Effective Date **2/1/2024**
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Coverage Policy Number **IP0243**

Anakinra

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Related Coverage Resources

COVID-19: Drug and Biologic Therapeutics

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for anakinra (Kineret®).

Anakinra for COVID-19-related uses is addressed in a separate coverage policy. Please refer to the related coverage policy link above (COVID-19: Drug and Biologic Therapeutics).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Anakinra (Kineret) is considered medically necessary when ONE of the following is met:

1. **Cryopyrin-Associated Periodic Syndromes (CAPS).** Individual meets **BOTH** of the following criteria:
   A. Medication is being used for treatment of **ONE** of the following:
      i. Chronic infantile neurological cutaneous and articular (CINCA) syndrome
      ii. Familial Cold Autoinflammatory Syndrome (FCAS)

iii. Muckle-Wells Syndrome (MWS)
iv. Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

B. Medication is prescribed by, or in consultation with, a rheumatologist, geneticist or dermatologist

2. **Deficiency of Interleukin-1 Receptor Antagonist (DIRA).** Individual meets **BOTH** of the following criteria:
   A. Genetic testing has confirmed a mutation in the *IL1RN* gene
   B. Medication is prescribed by, or in consultation with, a rheumatologist, geneticist, dermatologist, or a prescriber specializing in the treatment of autoinflammatory disorders

3. **Rheumatoid Arthritis.** Individual meets **ALL** of the following criteria:
   A. Documentation of **ONE** of the following:
      i. Failure after 3 months to **ONE** conventional synthetic disease-modifying antirheumatic drug (csDMARD), unless contraindicated or intolerant to **ALL** csDMARDs
      ii. Already tried a biologic or targeted synthetic DMARD for rheumatoid arthritis
   B. Medication is prescribed by, or in consultation with, a rheumatologist
   C. Non-Preferred Product Criteria is met, refer to the below table(s) [Employer Group Plans, Individual and Family Plans]

4. **Still's Disease.** The medication is being prescribed by, or in consultation with, a rheumatologist.

5. **Systemic Juvenile Idiopathic Arthritis (SJIA).** The medication is prescribed by, or in consultation with, a rheumatologist.

Coverage varies across plans and requires the use of Preferred Products. Refer to the customer's benefit plan document for coverage details.

Employer Group Plans	
Condition	**Non-Preferred Product Criteria**
Rheumatoid Arthritis	**<u>Standard/Performance/Legacy Drug List Plans</u>** Documentation of failure, contraindication or intolerance to **TWO** of the following: A. **Actemra SC** [requires prior authorization] B. **Adalimumab Product: Adalimumab-adaz/Hyrimoz** (by Sandoz/Novartis)**, Adalimumab – adbm/Cyltezo**, or **Humira** [requires prior authorization] C. **Cimzia** [requires prior authorization] D. **Enbrel** [requires prior authorization] E. **Rinvoq** [requires prior authorization] F. **Xeljanz/XR** [requires prior authorization] **<u>Value/Advantage/Cigna Total Savings Drug List Plans</u>** Documentation of failure, contraindication or intolerance to **TWO** of the following: A. **Actemra SC** [requires prior authorization] B. **Adalimumab Product: Adalimumab-adaz/Hyrimoz** (by Sandoz/Novartis)**, Adalimumab – adbm/Cyltezo**, **Hadlima**, or **Humira** [requires prior authorization] C. **Cimzia** [requires prior authorization] D. **Enbrel** [requires prior authorization] E. **Rinvoq** [requires prior authorization] F. **Xeljanz/XR** [requires prior authorization]

Individual and Family Plan	
Condition	**Non-Preferred Product Criteria**
Rheumatoid Arthritis	Documentation of failure, contraindication or intolerance to **TWO** of the following: A. **Actemra SC** [requires prior authorization] B. **Adalimumab Product: Adalimumab-adaz/Hyrimoz** (by Sandoz/Novartis) **, Adalimumab – adbm/Cyltezo**, **Hadlima**, or **Humira** [requires prior authorization] C. **Cimzia** [requires prior authorization] D. **Enbrel** [requires prior authorization] E. **Rinvoq** [requires prior authorization] F. **Xeljanz/XR** [requires prior authorization]

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of anakinra (Kineret) is considered medically necessary for **ALL** covered diagnoses when initial criteria are met AND beneficial response is demonstrated.

Authorization Duration

Initial approval duration is up to 12 months.

Reauthorization approval duration is up 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven including the following (this list may not be all inclusive):

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 (tsDMARD).** 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]

   This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Kineret.

3. **Inflammatory Bowel Disease.** Anakinra is not indicated for use in the treatment of inflammatory bowel dieseas.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.

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.[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.

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.[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.

6. **Reactive Arthritis**. Anakinra is not indicated for use in the treatment of reactive arthritis.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.

Background

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) – treatment.
- **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).

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).[22]

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]

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APPENDIX

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	JIA	AS	nr-axSpA	PsA	PsO	CD	UC
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Adalimumab products (Humira, biosimilars)	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitors; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Crohn's Disease	Ulcerative Colitis
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	√	--
Skyrizi Intravenous	--	--	--	--	√#	--
Skyrizi Subcutaneous	--	--	√	√	√^	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√^	√^
Stelara Intravenous	--	--	--	--	√#	√#

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; ^ Maintenance dosing only; # Induction dosing only

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
Janus Kinases Inhibitors							
Olumiant	√	--	--	--	--	--	--
Rinvoq	√	--	√	√	√	--	√
Xeljanz tablets	√	√#	√	--	√	--	√
Xeljanz oral solution	--	√#	--	--	--	--	--
Xeljanz XR	√	--	√	--	√	--	√
Phosphodiesterase Type 4 Inhibitor							
Otezla	--	--	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator							

	Rheumatology					Dermatology	Gastro-enterology
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Ankylosing Spondylitis**	**nr-axSpA**	**Psoriatic Arthritis**	**Plaque Psoriasis**	**Ulcerative Colitis**
Zeposia	--	--	--	--	--	--	√
Tyrosine Kinase 2 Inhibitor							
Sotyktu	--	--	--	--	--	√	--

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; # Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology		
	Rheumatoid Arthritis	**Juvenile Idiopathic Arthritis**	**Psoriatic Arthritis**
Interleukin-6 Blockers			
Actemra Intravenous	√	√^	--
Actemra Subcutaneous	√	√^	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√#	√
Orencia Subcutaneous	√	√#	√
CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; # Indicated in polyarticular JIA.