



# CIGNA HEALTHCARE COVERAGE POSITION

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Subject **Anakinra (Kineret®)**

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## Hyperlink to Related Coverage Positions

[Enbrel®](#)  
[Humira®](#)  
[Orencia®](#)  
[Remicade®](#)  
[Rituxan®](#)

### INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), 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 Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. 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 group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Position

**CIGNA HealthCare covers anakinra (Kineret®) as medically necessary for the treatment of active rheumatoid arthritis (RA) in adults (≥18 years of age) AND when EITHER of the following indications is met:**

- patients with the history of positive clinical response to anakinra therapy for RA condition
- patients with **NO** history of use of anakinra therapy:
  - **Initial authorization:** approval of 16 weeks when there is an inadequate response intolerance, or contraindication to at least **ONE** disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Sulfasalazine) **AND** to **ONE** tumor necrosis factor (TNF) antagonists [i.e. adalimumab (Humira®), etanercept (Enbrel®), infliximab (Remicade®)] as evidenced by documented disease progression based on the assessment of disease activity using **ANY** of the following:

- elevation of ESR (> 28 mm/hr), or C-reactive protein (CRP) (2x the upper limit of normal)
  - progression of radiographic damage of involved joints
  - Health Assessment Questionnaire Disease Index (HAQ-DI)
  - Visual Analogue scale (VAS)
  - Likert scales of global response to pain by the patient/doctor
  - Global Arthritis Score (GAS)
  - Clinical Disease Activity Index (CDAI)
  - Simplified Disease Activity Index (SDAI)
  - Disease Activity Scale (DAS) score
  - Disease Activity Score based on 28-joint evaluation (DAS28) score
- **Subsequent requests:** After 16 weeks, the approval of continuation of therapy for **ONE YEAR** when there is a clinical response to treatment and documented improvement indicated by using **ANY** of the following:
- ESR or CRP
  - 20% improvement according to ACR response criteria
  - HAQ-DI
  - VAS
  - Likert scales of global response to pain by the patient/doctor
  - GAS
  - CDAI
  - SDAI
  - DAS and DAS28 scores

**CIGNA HealthCare does not cover anakinra (Kineret®) for any of the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):**

- treatment of reactive arthritis
- treatment of inflammatory bowel disease
- treatment of ankylosing spondylitis

## General Background

### FDA Approved Indications

Anakinra, a synthetic form of naturally occurring cytokines regulating interleukin-1 (IL-1), is indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs (DMARDs). Anakinra can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF) blocking agents.

A major goal in the treatment of RA is to improve signs and symptoms. According to the 2002 update on guidelines for management of RA developed by the American College of Rheumatology (ACR), the reduction of these symptoms can be clinically measured using the ACR response criteria. An ACR-20 response is defined as a 20% improvement in tender and swollen joint count as well as a 20% improvement in 3 of the following 5 parameters: patient's global assessment, physician's global assessment, and patient assessment of pain, degree of disability, and level of acute-phase reactant. Another goal is to reduce radiographic progression, which is slowing the rate of joint damage visible on Xray. Due to the absence of a single "gold standard" measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. The most common measures used in the clinical settings include: Health Assessment Questionnaire Disease Index (HAQ-DI), Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, Global Arthritis Score (GAS), Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Disease Activity Scale (DAS) score, Disease Activity

Score based on 28-joint evaluation (DAS28) score, Elevation of ESR (> 28 mm/hr), or C-reactive protein (CRP).

The elimination half-life of anakinra is 4–6 hours, which is much shorter than the elimination half-life of other available biological response modifiers. Anakinra is substantially excreted by the kidney, so the risk of toxic reactions may be greater in patients with renal dysfunction.

There are no comparative trials measuring the effectiveness of all biological response modifiers (BRMs). The available data regarding the effectiveness of the BRMs comes from placebo-controlled trials and trials comparing these agents with methotrexate. Anakinra has been compared to placebo in two randomized, double-blind, placebo-controlled studies. Bresnihan et al. (1998) compared anakinra to placebo in 472 patients with active and severe RA. Patients were randomized to either anakinra 30 mg/day, 75 mg/day, 150 mg/day, or placebo and followed for 24 weeks. The percentage of patients showing improvement based on the American College of Rheumatology (ACR) criteria was 27% in the placebo group compared to 39%, 34%, and 43% of patients receiving anakinra 30 mg, 75 mg, and 150 mg, respectively. The combined active treatment groups improved significantly compared to placebo at study end ( $p=0.02$ ).

Nuki et al. (2002) published the results on the extension phase of the Breshinan trial. Three hundred and nine patients entered into the 52-week, double-blind, parallel group extension phase. Patients who received anakinra for the first 24 weeks continued receiving it at the same daily dose. Patients in the placebo group were randomized to anakinra 30 mg, 75 mg, or 150 mg daily. The primary outcome measure of this study was the percentage of patients who maintained an ACR 20 response at week 24 and week 48. Forty-six percent of patients continuing on all doses of anakinra demonstrated an ACR 20 response at week 48, which was similar to the 51% response at week 24 ( $p=0.22$ ). Among the patients who originally received placebo and were randomized to all doses of anakinra, 40% demonstrated a sustained ACR 20 response at 48 weeks compared to 15% at 24 weeks ( $p<0.001$ ).

There are no published studies comparing anakinra monotherapy to methotrexate monotherapy. There is only one published study comparing the combination of anakinra and methotrexate to methotrexate alone. Cohen et al. (2002) compared the efficacy of the combination of anakinra and methotrexate to methotrexate monotherapy in 419 patients with active RA. The primary efficacy endpoint was ACR 20 response at week 12. Secondary endpoints were ACR 20, ACR 50, and ACR 70 response at week 24, and the sustained response rates. The ACR responses for the 0.1 mg/kg, 1.0 mg/kg, and 2.0 mg/kg anakinra plus methotrexate regimens were significantly better than methotrexate alone at week 12 ( $p<0.01$ ). No significant differences between methotrexate monotherapy and the combination anakinra/methotrexate 0.04 mg/kg and 0.4 mg/kg were observed ( $p=NS$ ). Only the 1.0 mg/kg anakinra/methotrexate dose was better than methotrexate alone at week 24 ( $p=0.018$ ). A sustained ACR 20 response of 30%, 31%, and 35% was noted in the 0.1 mg/kg, 1.0 mg/kg, and 2.0 mg/kg combination groups, respectively ( $p$  value not stated).

Anakinra therapy can significantly reduce erosions, joint space narrowing, and total joint damage. Maximal benefit is achieved within the first 24 weeks of therapy and is maintained during continued therapy.

There are several radiographic scoring systems that attempt to achieve simplicity without compromising sensitivity. The Larsen method evaluates the level of abnormality within a joint, assigning each joint a score from zero (normal) to five (mutilating abnormality) and also incorporated clinical judgment. The Genant scoring method uses skilled clinicians to assign a score for judging the extent of erosion (range zero to 3.5) and joint space narrowing (range zero to four) from one radiograph to another for an individual over time. For both methods, the score for each joint is added up for a total score. Both scoring methods indicate worsening of disease by an increased score and improvement by a decreased score.

Bresnihan et al. (1998) compared anakinra to placebo in 472 patients with active and severe RA. Patients were randomized to anakinra 30 mg, 75 mg, 150 mg, or placebo and followed for 24 weeks. Hand radiographs were available for 74% of patients at baseline and week 24. Using the Larsen score, a 41%

reduction in the rate of radiologic progression was noted for the anakinra group compared to placebo ( $p=0.03$ ). There was also a 46% reduction in the rate of joint erosions ( $p=0.004$ ). Results were similar in the three anakinra dose groups; however, only the 30 mg and 75 mg groups reached statistical significance ( $p=0.02$  and  $p=0.004$ , respectively).

The results of this study were confirmed when the radiographs were re-read using the Genant-modified Sharp score. Using this scoring system, the rate of joint deterioration and the development of new joint erosions were reduced by 50% in the anakinra-treated patients. In this study, 14 joints were examined and scored by this method.

Jiang et al. (2000) conducted a 24-week continuation of the study by Bresnihan et al. This study determined the extent of radiologic progression in patients taking anakinra or placebo. A secondary endpoint was to assess the correlation between two different radiographic scoring methods, the Genant versus the Larsen scoring methods. A total of 472 patients were randomized, and 248 patients had radiographs obtained at week 48. All patients who received placebo and completed the first 24 weeks of the trial were randomized to either anakinra 30 mg/day, 75 mg/day, or 150 mg/day ( $n=76$ ). Patients who completed the study received radiographs of each hand and wrist at baseline, 24 weeks, and 48 weeks. All anakinra treatment groups significantly reduced disease progression as measured by the Genant score for joint space narrowing and Genant total score for the first 24 weeks ( $p<0.01$ ). Only the anakinra 30 mg/day regimen significantly reduced the Genant erosion score ( $p=0.01$ ). The combined treatment effect was a 38% reduction in erosion score, a 58% reduction in joint space narrowing, and a 47% reduction in total Genant score ( $p<0.01$  for all three endpoints). Using the Larsen scoring method, only anakinra 75 mg/day reduced the Larsen erosive joint count at 24 weeks ( $p=0.003$ ). During weeks 24 to 48, when patients taking placebo were re-randomized to anakinra treatment, significant slowing of disease progression was noted by the Genant scoring method ( $p=0.0001$  for erosion,  $p=0.019$  for joint space narrowing, and  $p=0.0005$  for total score), but not the Larsen scoring method ( $p=0.125$  for erosive joint count,  $p=0.28$  for total Larsen score). The Genant scoring method showed greater sensitivity than the Larsen scoring method in detecting the efficacy of anakinra. Overall, the authors concluded that both radiologic scoring methods showed that anakinra treatment reduced radiologic progression.

Anakinra should also not be used in combination with anti-TNF agents due to an increased risk of neutropenia and serious infection. These agents should be used with caution when used with other agents that could suppress the immune system or in patients who are immunocompromised. Live vaccines should not be administered to patients taking any of the BRMs.

Injection site reactions (erythema, itching, hemorrhage, and pain or swelling) are the most common adverse reactions with anakinra. These reactions are generally mild and do not necessitate discontinuation of therapy. Anakinra, like other BRMs, has warnings due to rare occurrences of serious infections and sepsis associated with the use of anti-TNF agents. Therapy should not be initiated in patients with active infections, and therapy should be discontinued if a serious infection or sepsis develops. Small reductions in the white blood cell count (WBC), platelets, and absolute neutrophil count (ANC) and small increases in the mean eosinophil differential percentage were observed in the placebo-controlled trials with anakinra.

The recommended dose of anakinra for the treatment of patients with rheumatoid arthritis is 100 mg administered daily by subcutaneous (SC) injection. The dose should be administered at approximately the same time every day. Anakinra is supplied in single-use 1 ml prefilled glass syringes.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

<b>CPT®*</b> <b>Codes</b>	<b>Description</b>

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>

<b>ICD-9-CM</b> <b>Diagnosis</b> <b>Codes</b>	<b>Description</b>

**Experimental/Investigational/Unproven/Not Covered:**

<b>CPT* Codes</b>	<b>Description</b>

<b>HCPCS</b> <b>Codes</b>	<b>Description</b>

<b>ICD-9-CM</b> <b>Diagnosis</b> <b>Codes</b>	<b>Description</b>

**\*Current Procedural Terminology (CPT®) © 2005 American Medical Association: Chicago, IL.**

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