



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Coverage Policy Number 4063

Subject **Anakinra (Kineret®)**

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Hyperlink to Related Coverage Policies

Enbrel®
Humira®
Orencia®
Remicade®
Rituxan®

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. 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 Policies are based. For example, a participant'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 participant's benefit plan document **always supercedes** 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 group 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. Proprietary information of CIGNA. Copyright ©2009 CIGNA

Coverage Policy

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

- history of a beneficial clinical response to anakinra therapy for RA condition
- 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:
 - progression of radiographic damage of involved joint
 - 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

Initial authorization: 16 weeks when criteria are met. Subsequent requests: After 16 weeks, approval of continuation of therapy for ONE YEAR when there is a beneficial clinical response to treatment and documented improvement indicated by ANY of the following:

- 20% improvement according to ACR response criteria
- HAQ-DI
- VAS
- Likert scales of global response to pain by the individual/doctor
- GAS
- CDAI
- SDAI
- DAS score
- DAS28 score

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

- reactive arthritis
 - inflammatory bowel disease
 - ankylosing spondylitis
-

General Background

U.S. Food and Drug Administration (FDA) Approved Indication

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) blockig agents.

FDA Recommended Dosing

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 an once-daily subcutaneous injection approved for the treatment of signs and symptoms of RA, in adults who have failed one or more DMARDs. 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.

Guidelines

The American College of Rheumatology (ACR) 2008 recommendations published in June 15, 2008 issue of Arthritis Care & Research include the use of nonbiologic and biologic therapies in patients with RA when starting or resuming these therapies. The 2008 ACR recommendations address five key areas including: the indications for use, monitoring for side-effects, assessing the clinical response, screening for tuberculosis which is a risk factor associated with biologic DMARDs, and the roles of cost and patient preference in choosing biologic agents under certain circumstances (i.e. high disease activity). The duration of RA disease duration, disease severity, and prognostic features were also considered when developing these recommendations. According to ACR guideline, it is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended at this point. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and Routine Assessment Patient Index Data. In addition it is recommended to use

the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, Evidence of radiographic erosions, Elevated erythrocyte sedimentation rate, Elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies. 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. Other commonly used measures in the clinical settings include: Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

Although there are other nonbiologic and biologic DMARDs that are either approved by the FDA or occasionally used for treating RA, only the nonbiologic agents hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine, and the biologics abatacept, adalimumab, etanercept, infliximab, and rituximab are included in the 2008 ACR recommendations. Following are the 2008 ACR recommendations for nonbiologic and biologic DMARD use in RA:

- Initiating methotrexate or leflunomide therapy is recommended for most RA patients.
- Methotrexate plus hydroxychloroquine is endorsed for patients with moderate to high disease activity.
- The triple DMARD combination of methotrexate plus hydroxychloroquine plus sulfasalazine for patients with poor prognostic features and moderate to high levels of disease activity.
- Prescribing anti-TNF α agents including etanercept, infliximab, or adalimumab, along with methotrexate in early RA (less than 3 months) only for patients with high disease activity who had never received DMARDs. In intermediate- and longer-duration RA, anti-TNF α agents were recommended for patients who had failed to respond adequately to methotrexate therapy.
- Reserving abatacept and rituximab for patients with at least moderate disease activity and poor disease prognosis for whom methotrexate in combination with or sequential administration of other nonbiologic DMARDs led to an inadequate response.
- Avoiding the initiation or resumption of treatment with methotrexate, leflunomide, or biologic agents for patients with active bacterial infection, active herpes-zoster viral infection, active or latent tuberculosis, or acute or chronic hepatitis B or C.
- Not prescribing anti-TNF α agents to patients with a history of heart failure, with a history of lymphoma, or with multiple sclerosis or demyelinating disorders.
- Avoiding the initiation or resumption of methotrexate, leflunomide, or minocycline for RA patients planning for pregnancy and throughout the duration of pregnancy and breastfeeding.

According to 2008 ACR, these recommendations are not meant to take the place of personalized patient care and are intended to provide guidance based on clinical evidence rather than prohibit appropriate therapies or limit a physician's clinical judgment. Additionally, these recommendations are extensive but not comprehensive.

Clinical Efficacy

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 ($p = \text{NS}$). 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 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.

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.

Drug Availability

Anakinra is supplied in single-use prefilled glass syringe containing 0.67 mL (100 mg) of anakinra. Kineret is dispensed in a pack containing 28 syringes.

Coding/Billing Information

Note: This section is not in use.

References

1. Amgen I. Anakinra (Kineret) injection package insert. Thousand Oaks, CA: Amgen, February, 2006.
2. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998; 41:2196-204.
3. Calabrese LH. Molecular differences in anticytokine therapies. *Clin Exp Rheumatol* 2003; 21:241-8.
4. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46:614-24.
5. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; 48:927-34.
6. Genant HK. Interleukin-1 receptor antagonist treatment of rheumatoid arthritis patients: radiologic progression and correlation of Genant/Sharp and Larsen scoring methods. *Semin Arthritis Rheum* 2001; 30:26-32.

7. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. *Arthritis Rheum* 2000; 43:1001-9.
8. Louie SG, Park B, Yoon H. Biological response modifiers in the management of rheumatoid arthritis. *Am J Health Syst Pharm* 2003; 60:346-55.
9. Nuki G, Bresnihan B, Bear MB, McCabe D. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002; 46:2838-46.
10. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis. *Arthritis Rheum* 2008 Jun 15;59(6):762-84.
11. Watt I, Cobby M. Treatment of rheumatoid arthritis patients with interleukin-1 receptor antagonist: radiologic assessment. *Semin Arthritis Rheum* 2001; 30:21-5.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare Great-West Healthcare	7/15/2008	4063	Anakinra (Kineret®)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.