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 (RA): The American College of Rheumatology (ACR) guidelines recommend disease-modifying antirheumatic drug (DMARD) monotherapy [methotrexate (MTX) preferred] as first-line treatment in individuals with early or established RA. If disease activity remains high despite DMARD monotherapy, combination traditional DMARDs, TNFi +/- MTX, non-TNFi biologic +/- MTX, or Xeljanz +/- MTX should be utilized. Due to superior efficacy, biologic therapy should be used in combination with MTX when possible. If disease activity remains high despite TNFi monotherapy, one or two additional DMARDs should be added. If an individual has failed TNFi therapy, options include switching to another TNFi or non-TNFi biologic +/- MTX. Non-TNFi biologics (such as IL-6 or IL-1 inhibitors) are preferred over JAK inhibitors due to potential long-term safety concerns.

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 children with active systemic features and varying degrees of synovitis, therapy with IL-1 inhibitors (anakinra or canakinumab) or tocilizumab may be considered after initial therapy with NSAIDs or corticosteroids. For children without active systemic features and varying degrees of synovitis, anakinra or tocilizumab may be considered after initial therapy with DMARDS (methotrexate or leflunomide). TNFi may be considered if polyarthritis is present (ACR 2013). For children with active polyarthritis, biologic therapy including TNFi, abatacept, or tocilizumab +/- DMARD is recommended following initial DMARD therapy (preferably methotrexate) (ACR 2019). Canakinumab is FDA approved for the entire spectrum of Still's Disease which includes SJIA and adult-onset Still's Disease (AOSD).

Cryopyrin-associated periodic syndromes (CAPS): 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. NOIMD 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.

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.

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

I. Individual is 12 years of age or older with either of the following cryopyrin-associated periodic syndromes:
   A. Familial cold autoinflammatory syndromes; **OR**
   B. Muckle-Wells syndrome.

Continuation requests for Arcalyst (rilonacept) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease.

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

I. All other indications not included above; **OR**
II. In combination with other IL-1 inhibitors, JAK inhibitors, apremilast, or other biologic drugs (such as IL-6 inhibitors, TNF antagonists, or selective co-stimulation modulators); **OR**
III. Tuberculosis, other active serious infections, or a history of recurrent infections; **OR**
IV. Prior to initiating therapy, ~~I~~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 ~~prior to initiating rilonacept~~(unless switching therapy from another targeted immune modulator and no risk factors).

Ilaris (canakinumab)

Initial ~~R~~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 confirmation of the diagnosis (MEFV gene exon 10 mutation) (De Benedetti 2018); **AND**
   B. Individual has confirmed 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 confirmation 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 confirmation 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 each of the following criteria are met:
   A. Individual is 2 years of age or older with Still's Disease as either ASOD or SJIA; **AND**
   B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs).

Continuation requests for Ilaris (canakinumab) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease.

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

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I. All other indications not included above; **OR**
II. In combination with other IL-1 inhibitors, JAK inhibitors, apremilast, or other biologic drugs (such as IL-6 inhibitors, TNF antagonists, or selective co-stimulation modulators); **OR**
III. Tuberculosis, other active serious infections, or a history of recurrent infections; **OR**
IV. Prior to initiating therapy, ~~I~~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 ~~prior to initiating canakinumab~~(unless switching therapy from another targeted immune modulator and no risk factors).

Kineret (anakinra)

Initial ~~R~~requests for Kineret (anakinra) may be approved for ~~if~~ 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. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, leflunomide, or hydroxychloroquine)] or a tumor necrosis factor (TNF) antagonist;

OR

II. 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

III. Individual has a diagnosis of relapsed/refractory or progressive multicentric Castleman's Disease (MCD) (NCCN 2A);

OR

IV. Systemic juvenile idiopathic arthritis (SJIA) when each of the following criteria are met (ACR 2013):
   A. Individual is 2 years of age or older with SJIA; **AND**
   B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs).

Continuation requests for Kineret (anakinra) may be approved if the following criterion is met:

I. There is confirmation of clinically significant improvement or stabilization in clinical signs and symptoms of disease.

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

I. All other indications not included above; **OR**
II. In combination with other IL-1 inhibitors, JAK inhibitors, apremilast, or other biologic drugs (such as IL-6 inhibitors, TNF antagonists, or selective co-stimulation modulators); **OR**
III. Tuberculosis, other active serious infections, or a history of recurrent infections; **OR**
IV. Prior to initiating therapy, ~~I~~individual has not had a tuberculin skin test (TST) or Centers for Disease Control (CDC) and Prevention -recommended equivalent to evaluate for latent tuberculosis ~~prior to initiating anakinra~~(unless switching therapy from another targeted immune modulator and no risk factors).

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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.	

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

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]
J3490	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]
M04.2	Cryopyrin-associated periodic syndromes [Arcalyst, Ilaris, (Kineret)]
M04.1	Periodic fever syndromes (TRAPS) [Ilaris]
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
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]

Document History

Revised: 11/20/2020
Document History:

- 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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