Kineret (Anakinra) Prior Approval Criteria
February 2016

OVERVIEW
Kineret is an interleukin-1 (IL-1) receptor antagonist. IL-1 production is induced in response to inflammation and mediates various physiologic responses including inflammatory and immunological responses.

Kineret is 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). 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 (TNF) blocking agents (e.g., Cimzia® [certolizumab pegol SC injection], Enbrel® [etanercept SC injection], Humira® [adalimumab SC injection], Remicade® [infliximab intravenous {IV} infusion], Simponi® [golimumab SC injection], or Simponi Aria™ [golimumab for IV infusion]).

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. Drug(s) in this policy also follow the Inflammatory Conditions preferred step therapy requirements.

RECOMMENDED AUTHORIZATION CRITERIA
Coverage of Kineret is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Rheumatoid Arthritis (RA).
   
   A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):
   
   i. The patient has had a 3-month trial of a biologic disease-modifying antirheumatic drug (DMARD) OR targeted synthetic DMARD for this condition, unless intolerant (NOTE: examples of biologic DMARDs include: Actemra® [tocilizumab for IV infusion, tocilizumab for SC injection], Ocrevus® [ofatumumab for SC injection], Rituxan® [rituximab for IV infusion], tumor necrosis factor [TNF] antagonists [e.g., Humira, Cimzia, Enbrel, Remicade, Simponi SC, or Simponi Aria]. Example of targeted synthetic DMARD: Xeljanz® [tofacitinib tablets]). [NOTE: Conventional synthetic
DMARDs such as methotrexate (MTX), leflunomide, hydroxychloroquine, and sulfasalazine do not count]; AND

ii. Kineret is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Kineret. Approve for 1 year if the patient has had a response (e.g., 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), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Kineret.


A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i and ii):

i. Kineret is being used for treatment of Cryopyrin-Associated Periodic Syndromes (CAPS): Neonatal Onset Multisystem Inflammatory Disease (NOMID), also called chronic infantile neurolological cutaneous and articular (CINCA) syndrome, Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS); AND

ii. Kineret is prescribed by or in consultation with a rheumatologist, geneticist, or a dermatologist.

B) Patients Currently Receiving Kineret. Approve for 1 year if the patient has had a response, as determined by the prescriber. 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


A) Initial Therapy. Approve for 3 months if the patient meets 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 (e.g., a corticosteroid [oral, IV]; a conventional synthetic disease-modifying antirheumatic drug [DMARD; e.g., methotrexate {MTX}, leflunomide, sulfasalazine]; a biologic DMARD such as Actemra IV, a tumor necrosis factor [TNF] inhibitor [e.g., Enbrel, Humira, or Remicade], or Ilaris [canakinumab for SC injection]; or a 1-month trial of a nonsteroidal anti-inflammatory drug [NSAID]). NOTE: NSAID trial must be at least 1-month duration to qualify; OR
b) The patient has at least moderate to severe active systemic features of this condition (e.g., fever, rash, lymphadenopathy, hepatomegaly, splenomegaly, serositis) OR the patient has active systemic features with an active joint count of one joint or greater, according to the prescribing physician; OR

c) The patient has active systemic features with concerns of progression to macrophage activation syndrome (MAS), as determined by the prescribing physician; AND

ii. Kineret is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Kineret. Approve for 1 year if the patient has responded (e.g., has 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), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Kineret.

4. Still’s Disease.

A) Initial Therapy. Approve for 1 year if the patient meets the following criteria (i, ii, and iii)

i. The patient has tried one corticosteroid; AND

ii. 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; AND

iii. Kineret is prescribed by or in consultation with a rheumatologist.

B) Patients Currently Receiving Kineret. Approve for 1 year if the patient has responded (e.g., has 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), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Kineret.

5. Patient has been Established on Kineret for ≥ 90 days. For conditions that do not have criteria for Patients Currently Receiving Kineret but are indications or conditions addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications and Other Uses with Supportive Evidence), approve Kineret for 1 year, if the patient is currently taking Kineret for ≥ 90 days. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)

Approval Duration
Initial Approval 90 days (3 months) if specified above or 365 days (1 year)
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. In a small open-label study, patients with active AS who were refractory to NSAIDs (n = 20) received Kineret 100 mg daily. 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 [P > 0.05], and 4.8 at Week 24 [P > 0.05]). 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 [ITT] 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. According to the ASAS working group and the European League Against Rheumatism (EULAR) recommendations for AS (2010), there is no evidence to support the use of any biologic agent besides TNF antagonists in ankylosing spondylitis.

2. **Concurrent Use with a Biologic Disease-Modifying Antirheumatic Drug (DMARD) or Targeted Synthetic DMARD.** Kineret should not be administered in combination with another biologic DMARD for an inflammatory condition (e.g., Actemra [IV or SC], Orencia IV or SC], Rituxan, or TNF antagonists [Cimzia, Enbrel, Humira, Remicade, or Simponi {Aria or SC}]). Combination therapy with two biologic agents is not recommended due to a higher rate of adverse effects with combinations and lack of additive efficacy. Targeted synthetic DMARDs such as Xeljanz should not be used in combination with biologic DMARDs such as Kineret. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Kineret.

3. **Gout, Acute.** Current data are limited. In an open-label pilot study, ten patients with acute gout who had a long history of either recurrent gouty attacks or tophaceous gout were treated with Kineret 100 mg daily for 3 days. All patients had either failed conventional therapy with NSAIDs, colchicine, or corticosteroids for at least 48 hours or had developed significant side effects on these drugs in the past. All patients responded rapidly to Kineret with subjective symptoms of gout being greatly relieved by 48 hours after the first injection. A separate retrospective chart review identified ten patients who received Kineret (mean of 3.2 injections) for an acute flare of gout that responded poorly to oral or intra-articular steroids. Six patients had a good response, three patients had a partial response, and one patient had no response. Nine of the patients had recurrent flares after discontinuation of Kineret. A randomized controlled trial is needed to determine if Kineret is effective in acute gout.

4. **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. 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.

5. **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. 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. 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.

6. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**REFERENCES**

- Ilaris® for subcutaneous injection [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; October 2014.
- Arcalyst® for injection [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals Inc; September 2014.


• Xeljanz® tablets [prescribing information]. New York, NY: Pfizer Inc; May 2014.


**OTHER REFERENCES UTILIZED**


<table>
<thead>
<tr>
<th>Type of Revision</th>
<th>Summary of Changes</th>
<th>PQM Approval Date</th>
<th>Criteria Effective Date</th>
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<tbody>
<tr>
<td>Annual revision</td>
<td>Adding indication for SJIA and Still’s Disease, removing over 18 years old indication for RA, reformatting.</td>
<td>2/18/16</td>
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