as a single agent;

OR

X. Still's disease (Adult-onset Still's Disease [AOSD] or Systemic juvenile idiopathic arthritis (SJIA) when the following is met (ACR 2021):
   A. Individual is 2 years of age or older with Still's Disease as either AOSD or SJIA.

Continuation requests for Kineret (anakinra) may be approved if the following criteria are met:

I. Individual has been receiving and is maintained on a stable dose of Kineret; **AND**
II. There is clinically significant improvement or stabilization in clinical signs and symptoms of disease.

Requests for Kineret (anakinra) may not be approved for the following:

I. In combination with topical or oral JAK inhibitors, ozanimod, etrasimod, deucravacitinib, or any of the following biologic immunomodulators: TNF antagonists, IL-23 inhibitors, IL-17 inhibitors, vedolizumab, ustekinumab, abatacept, other IL-1 inhibitors, IL-6 inhibitors, rituximab, or natalizumab; **OR**
II. Tuberculosis, other active serious infections, or a history of recurrent infections [repeat TB testing not required for ongoing therapy]; **OR**
III. If initiating therapy, individual has not had a tuberculin skin test (TST) or Centers for Disease Control (CDC) and Prevention - recommended equivalent to evaluate for latent tuberculosis (unless switching therapy from another targeted immune modulator and no new risk factors); **OR**
IV. When the above criteria are not met and for all other indication.

Quantity Limits

Arcalyst (rilonacept) Quantity Limit

Drug	Limit
Arcalyst 160 mg/2 mL (220 mg) single-use vial*	4 vials per 28 days
Override Criteria	
*Initiation of therapy for Familial Cold Auto-inflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS): May approve 1 (one) additional vial (160 mg/2 mL) in the first 28 days (4 weeks) of treatment. * For the treatment of deficiency of interleukin-1 receptor antagonist (DIRA): May approve up to 8 vials per 28 days.	

Ilaris (canakinumab) Quantity Limit

Drug	Limit
Ilaris (canakinumab) 150 mg/mL (180 mg) single use vial*	2 vials per 28 days

**Indicates FDA maximum dosing to accommodate Still's Disease, TRAPS, HIDS/MKD, and FMF indications.*

Kineret (anakinra) Quantity Limit

Drug	Limit
Kineret (anakinra) 100 mg/0.67 mL prefilled syringe*	1 prefilled syringe per day
Override Criteria	
*For the treatment of neonatal-onset multisystem inflammatory disease (NOMID) or deficiency of interleukin-1 receptor antagonist (DIRA): May approve up to 8 mg/kg/day	

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J2793	Injection, rilonacept, 1 mg [Arcalyst]
J0638	Injection, canakinumab, 1 mg [Ilaris]
C9399	Unclassified drugs [when specified as anakinra (Kineret)]
J3590	Unclassified drugs and biologics [when specified as anakinra (Kineret)]

ICD-10 Diagnosis

D47.Z2	Castleman disease [Kineret]
G92.0	Immune effector cell-associated neurotoxicity syndrome [Kineret]
I31.9	Disease of pericardium, unspecified
M04.2	Cryopyrin-associated periodic syndromes [Arcalyst, Ilaris, (Kineret)]
M04.1	Periodic fever syndromes (TRAPS) [Ilaris]
M04.8	Deficiency of interleukin 1 receptor antagonist [DIRA]
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor [Kineret]
M06.00-M06.09	Rheumatoid arthritis without rheumatoid factor [Kineret]
M06.1	Adult-onset Still's disease [Ilaris, Kineret]
M06.4	Inflammatory polyarthropathy [Kineret]
M06.80-M06.89	Other specified rheumatoid arthritis [Kineret]
M06.9	Rheumatoid arthritis, unspecified [Kineret]
M08.00-M08.3	Juvenile rheumatoid arthritis [Kineret, Ilaris]
M08.80-M08.89	Other juvenile arthritis [Kineret, Ilaris]
M10.00-M10.9	Gout [Ilaris]

Document History

Revised: 11/15/2024
Document History:

- 11/15/2024 – Annual Review: Update Kineret criteria with NCCN recommendation for use in Chimeric antigen receptor (CAR) T cell-induced neurotoxicity; wording and formatting updates. Coding Reviewed: Delete HCPCS J3490 for Kineret and add HCPCS C9399 for Kineret. Add ICD-10-CM G92.0 for Kineret. Changed descriptor of ICD-10-CM and added [Ilaris, Kineret] to M06.1 and M08.80-M08.89. Added descriptor [Ilaris] to M10.00-M10.9 ICD-10-CM.
- 03/01/2024 – Administrative update to add documentation.
- 11/17/2023 – Annual Review: Update Kineret criteria with NCCN recommendations for Castleman Disease, Erdheim-Chester Disease, and cytokine release syndrome; update contraindication to prior therapy language for clarity; clarify repeat TB testing requirements; include etrasimod in combination exclusion; add continuation of use language; wording and formatting updates. Coding Reviewed: No changes.
- 09/11/2023 – Select Review: Add new indication and approval duration for gout flares in canakinumab criteria. Coding Reviewed: Added ICD-10-CM M10.00-M10.9.
- 11/18/2022 – Annual Review: Update Kineret criteria in systemic juvenile idiopathic arthritis to remove prior trial requirements and include adult onset disease; update Ilaris criteria in systemic juvenile idiopathic arthritis to remove prior trial requirements; update references; update combination exclusion list to include immunomodulator agents; wording and formatting updates. Coding Reviewed: Added ICD-10-CM M08.80-M08.89
- 11/19/2021 – Annual Review: Clarify tuberculosis testing requirements; update RA criteria to emphasize prior trial of methotrexate and to remove option of prior TNF for consistency. Coding Reviewed: No changes.
- 05/21/2021 – Selected Review: Update Arcalyst criteria and quantity limit with new FDA indication in recurrent pericarditis. Coding Reviewed: Added ICD-10-CM I31.9.
- 03/15/2021 – Selected Review: Add DIRA indication for Arcalyst and Kineret; update quantity limit overrides for Arcalyst and Kineret; updates to may not be approved sections for clarity. Coding Reviewed: Added ICD-10-CM M04.8.

- 11/20/2020 – Annual Review: Add continuation of use section; update tuberculosis testing language. Coding reviewed: No changes.
- 08/21/2020 – Select Review: Update canakinumab criteria and QL to include Still's Disease per label. Administrative update to add drug specific quantity limit. Coding Reviewed: Added ICD-10-CM M06.1
- 11/15/2019 – Annual Review: Wording and formatting changes; update combination therapy criteria for consistency with other agents. Coding Reviewed: No Changes.
- 11/16/2018 – Annual Review: Initial P&T review of Interleukin-1 Inhibitors Clinical Guideline – combined Arcalyst (rilonacept) and Ilaris (canakinumab) policies and added Kineret (anakinra) criteria. Update clinical criteria to delete "active" disease wording. Update criteria to delete requirement agent is being used "to reduce signs and symptoms, maintain clinical response", etc. Add examples of conventional therapy to approval criteria for clarity. Wording and formatting changes to criteria for consistency. HCPCDs and ICD-10 Coding Review: Add J3490, J3590 for Kineret. Add D47.22 for Castleman's disease and M05.00-M05.9, M06.00-M06.09, M06.4, M06.80-M06.89, M06.9 for RA.

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12. NCCN Clinical Practice Guidelines in Oncology™. © 2024 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on September 18, 2024.
    a. Castleman Disease. V1.2024. Revised January 18, 2024.
    b. Management of Immunotherapy-related Toxicities. V1.2024. Revised December 7, 2023.
    c. Histiocytic Neoplasms. V2.2024. Revised July 19, 2024.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.