PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Kineret Prior Authorization
- Kineret® (anakinra for subcutaneous injection – Biovitrim)

REVIEW DATE: 01/20/2021

OVERVIEW

Kineret, an interleukin-1 (IL-1) receptor antagonist, indicated for the following uses:[1]

- **Cryopyrin-associated periodic syndromes** (CAPS) for treatment of neonatal-onset multisystem inflammatory disease (NOMID).
- **Deficiency of interleukin-1 receptor antagonist** (DIRA).
- **Rheumatoid arthritis**, to reduce the signs and symptoms and slow the progression of structural damage in adult patients with moderately to severely active disease who have failed one or more disease-modifying antirheumatic drugs (DMARDs) given ± DMARDs other than tumor necrosis factor inhibitors (TNFis).

Guidelines

IL-1 blockers are used for treatment of multiple inflammatory conditions:

- **CAPS:** CAPS encompasses three rare genetic syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and NOMID or chronic infantile neurological cutaneous and articular syndrome) that are thought to be one condition along a spectrum of disease severity.[2,3] In many cases, patients with CAPS reported an immediate clinical response to Kineret with rash, fever, and arthritis disappearing within a few days and not recurring during follow-up.[4] Dramatic and persistent normalization of inflammatory markers and hematologic tests have also been achieved.
- **DIRA:** Dysregulation of IL-1 signaling is prominent among autoinflammatory conditions such as DIRA. Thus, Kineret has been successfully used and is indicated to treat DIRA. The approval was based on a natural-history study in nine patients (aged 1 month to 9 years at baseline) with genetically confirmed DIRA.[1] Patients were treated with Kineret for up to 10 years. All nine patients achieved remission while on Kineret for DIRA. In some patients, skin and bone manifestations resolved within days and weeks, respectively.
- **Rheumatoid Arthritis:** Current recommendations for the treatment of rheumatoid arthritis from the American College of Rheumatology (ACR) [2015] do not make a recommendation for the use of Kineret.[5] The recommendations also note that Kineret is used infrequently for rheumatoid arthritis and that TNFis and other non-TNFi biologics (i.e., rituximab, Actemra (tocilizumab intravenous infusion, tocilizumab subcutaneous injection], and Orencia [abatacept intravenous infusion, abatacept subcutaneous injection]) are appropriate initial biologic therapy for most patients with rheumatoid arthritis.
- **Systemic Juvenile Idiopathic Arthritis (SJIA):** The 2013 update of the 2011 ACR recommendations for the treatment of SJIA advise Kineret as appropriate initial therapy in SJIA for patients with active systemic features and varying degrees of synovitis. Kineret is also considered an appropriate second- and third-line agent for all patients with SJIA (in patients with and without active systemic features). Macrophage activation syndrome is a severe and potentially lethal complication associated with SJIA.[7] Case-series have shown rapid remission of macrophage activation syndrome as well as treatment of the underlying condition with the use of Kineret.

- **Still's Disease:** Still's disease presents in adults with features similar to those of SJIA.[8] As in SJIA, Kineret has been effective in reducing fever, symptoms, and markers of inflammation in patients with adult-onset Still's disease who were refractory to conventional treatment with a corticosteroid, nonsteroidal anti-inflammatory drug (NSAID), and/or conventional synthetic DMARDs such as methotrexate.[9-14]

POLICY STATEMENT

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

All reviews for use of Kineret 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 Kineret is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes.** 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 BOTH of the following criteria (i and ii):
     - **i.** The medication is being used for treatment of neonatal onset multisystem inflammatory disease (NOMID), familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS), and/or chronic infantile neurological cutaneous and articular (CINCA) syndrome; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, or a dermatologist.
   - **B)** Patient is Currently Receiving Kineret. Approve for 3 years if the patient has had a response, as determined by the prescriber.
     Note: Patient may not have a full response, but there should have been a recent or past response to Kineret.

2. **Deficiency of Interleukin-1 Receptor Antagonist**. 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 BOTH of the following (i and ii):
     - **i.** Genetic testing has confirmed a mutation in the *IL1RN* gene; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory disorders.
   - **B)** Patient is Currently Receiving Kineret. Approve for 3 years if the patient had a response, as determined by the prescriber.

Note: Examples of a response include normalized acute phase reactants; resolution of fever, skin rash, and bone pain; and reduced dosage of corticosteroids.

3. **Rheumatoid Arthritis**. 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 BOTH of the following criteria (i and ii):
     - **i.** Patient has had a 3-month trial of a biologic OR targeted synthetic disease-modifying antirheumatic drug (DMARD) for this condition, unless intolerant; AND
       Note: Refer to Appendix for examples of biologics and targeted synthetic DMARDs used for rheumatoid arthritis. Conventional synthetic DMARDs such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine do not count.
     - **ii.** The medicaion is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Kineret. Approve for 3 years if the patient has had a response, as determined by the prescriber.
     Note: Examples of response include less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Kineret.

Other Uses with Supportive Evidence

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 if the patient meets BOTH of the following criteria (i and ii):
     - **i.** Patient meets ONE of the following conditions (a, b, or c):
       - **a)** Patient has tried one other systemic agent for this condition; OR
         Note: Examples of one other systemic agent include a corticosteroid (oral, intravenous); a conventional synthetic disease-modifying antirheumatic drug (DMARD; e.g., methotrexate, leflunomide, sulfasalazine); or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic (e.g, Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection), a tumor necrosis factor inhibitor (e.g., an etanercept product [Enbrel, biosimilars], an adalimumab product [Humira, biosimilars], or an infliximab product [Remicade, biosimilars), or Ilaris (canakinumab subcutaneous injection) also counts towards a trial of one other systemic agent for SJIA.
       - **b)** Patient has at least moderate to severe active systemic features of this condition OR the patient has active systemic features with an active joint count of one joint or greater, according to the prescriber; OR
         Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis.
       - **c)** Patient has active systemic features with concerns of progression to macrophage activation syndrome (MAS), as determined by the prescriber; AND
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving Kineret. Approve for 3 years if the patient has responded, as determined by the prescriber.
     Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of

daily living; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Kineret.

5. Still's Disease. 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 BOTH of the following criteria (i and ii):

i. Patient meets ONE of the following conditions (a, b, or c):

a) Patient meets ALL of the following criteria (1 and 2):

(1) Patient has tried one corticosteroid; AND

(2) Patient has had an inadequate response to one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate given for at least 2 months or was intolerant to a conventional synthetic DMARD; OR

Note: A previous trial of a biologic (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) also counts towards a trial of one other systemic agent for Still's disease.

b) Patient has at least moderate to severe active systemic features of this condition, according to the prescriber; OR

Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis.

c) Patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist; OR

B) Patient is Currently Receiving Kineret. Approve for 1 year if the patient has responded, as determined by the prescriber.

Note: Examples of response include improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living; reduced dosage of corticosteroids. The patient may not have a full response, but there should have been a recent or past response to Kineret.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Kineret is not recommended in the following situations:

1. Ankylosing Spondylitis. Kineret has been beneficial in a few patients with ankylosing spondylitis, but results are not consistent.[15,16] In a small open-label study, patients with active ankylosing spondylitis who were refractory to NSAIDs (n = 20) received Kineret 100 mg daily.[16] The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score decreased over a 6-month period but was not significant (5.8 at baseline vs. 5.0 at Week 12, and 4.8 at Week 24). No significant change was found in Bath Ankylosing Spondylitis Functional Index (BASFI), patients' and physicians' global assessment or general pain during the study. After 12 weeks, both the assessment in ankylosing spondylitis (ASAS) 20 and 40 responses improved in 10.5% of patients (intent-to-treat analysis). After 24 weeks, ASAS 20 was attained in 26% of patients, ASAS 40 in 21% of patients, and ASAS 70 in 10.5% of patients. Guidelines for axial spondyloarthritis from the Assessment of SpondyloArthritis International Society (ASAS)/European Union Against Rheumatism (EULAR) [2016] do not mention Kineret as a treatment option.[17]

2. Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD). Data are lacking evaluating concomitant use of Kineret in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (See

Appendix for examples). Combination therapy with biologics and/or biologics + targeted synthetic DMRADs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.[18]
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Kineret.

3. **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. **Lupus Arthritis.** The effectiveness and safety of Kineret were evaluated in an open 3-month pilot trial in patients (n = 4) with systemic lupus erythematosis (SLE) and severe, therapy-refractory non-erosive polyarthritis (three patients had deforming Jaccoud's arthropathy) and no other uncontrolled major organ involvement.[19] Patients were refractory to NSAIDs, antimalarials, corticosteroids, methotrexate, cyclophosphamide, and azathioprine. SLE was controlled with stable doses of corticosteroids and/or antirheumatic or immunosuppressive agents; pain was managed with NSAIDs and/or other medications. Patients had improved clinically after 4 weeks on Kineret, but after 12 weeks the clinical activity parameters tended to increase again. The results from this study are preliminary and a larger controlled study is needed.

4. **Osteoarthritis.** In a Phase II study in patients with painful osteoarthritis of the knee, Kineret 150 mg administered by intraarticular injection was well tolerated.[20] The study was not designed to assess the analgesic efficacy of Kineret. Patients with osteoarthritis of the knee were enrolled in a multicenter, double-blind, placebo-controlled study and randomized to Kineret 50 mg, Kineret 150 mg, or placebo for intraarticular injection.[21] Although the injections were well tolerated, there were no significant differences in improvement in knee pain, stiffness, function or cartilage turnover between Kineret doses and placebo. Similar to other studies in this population, there was a significant placebo effect noted.

5. 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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APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, 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, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, 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: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
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 JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	RA
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of 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; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; 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; ^ Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.