PRIOR AUTHORIZATION POLICY

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

DATE REVIEWED: 04/01/2020

OVERVIEW

Kineret is an interleukin-1 (IL-1) receptor antagonist indicated to reduce the signs and symptoms and slow the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis (RA) who have failed one or more disease-modifying antirheumatic drugs (DMARDs).[1] Kineret is also indicated in Cryopyrin-Associated Periodic Syndromes (CAPS) for treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID). In RA, Kineret can be used alone or in combination with DMARDs other than tumor necrosis factor inhibitors (TNFis).

Disease Overview

IL-1 production is induced in response to inflammation and mediates various physiologic responses including inflammatory and immunological responses.[1] In patients with RA, there are elevated amounts of IL-1 produced in the synovium and synovial fluid. Kineret blocks the biologic activity of IL-1 alpha and beta by competitively inhibiting IL-1 binding to the IL-1 type I receptor, which is expressed on a variety of cells. CAPS is a rare inherited inflammatory disease associated with overproduction of IL-1. In CAPS, spontaneous mutations in the CIAS1/NLRP3 gene leads to secretion of IL-1 beta, which has an important role in the systemic inflammation and manifestations of disease.

CAPS encompasses three rare genetic syndromes. Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, and NOMID or chronic infantile neurological cutaneous and articular syndrome are thought to be one condition along a spectrum of disease severity.[2,3] There are no reliable prevalence statistics for CAPS, but the estimated number of persons with CAPS in the US is 200 to 500. In many cases, patients have had 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.

Guidelines

Il-1 blockers are mentioned in multiple guidelines for treatment of inflammatory conditions.

- Rheumatoid Arthritis: Current recommendations for the treatment of RA 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 RA and that TNFis and other non-TNFi biologics (i.e., rituximab, Actemra (tocilizumab IV infusion, tocilizumab SC injection], and Orencia [abatacept IV infusion, abatacept SC injection]) are appropriate initial biologic therapy for most patients with RA.
- 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).

Other Uses With Supportive Evidence

SJIA is a subtype of JIA characterized by arthritis of unknown origin and extra-articular symptoms such as spiking fever, macular rash, serositis, hepatosplenomegaly, and generalized lymphadenopahty due to reticuloendothelial involvement.[7] Macrophage activation syndrome (MAS) is a severe and potentially lethal complication associated with SJIA. Symptoms include non-remitting fever, hepatosplenomegaly, lymphadenopathy, encephalopathy, and coagulopathy and may also include multi-organ failure. Laboratory abnormalities may include pancytopenia, hyperferritinemia, hypertriglyceridemia, and elevated serum transaminases. There is insufficient evidence for the use of TNFis in MAS associated with SJIA. Case-series have shown rapid remission of MAS as well as treatment of the underlying condition with the use of Kineret. 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 (MTX).[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. **Rheumatoid Arthritis (RA)**. 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 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 (MTX), leflunomide, hydroxychloroquine, and sulfasalazine do not count.
     - **ii.** Kineret is prescribed by or in consultation with a rheumatologist.
   - **B)** Patients 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.

2. **Cryopyrin-Associated Periodic Syndromes (CAPS).** 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.** Kineret 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.** Kineret is prescribed by or in consultation with a rheumatologist, geneticist, or a dermatologist.
   - **B)** Patients Currently Receiving Kineret. Approve for 3 years 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 Kineret.

Other Uses with Supportive Evidence

3. **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)** The patient has tried one other systemic agent for this condition; OR
         Note: Examples of one other systemic agent include a corticosteroid (oral, IV); a conventional synthetic disease-modifying antirheumatic drug (DMARD; e.g., methotrexate [MTX], leflunomide, sulfasalazine); or a 1-month trial of a nonsteroidal anti-inflammatory drug (NSAID). A previous trial of a biologic (e.g, Actemra IV), a tumor necrosis factor (TNF) inhibitor (e.g., an etanercept product, an adalimumab product, or an infliximab product), or Ilaris (canakinumab for SC injection) also counts towards a trial of one other systemic agent for SJIA.
       - **b)** The 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)** The patient has active systemic features with concerns of progression to macrophage activation syndrome (MAS), as determined by the prescriber; AND
     - **ii.** Kineret is prescribed by or in consultation with a rheumatologist.
   - **B)** Patients 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.

4. **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)** The patient meets ALL of the following criteria (1 and 2):
    - **(1)** The patient has tried one corticosteroid; AND
    - **(2)** The patient has had an inadequate response to one conventional synthetic disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX) given for at least 2 months or was intolerant to a conventional synthetic DMARD.
      Note: A previous trial of a biologic (e.g., Actemra IV, Arcalyst, Ilaris) also counts towards a trial of one other systemic agent for Still's disease; OR
  - **b)** The patient has at least moderate to severe active systemic features of this condition, according to the prescriber.
    Note: Examples of moderate to severe active systemic features include fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, and serositis; OR
  - **c)** The patient has active systemic features with concerns of progression to macrophage activation syndrome, as determined by the prescriber; AND
- **ii.** Kineret is prescribed by or in consultation with a rheumatologist; OR

B) Patients 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

Kineret has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Ankylosing Spondylitis (AS).** Kineret has been beneficial in a few patients with AS, but results are not consistent.[15,16] In a small open-label study, patients with active AS 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 AS (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, MTX, 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 (OA), Symptomatic.** In a Phase II study in patients with painful OA 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 since there was no control group. Intraarticular injections are often associated with a significant placebo effect. Patients with OA 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 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, 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, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, 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; TNF – Tumor necrosis factor; IV – Intravenous, 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 – Sytemice juvenile idiopathic arthritis; UC – Ulcerative colitis. ^ Off-label use of SJIA supported in guidelines.