



## Prior Authorization Inflammatory Conditions – Kineret® (anakinra subcutaneous injection)

### Table of Contents

National Formulary Medical Necessity .....	1
Conditions Not Covered.....	4
Background.....	5
References .....	6
Revision History .....	7

### Product Identifier(s)

**Effective through 12/31/2022:** 12922  
**Effective 1/1/2023:** 112318

#### 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.

### National Formulary Medical Necessity

**Cigna covers anakinra (Kineret®) as medically necessary when the following criteria are met for FDA Indications or Other Uses with Supportive Evidence:**

Prior Authorization is recommended for prescription benefit coverage of Kineret. Because of the specialized skills required for evaluation and diagnosis of individuals 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.

#### FDA Indication(s)

- Cryopyrin-Associated Periodic Syndromes.** Approve for the duration noted if the individual meets ONE of the following (A or B):
  - Initial Therapy.** Approve for 6 months if the individual 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) Individual is Currently Receiving Kineret.** Approve for 1 year if the individual meets BOTH of the following (i and ii):
- i. Individual has been established on this medication for at least 6 months; AND  
Note: An individual who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
  - ii. Individual meets at least one of the following (a or b):
    - a) When assessed by at least one objective measure, individual 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), individual 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.** Approve for the duration noted if the individual meets one of the following (A or B):
- A) Initial Therapy.** Approve for 6 months if the individual 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) Individual is Currently Receiving Kineret.** Approve for 1 year if the individual meets BOTH of the following (i and ii):
- i. Individual has been established on this medication for at least 6 months; AND  
Note: An individual who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
  - ii. Individual meets at least one of the following (a or b):
    - a) When assessed by at least one objective measure, individual 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), individual 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 individual meets ONE of the following (A or B):
- A) Initial Therapy.** Approve for 6 months if the individual meets BOTH of the following criteria (i and ii):
- i. Individual 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.
  - ii. The medication is prescribed by or in consultation with a rheumatologist.
- B) Individual is Currently Receiving Kineret.** Approve for 1 year if the individual meets BOTH of the following (i and ii):
- i. Individual has been established on therapy for at least 6 months; AND  
Note: An individual who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

- ii. Individual meets at least one of the following (a or b):
  - a) Individual 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), Individual Activity Scale (PAS)-II, Rapid Assessment of Individual Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).
  - b) Individual 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).**

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 individuals 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 individual meets ONE of the following (A or B):

#### **A) Initial Therapy.** Approve for 6 months if the individual meets BOTH of the following criteria (i and ii):

- i. Individual meets ONE of the following conditions (a, b, or c):
  - a) Individual 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 one biologic other than the requested drug (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. A biosimilar of the requested biologic does not count.
  - b) Individual has at least moderate to severe active systemic features of this condition OR the individual 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) Individual 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) Individual is Currently Receiving Kineret.** Approve for 1 year if the individual meets BOTH of the following (i and ii):

- i. Individual has been established on this medication for at least 6 months; AND
 

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

- ii. Individual meets at least one of the following (a or b):
    - a) When assessed by at least one objective measure, individual 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), individual 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.** Approve for the duration noted if the individual meets ONE of the following (A or B):
- A) **Initial Therapy.** Approve for 6 months if the individual meets BOTH of the following criteria (i and ii):
- i. Individual meets ONE of the following conditions (a, b, or c):
    - a) Individual meets ALL of the following criteria [(1) and (2)]:
      - (1) Individual has tried one corticosteroid; AND
      - (2) Individual 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) Individual 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) Individual 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) **Individual is Currently Receiving Kineret.** Approve for 1 year if the individual meets BOTH of the following (i and ii):
- i. Individual has been established on this medication for at least 6 months; AND  
Note: An individual who has received < 6 months of therapy or who is restarting therapy with this medication is reviewed under criterion A (Initial Therapy).
  - ii. Individual meets at least one of the following (a or b):
    - a) When assessed by at least one objective measure, individual 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), individual 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 Covered

Anakinra (Kineret®) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):

1. **Ankylosing Spondylitis.** Kineret has been beneficial in a few individuals with ankylosing spondylitis, but results are not consistent.<sup>15,16</sup> In a small open-label study, individuals 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), individuals' 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 individuals (intent-to-treat analysis). After 24 weeks, ASAS 20 was attained in 26% of individuals, ASAS 40 in 21% of individuals, and ASAS 70 in 10.5% of individuals. 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 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 DMARDs has a potential for a higher rate of adverse effects and lack controlled trial data in support of additive efficacy.<sup>18</sup>

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

- 3. Lupus Arthritis.** The effectiveness and safety of Kineret were evaluated in an open 3-month pilot trial in individuals (n = 4) with systemic lupus erythematosus (SLE) and severe, therapy-refractory non-erosive polyarthritis (three individuals had deforming Jaccoud's arthropathy) and no other uncontrolled major organ involvement.<sup>19</sup> Individuals 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. Individuals 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 individuals 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. Individuals 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.

## Background

### Overview

Kineret, an interleukin-1 (IL-1) receptor antagonist, 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).**
- **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).<sup>22</sup>

### 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.<sup>2,3</sup> 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-history 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.
- **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.<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® [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.<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:** 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.

## References

1. Kineret® subcutaneous injection [prescribing information]. Stockholm, Sweden: Swedish Orphan Biovitrum; December 2020.
2. Shinkai K, McCalmont TH, Leslie KS. Cryopyrin-associated periodic syndromes and autoinflammation. *Clin Exp Dermatol*. 2008;33:1-9.
3. Ozen S, Hoffman HM, Frenkel J, et al. Familial Mediterranean Fever (FMF) and beyond: a new horizon. Fourth International Congress on the Systemic Autoinflammatory Diseases held in Bethesda, USA, 6-10 November 2005. *Ann Rheum Dis*. 2006;65:961-964.
4. Lepore L, Paloni G, Caorsi R, et al. Follow-up and quality of life of patients with cryopyrin-associated periodic syndromes treated with anakinra. *J Pediatr*. 2010;157(2):310-315.
5. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68(1):1-26.
6. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013;65(10):2499-2512.
7. Boom V, Anton J, Lahdenne P, et al. Evidence-based diagnosis and treatment of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*. 2015;13(1):55.
8. Riera E, Olivé A, Narváez J, et al. Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol*. 2011;29(2):331-336.

9. Lequerré T, Quartier P, Rosellini D, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still's disease. Preliminary experience in France. *Ann Rheum Dis*. 2008;67:302-308.
10. Fitzgerald AA, Leclercq SA, Yan A, et al. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. *Arthritis Rheum*. 2005;52:1794-1803.
11. Kötter I, Wacker A, Koch S, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease: Four case reports with serial cytokine measurements and a review of the literature. *Semin Arthritis Rheum*. 2007;37:189-197.
12. Kalliolias GD, Georgiou PE, Antonopoulos IA, et al. Anakinra treatment in patients with adult-onset Still's disease is fast, effective, safe and steroid sparing: experience from an uncontrolled trial. *Ann Rheum Dis*. 2007;66:842-843.
13. Giampietro C, Ridene M, Lequerre T, et al. Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. *Arthritis Care Res (Hoboken)*. 2013;65(5):822-826.
14. Ortiz-Sanjuán F1, Blanco R, Riancho-Zarrabeitia L, et al. Efficacy of anakinra in refractory adult-onset Still's disease: multicenter study of 41 patients and literature review. *Medicine (Baltimore)*. 2015;94(39):e1554.
15. Tan AL, Marzo-Ortega H, O'Connor P, et al. Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. *Ann Rheum Dis*. 2004;63:1041-1045.
16. Haibel H, Rudwaleit M, Listing J, et al. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. *Ann Rheum Dis*. 2005;64:296-298.
17. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis*. 2017;76(6):978-991.
18. Furst DE, Keystone EC, So AK, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. *Ann Rheum Dis*. 2013;72 Suppl 2:ii2-34.
19. Ostendorf B, Iking-Konert C, Kurz K, et al. Preliminary results of safety and efficacy of the interleukin 1 receptor antagonist anakinra in patients with severe lupus arthritis. *Ann Rheum Dis*. 2005;64:630-683.
20. Chevalier X, Giraudeau B, Conrozier T, et al. Safety study of intraarticular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. *J Rheumatol*. 2005;32:1317-1323.
21. Chevalier X, Goupille P, Beaulieu AD, et al. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2009;61(3):344-352.
22. US Food and Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Kineret. November 2022. Available at: <https://www.fda.gov/media/163075/download>. Accessed on November 14, 2022.
23. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: version 2. *Arthritis Rheumatol*. 2021;73(4):e13-e29.

## Revision History

Type of Revision	Summary of Changes	Approval Date
Annual Revision	No criteria changes.	02/16/2022
Selected Revision	<b>Coronavirus Disease 2019 (COVID-19):</b> Due to the Emergency Use Authorization for this indication, COVID-19 was moved from the Conditions Not Recommended for Approval to the Other Uses with Supportive Evidence.	11/30/2022

## Appendix

	Mechanism of Action	Examples of Inflammatory Indications*
<b>Biologics</b>		
<b>Adalimumab SC Products</b> (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
<b>Cimzia®</b> (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
<b>Etanercept SC Products</b> (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA, RA
<b>Infliximab IV Products</b> (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
<b>Simponi®, Simponi® Aria™</b> (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
<b>Actemra®</b> (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA IV formulation: PJIA, RA, SJIA
<b>Kevzara®</b> (sarilumab SC injection)	Inhibition of IL-6	RA
<b>Orencia®</b> (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PsA, RA
		IV formulation: JIA, PsA, RA
<b>Rituximab IV Products</b> (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
<b>Kineret®</b> (anakinra SC injection)	Inhibition of IL-1	JIA <sup>^</sup> , RA
<b>Stelara®</b> (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
<b>Siliq™</b> (brodalumab SC injection)	Inhibition of IL-17	PsO
<b>Cosentyx™</b> (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
<b>Taltz®</b> (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
<b>Ilumya™</b> (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
<b>Skyrizi™</b> (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
<b>Tremfya™</b> (guselkumab SC injection)	Inhibition of IL-23	PsO
<b>Entyvio™</b> (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
<b>Targeted Synthetic DMARDs</b>		
<b>Otezla®</b> (apremilast tablets)	Inhibition of PDE4	PsO, PsA
<b>Olumiant®</b> (baricitinib tablets)	Inhibition of JAK pathways	RA
<b>Rinvoq®</b> (upadacitinib extended-release tablets)	Inhibition of JAK pathways	RA
<b>Xeljanz®</b> (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
<b>Xeljanz® XR</b> (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; <sup>^</sup> Off-label use of Kineret in JIA supported in guidelines; DMARDs – Disease-modifying antirheumatic drug.

“Cigna Companies” refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Evernorth Behavioral Health, Inc., Cigna Health Management, Inc. and HMO or service company subsidiaries of Cigna Health Corporation. The Cigna name, logo, and other Cigna marks are owned by Cigna Intellectual Property, Inc. © 2022 Cigna.