

## PRIOR AUTHORIZATION POLICY

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

**REVIEW DATE:** 02/28/2024; selected revision 4/24/2024, 09/11/2024

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### OVERVIEW

Kineret, an interleukin-1 (IL-1) blocker, is indicated for the following uses:<sup>1</sup>

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

In addition to the FDA-approved uses, Kineret has been granted Emergency Use Authorization for treatment of Coronavirus disease 2019 (COVID-19) in hospitalized adults with positive viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).<sup>22</sup>

### Guidelines

Kineret is used for treatment of a variety of inflammatory conditions. The European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) [2021] provide treatment guidelines for IL-1 mediated autoinflammatory diseases and indicate IL-blocking therapy has become the preferred treatment.<sup>24</sup> The guidelines also provide additional diagnosis-specific treatment recommendations:

- **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.<sup>2,3</sup> The EULAR/ACR guidelines state IL-1 blockers are recommended as standard of care across the spectrum of disease for improved symptom control and reduced systemic and tissue/organ inflammation.<sup>24</sup> The dose and/or frequency of administration should be adjusted to control disease activity, normalize markers of systemic inflammation, and for appropriate weight gain and development in the growing patient. 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.<sup>4</sup> 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- study in nine patients (aged 1 month to 9 years at baseline) with genetically confirmed DIRA.<sup>1</sup> 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. Treatment with agents that block both IL- $\alpha$  and IL- $\beta$  is recommended and includes Kineret and Arcalyst® (riloncept subcutaneous injection).<sup>24</sup>

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### *Rheumatoid Arthritis*

Current recommendations for the treatment of rheumatoid arthritis from the American College of Rheumatology (ACR) [2021] do not make a recommendation for the use of Kineret.<sup>5</sup> The recommendations also note that Kineret is used infrequently for rheumatoid arthritis and that TNFi and other non-TNFi biologics (i.e., rituximab, Actemra<sup>®</sup> [tocilizumab intravenous infusion, tocilizumab subcutaneous injection], and Orenia<sup>®</sup> [abatacept intravenous infusion, abatacept subcutaneous injection]) are appropriate initial biologic therapy for most patients with rheumatoid arthritis.

### *Systemic Juvenile Idiopathic Arthritis (SJIA)*

The 2021 ACR Guideline for the treatment of juvenile idiopathic arthritis conditionally recommends biologic DMARDs (IL-1 and IL-6 blockers) as initial monotherapy for certain SJIA patients and note there is no preferred agent.<sup>6</sup> Macrophage activation syndrome is a severe and potentially lethal complication associated with SJIA.<sup>7</sup> 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, Adult Onset (AOSD)*

Still's disease presents in adults with features similar to those of SJIA.<sup>8</sup> 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.<sup>9-14</sup>

### *COVID-19*

Guidelines from ACR recommend consideration of Kineret (>4 mg/kg/day) for children with hyperinflammation refractory to intravenous immunoglobulin and glucocorticoids, or in patients with contraindications to long-term use of glucocorticoids.<sup>23</sup> Kineret is also recommended in a similar population of children with multisystem inflammatory syndrome and features of macrophage activation syndrome associated with COVID-19.

## **POLICY STATEMENT**

Prior Authorization is recommended for prescription benefit coverage of Kineret. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. 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 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 (CAPS).** Approve for the duration noted if the patient meets ONE of the following (A or B):

- A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (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 1 year if the patient meets BOTH of the following (i and ii):
- i. Patient has been established on this medication for at least 6 months; AND  
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
  - ii. Patient meets at least ONE of the following (a or b):
    - a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR  
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.
    - b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.
2. **Deficiency of Interleukin-1 Receptor Antagonist (DIRA)**. Approve for the duration noted if the patient meets ONE of the following (A or B):
- A) Initial Therapy. Approve for 6 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 1 year if the patient meets BOTH of the following (i and ii):
- i. Patient has been established on this medication for at least 6 months; AND  
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
  - ii. Patient meets at least ONE of the following (a or b):
    - a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR  
Note: Examples of objective measures include improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), reduction in proteinuria, and/or stabilization of serum creatinine.
    - b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as improvement of skin or bone symptoms; less joint pain/tenderness, stiffness, or swelling.
3. **Rheumatoid Arthritis**. Approve for the duration noted if the patient meets ONE of the following (A or B):
- A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- i. Patient is  $\geq$  18 years of age; AND

- ii. 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: This is a 3-month trial of at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. 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.
  - iii. The medication is prescribed by or in consultation with a rheumatologist.
- B) Patient is Currently Receiving Kineret.** Approve for 1 year if the patient meets BOTH of the following (i and ii):
- i. Patient has been established on therapy for at least 6 months; AND  
Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).
  - ii. Patient meets at least ONE of the following (a or b):
    - a) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR  
Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).
    - b) Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

### Other Uses with Supportive Evidence

- 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. Kineret has been granted Emergency Use Authorization (EUA) for treatment of Coronavirus disease 2019 (COVID-19) in hospitalized adults with positive viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR).<sup>22</sup> The recommended dose under the EUA is 100 mg daily by subcutaneous injection for 10 days.

Additionally, guidelines from ACR recommend consideration of Kineret (>4 mg/kg/day) for children with COVID-19 and hyperinflammation refractory to intravenous immunoglobulin and glucocorticoids, or in patients with contraindications to long-term use of glucocorticoids.<sup>23</sup> Initiation of Kineret prior to invasive mechanical ventilation may be beneficial. Kineret is also recommended in a similar population of children with multisystem inflammatory syndrome and features of macrophage activation syndrome associated with COVID-19. Per these guidelines, a prolonged course of immunomodulatory treatment extending for 2 or 3 weeks or longer may be necessary to avoid rebound inflammation.

- 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 6 months if the patient meets BOTH of the following (i and ii):
    - i. Patient is  $\geq 2$  years of age; AND
    - ii. The medication is prescribed by or in consultation with a rheumatologist.
  - B) Patient is Currently Receiving Kineret. Approve for 1 year if the patient meets BOTH of the following (i and ii):
    - i. Patient has been established on this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).

- ii. Patient meets at least ONE of the following (a or b):
  - a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR  
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement, or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
  - b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

**5. Still's Disease, Adult Onset (AOSD).** Approve for the duration noted if the patient meets ONE of the following (A or B):

**A) Initial Therapy.** Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

- i. Patient is  $\geq$  18 years of age; AND
- ii. Patient meets ONE of the following (a, b, or c):
  - a) Patient meets BOTH of the following [(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 one biologic (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) other than the requested drug also counts towards a trial of one other systemic agent for Still's disease. A biosimilar of the requested biologic does not count.
  - 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
- iii. The medication is prescribed by or in consultation with a rheumatologist.

**B) Patient is Currently Receiving Kineret.** Approve for 1 year if the patient meets BOTH of the following (i and ii):

- i. Patient has been established on this medication for at least 6 months; AND  
Note: A patient who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
- ii. Patient meets at least ONE of the following (a or b):
  - a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR  
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
  - b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

## 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.<sup>15,16</sup> In a small open-label study, patients with active ankylosing spondylitis who were refractory to NSAIDs (n = 20) received Kineret 100 mg daily.<sup>16</sup> 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) and patients' and physicians' global assessment of 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 (intention-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.<sup>17</sup>
- 2. Concurrent Use with a Biologic or with a Targeted Synthetic Oral Small Molecule Drug.** This medication should not be administered in combination with another biologic or with a targeted synthetic oral small molecule drug used for an inflammatory condition (see [Appendix](#) for examples). Combination therapy is generally not recommended due to a potentially higher rate of adverse events and lack of controlled clinical data supporting additive efficacy.<sup>18</sup>  
Note: This does NOT exclude the use of conventional synthetic disease-modifying antirheumatic drugs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with this medication.
- 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 erythematosus (SLE) and severe, therapy-refractory non-erosive polyarthritis (three patients had deforming Jaccoud's arthropathy) and no other uncontrolled major organ involvement.<sup>19</sup> 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.
- 5. Osteoarthritis.** In a Phase II study in patients with painful osteoarthritis of the knee, Kineret 150 mg administered by intraarticular injection was well tolerated.<sup>20</sup> 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.<sup>21</sup> 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

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## APPENDIX

**APPENDIX (CONTINUED)**

\* Not an all-inclusive list of indications. Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; 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; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; AA – Alopecia areata; TYK2 – Tyrosine kinase 2.