

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru049

Topic: Kineret[®], anakinra

Date of Origin: February 8, 2002

Revised/Effective Date: November 14, 2008

Next Review Date: November 2009

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Anakinra (Kineret[®]) blocks the activity of interleukin-1 (IL-1), a protein involved in the inflammatory process. It is administered as a subcutaneous injection and is used for the treatment of rheumatoid arthritis.

Policy/Criteria

- I.** Most contracts require prior authorization approval of anakinra prior to coverage. Anakinra may be considered medically necessary in patients with rheumatoid arthritis (RA) when all of the following criteria (A through D) are met:

- A.** The diagnosis of RA has been established by a rheumatologist OR by the criteria in Appendix 1.

AND

- B.** Methotrexate alone is not effective after at least a 6 - 12 week treatment course based on documentation which includes one or more of the assessment components listed in Appendix 2 except if:

- 1.** Documentation is submitted that methotrexate is absolutely or relatively contraindicated based on current medical literature.

OR

- 2.** Methotrexate is not tolerated due to documented clinical side effects. Submission of medical records is necessary to establish this exception.

AND

- C.** Either etanercept (Enbrel[®]) or adalimumab (Humira[®]) is not effective after at least a 12-week treatment course except if not tolerated due to documented clinical side effects.

AND

- D.** Therapy does not exceed administration of 100mg of anakinra subcutaneously once daily.

II. Administration, Quantity Limitations, and Authorization Period

- A.** Regence considers anakinra to be a self-administered medication.
- B.** When prior authorization is approved, anakinra may be authorized in quantities of 28 syringes (1 syringe dispensing pack) every 4 weeks.
- C.** Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

- III.** Anakinra is considered investigational when used for all conditions other than rheumatoid arthritis including, but not limited to, the following:
- A.** Ankylosing spondylitis.
 - B.** In combination with a tumor necrosis factor (TNF) inhibitor, such as infliximab, etanercept, or adalimumab.
 - C.** Inflammatory bowel disease.
 - D.** Juvenile idiopathic arthritis (juvenile rheumatoid arthritis).
 - E.** Osteoporosis.
 - F.** Reactive arthritis.
 - G.** Type 2 diabetes mellitus.

Position Statement

Treatment of rheumatic disorders (rheumatic arthritis, psoriatic arthritis, juvenile idiopathic arthritis, ankylosing spondylitis) [21-29]

- There are many treatments for rheumatic disorders that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Nonmedical therapies, such as prescribed exercise therapy, physical therapy and weight loss, are important components in any treatment plan for patients suffering from a rheumatic disorder.
- When a systemic medication therapy is needed to manage one of the rheumatic disorders, oral therapies are usually the best value.
 - * Medications to control inflammation, such as nonsteroidal antiinflammatory medications (e.g. ibuprofen, indomethacin, and naproxen) and glucocorticoids (oral and injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.

- * Orally administered disease modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), hydroxychloroquine, leflunomide, and sulfasalazine, are effective for decreasing symptoms and slowing disease progression, have a proven track record, and have been the standard of care for many years.
 - * Oral therapies have known potential risks. The management of these risks is well established.
- Methotrexate is considered effective in the treatment of RA and the standard reference disease modifying antirheumatic drug (DMARD) to which newer DMARDs (etanercept, anakinra, adalimumab, and leflunomide) are compared for efficacy.
 - When non-medical therapies and oral medications are inadequate, the biologic medications (e.g., adalimumab, etanercept, infliximab, or abatacept) may be appropriate. Certolizumab and rituximab have been studied in rheumatoid arthritis, but their role in therapy remains uncertain at this time.
 - No studies have shown that any of biologic medications are more effective than another in the treatment of rheumatic disorders, with the exception that there is indirect evidence that anakinra may be less effective than other alternatives.
- * The biologic DMARDs can decrease symptoms, help preserve joint functioning, and slow the progression of rheumatic disease.
 - * There have been no reliable, direct comparative trials that have demonstrated a difference in clinical effect or safety of one agent over another.
 - * Individual responses and tolerability are unpredictable and may vary between patients.
 - * Because responses vary, if one of the biologic DMARDs provides an inadequate response, another biologic medication may yet be effective.
 - * In rheumatoid arthritis, the best response is seen when methotrexate is used concomitantly with any of the biologics. Infliximab has been shown to be effective only when used with methotrexate.

The benefit of medications can be indirectly compared by calculating their number needed to treat (NNT). The number needed to treat is a measure of the chances of a patient achieving a benefit (how many patients need to be treated before a benefit is achieved over a certain period of time). The lower the number needed to treat, the more likely the medication will have benefit.

Table 1 summarizes the chances that certain biologic rheumatologic medications will improve joint pain and stiffness in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis:

| Table 1: Chances of improving joint pain and stiffness by at least 20% after six months of treatment with biologic medications (compared to no treatment). ^[21-29] | | | |
|--|--|--|--|
| Biologic Medications (when used with methotrexate) | Rheumatoid Arthritis | Psoriatic Arthritis | Ankylosing Spondylitis |
| adalimumab (Humira) etanercept (Enbrel) infliximab (Remicade) | About 1 in 3 likely to benefit ^a NNT = 3 (Range 2-4) | About 1 in 3 likely to benefit ^a NNT = 3 | About 1 in 4 likely to benefit ^a NNT = 4 (Range 3-4) |
| abatacept (Orencia) | About 1 in 4 likely to benefit ^a NNT = 4 (Range 3-4) | N/A | N/A |
| anakinra (Kineret) | About 1 in 7 likely to benefit ^a NNT = 7 | N/A | N/A |
| certolizumab (Cimzia) | Uncertain ^b | N/A | N/A |
| rituximab (Rituxan) | Uncertain ^b | N/A | N/A |

^a Benefit = at least 20% improvement in joint pain and stiffness after six months of treatment.

^b The trials for these medications had flaws that make estimating their efficacy uncertain. These flaws included large numbers of patients not completing the clinical trials, not all patients counted in the final results, and uncertainty about whether patients and caregivers were truly unaware of the assigned treatments.

- There is reliable evidence that etanercept, adalimumab, and abatacept (when given with methotrexate) are effective in the management of patients with juvenile idiopathic arthritis (JIA). The design of the clinical studies prevents calculation of “number-needed-to-treat” (NNT) for this use. ^[21, 22, 24]

Efficacy and safety of anakinra in rheumatic conditions

- Anakinra can be used alone or in combination with DMARDs other than tumor necrosis factor (TNF) blocking agents such as etanercept, infliximab, or adalimumab. ^[1]
- The prescribing information for anakinra includes a bolded warning regarding serious infections, which occurred at an incidence of 2% in patients receiving anakinra compared to <1% in patients receiving placebo. ^[1] It also states that a higher rate of serious infection (7%) was observed in patients receiving the combination of etanercept and anakinra as compared to that seen when either agent was used alone. Additionally, concurrent use of anakinra and etanercept has not demonstrated increased clinical benefit.
 - * In an open-label extension trial, 1,346 patients received anakinra for up to 3 years. Patients had varying levels of disease severity, concomitant drug use, and comorbid conditions. The most frequent AEs were injection site reactions (122.26 events/100 patient years), rheumatoid arthritis progression (67.80 events/100 patient years), and upper respiratory infections (26.09 events/100 patient years). ^[18]
 - * Serious infections were noted at a rate of 5.37 events/100 patient years, but was substantially lower in the in those patients NOT receiving corticosteroids at baseline (2.87 events/100 patient years). ^[18]
- Anakinra is not approved for dosing beyond 100mg per day. Higher doses do not result in a higher response. ^[1]
- There are no data available to support the use of anakinra in the treatment of any condition other than RA.
- There is insufficient data to establish the safety and efficacy of anakinra for the treatment of osteoporosis, reactive arthritis, inflammatory bowel disease or ankylosing spondylitis, juvenile idiopathic arthritis (juvenile rheumatoid arthritis). ^[19,20]

Appendix 1: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA)^[16]

Diagnosis of RA requires the presence of at least 4 of 7 criteria below:

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|----|--|
| 1. | Morning stiffness in and around joints lasting more than 1 hour. |
| 2. | Arthritis in at least 1 area in a wrist, metacarpophalangeal (MCP), or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks. |
| 3. | Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks. |
| 4. | Symmetric (bilateral joint) involvement for > 6 weeks. |
| 5. | Presence of rheumatoid nodules. |
| 6. | Positive serum rheumatoid factor. |
| 7. | Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present. |

Appendix 2: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA)^[17]

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| - | Tender joint count. |
| - | Swollen joint count. |
| - | Patient's assessment of pain. |
| - | Patient's global assessment of disease activity. |
| - | Physician's global assessment of disease activity. |
| - | Patient's assessment of physical function. |
| - | Acute phase reactant measures (erythrocyte sedimentation rate or C-reactive protein levels). |

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| Cross References |
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| Enbrel [®] , etanercept dru035 |
| Humira [®] , adalimumab dru081 |
| Remicade [®] , infliximab dru036 |
| Orencia [®] , abatacept dru129 |
| Cimzia [®] , certolizumab dru160 |

| Codes | Number | Description |
|--------------|--------------|--|
| | | Retail Prescription Drug |
| HCPCS | J3590 | Unclassified biologics |
| | NOTE: | Kineret is a self-administered injectable medication and is covered according to the member's benefit for self-administered injectables. |