anakinra (Kineret®)

Policy # 00585
Original Effective Date: 01/01/2018
Current Effective Date: 02/14/2022

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Rheumatoid Arthritis

Based on review of available data, the Company may consider anakinra (Kineret®)‡ for the treatment of patients with moderately to severely active rheumatoid arthritis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for anakinra (Kineret) will be considered when the following criteria are met:

- Patient has a diagnosis of moderately to severely active rheumatoid arthritis; AND
- Patient is 18 years of age or older; AND
- Patient has failed treatment with one or more traditional disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate, unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient; AND
- Patient has a negative TB (tuberculosis) test (e.g., purified protein derivative [PPD], blood test) prior to treatment; AND
- Kineret will NOT be used in combination with other biologic DMARDs used to treat inflammatory conditions (e.g., adalimumab [Humira®]‡, etanercept [Enbrel®]‡) OR drugs such as tofacitinib (Xeljanz/XR®)‡ or apremilast (Otezla®)‡; AND
- Patient has failed treatment with TWO of the following after at least TWO months of therapy with EACH product: etanercept (Enbrel), adalimumab (Humira), tofacitinib (Xeljanz/XR), upadacitinib (Rinvoq™)‡, or subcutaneous tocilizumab (Actemra®)‡ unless there is clinical evidence or patient history that suggests the use of these products will be ineffective or cause an adverse reaction to the patient.

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*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
Based on review of available data, the Company may consider anakinra (Kineret) for the treatment of neonatal-onset multisystem inflammatory disease (NOMID) to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for anakinra (Kineret) will be considered when the following criteria are met:
- Patient has a diagnosis of NOMID; AND
- Patient has a negative TB test (e.g., PPD, blood test) prior to treatment; AND
- Kineret will NOT be used in combination with other biologic DMARDs used to treat inflammatory conditions (e.g., adalimumab [Humira], etanercept [Enbrel]) OR drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla).

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)
Based on review of available data, the Company may consider anakinra (Kineret) for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for anakinra (Kineret) will be considered when the following criteria are met:
- Patient has a diagnosis of DIRA as confirmed by genetic testing resulting in a mutation in the IL1RN gene; AND
- Patient has a negative TB test (e.g., PPD, blood test) prior to treatment; AND
- Kineret will NOT be used in combination with other biologic DMARDs used to treat inflammatory conditions (e.g., adalimumab [Humira], etanercept [Enbrel]) OR drugs such as tofacitinib (Xeljanz/XR) or apremilast (Otezla).

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of anakinra (Kineret) in moderately to severely active rheumatoid arthritis when the patient has NOT failed treatment with TWO of the following after at least TWO months of therapy with EACH product: etanercept

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(Enbrel), adalimumab (Humira), tofacitinib (Xeljanz/XR), upadacitinib (Rinvoq), or subcutaneous tocilizumab (Actemra) to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of anakinra (Kineret) when patient selection criteria are not met (with the exception of the criterion that is deemed to be **not medically necessary****) to be **investigational.***

Background/Overview

Kineret is approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis in adults who have failed one or more non-biologic (i.e., traditional) DMARDs, for the treatment of NOMID, and for the treatment of DIRA. Kineret blocks the biologic activity of IL-1 (interleukin-1) alpha and beta by competitively inhibiting IL-1 binding to the interleukin type 1 receptor, which is expressed in a wide variety of tissues and organs. IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammatory and immunological responses. Spontaneous mutations in the *CIAS1/NLRP3* gene have been identified in a majority of patients with cryopyrin associated periodic syndromes (CAPS) such as NOMID. *CIAS1/NLRP3* encodes for cryopyrin, a component of the inflammasome. The activated inflammasome results in proteolytic maturation and secretion of IL-1 beta, which has an important role in the systemic inflammation and manifestations of NOMID. Mutations in the *IL1RN* gene have been identified as causing DIRA. Dosing for rheumatoid arthritis is 100 mg per day given subcutaneously. Dosing for NOMID and DIRA is weight based (1-2 mg/kg/day) given subcutaneously and can be adjusted to a maximum of 8 mg/kg/day.

Rheumatoid Arthritis

Rheumatoid Arthritis is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. It is considered an autoimmune disease. In an autoimmune disease, the immune system confuses healthy tissue for foreign substances. Typically, first line treatments such as traditional DMARDs are used to treat this condition. An example of a traditional DMARD would include methotrexate.

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Traditional Disease-Modifying Anti-Rheumatic Drugs (DMARDs)
Traditional DMARDs are used for the treatment of rheumatoid arthritis and other inflammatory conditions. These drugs slow the disease process by modifying the immune system:

- methotrexate
- cyclosporine
- sulfasalazine
- mercaptopurine
- gold compounds

Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
NOMID is one of the three diseases that make up the grouping of CAPS. The other two conditions are Muckle-Wells syndrome and familial cold autoinflammatory syndrome (FCAS). The CAPS all originate from point mutations in a single gene (*NLRP3*), which encodes for the cryopyrin protein. NOMID is the most severe of the CAPS conditions and is also known as chronic infantile neurologic cutaneous and articular (CINCA) syndrome. Clinical features of NOMID include a migratory, erythematous rash resembling urticaria, fever, impaired growth, abnormal facies with frontal bossing, protruding eyes, and saddle shaped nose. These develop at or near the time of birth. Other manifestations include chronic meningitis, sensorineural hearing loss, cerebral atrophy, uveitis, lymphadenopathy, and hepatosplenomegaly. NOMID can cause premature death. IL-1 blocking therapy makes up the centerpiece of treatment for NOMID.

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)
DIRA is a rare autoinflammatory condition caused by a mutation in *IL1RN*, the gene that encodes for the interleukin-1 receptor antagonist. This mutation leads to a deficit in the production of interleukin-1 receptor antagonist, which inhibits the pro-inflammatory cytokines, interleukin-1 alpha and beta. This condition is characterized by early onset (around birth) generalized pustulosis, multifocal osteomyelitis, and elevation of acute phase reactants. Kineret works in DIRA by supplying the interleukin-1 receptor antagonist that the body is lacking.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Kineret is approved by the FDA for the treatment of rheumatoid arthritis in adults who have failed one or more non-biologic (i.e., traditional) DMARDs, for the treatment of NOMID, and for the treatment of DIRA.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Rheumatoid Arthritis
The safety and efficacy of Kineret for rheumatoid arthritis was studied in three, randomized, double-blind, placebo-controlled trials of 1,790 patients that were greater than or equal to 18 years of age. A fourth study was also done to assess the safety of Kineret. The American College of Rheumatology response criteria was used to measure the response to therapy (ACR20, ACR50, ACR70). In these studies, subjects on Kineret were more likely to achieve an ACR20, or higher, than patients treated with placebo. Most clinical responses occurred within 12 weeks of beginning therapy

Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
Kineret was studied in 43 NOMID (prospective, long-term, open label, uncontrolled) subjects aged 0.7 to 46 years who were treated for up to 60 months. The average maintenance dose during the trial was 3-4 mg/kg/daily. The endpoint studied were the NOMID symptoms (assessed by a disease specific Diary Symptom Sum Score [DSSS]) and their changes versus baseline. The DSSS included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. Laboratory values were also measured, including serum amyloid A, C reactive protein, and erythrocyte sedimentation rate. Changes in these values from baseline to various points in therapy were examined. From baseline to 60 months (and various points in between), Kineret decreased the DSSS score (including the various components of the DSSS score) and those changes remained throughout therapy.

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Deficiency of Interleukin-1 Receptor Antagonist (DIRA)
The safety and efficacy of Kineret were evaluated in a long-term natural history study including 9 DIRA patients (ages 1 month to 9 years at the start of Kineret treatment) treated with Kineret for up to 10 years. All patients had genetically confirmed DIRA. The starting dose of Kineret was 1 to 2 mg/kg/day in the 6 patients for which the dose was reported. The dose was then individually adjusted to reach a stable efficacious dose to control active inflammation. The highest Kineret dose studied was 7.5 mg/kg/day. At the last visit during the first Kineret treatment period, the dose ranged between 2.2 and 6.1 mg/kg/day. Inflammatory remission was defined as achievement of all of the following criteria: CRP ≤ 5 mg/L, no pustulosis, no inflammatory bone disease, and no concomitant glucocorticoid use. All 9 patients achieved inflammatory remission while on Kineret treatment.

References

1. Kineret [package insert]. Swedish Orphan Biovitrum. Stockholm, Sweden. Updated December 2020.
2. Cryopyrin Associated Periodic Syndromes (CAPS). UpToDate. Accessed September 2017.
3. Mendonca et al, Deficiency of Interleukin-1 Receptor Antagonist (DIRA): Report of the First Indian Patient and a Novel Deletion Affecting *IL1RN*. *Pediatric Rheumatology*. 2015. p143.
4. Aksentijevich I, Masters SL, Ferguson PJ, et al. An Autoinflammatory Disease with Deficiency of the Interleukin-1 Receptor Antagonist. *NEJM*. 2009; 360:2426-2437.

Policy History

Original Effective Date: 01/01/2018
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10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. New policy.
10/04/2018	Medical Policy Committee review
10/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Added Rinvoq as a preferred option for rheumatoid arthritis.
11/05/2020	Medical Policy Committee review

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11/11/2020	Medical Policy Implementation Committee approval. Removed Actemra SubQ as an option for use before Kineret in rheumatoid arthritis.
06/03/2021	Medical Policy Committee review
06/09/2021	Medical Policy Implementation Committee approval. Updated the policy with new criteria for a new FDA approved indication, deficiency of interleukin-1 receptor antagonist. Updated the background and rationale sections with new information for the new FDA approved indication.
01/06/2022	Medical Policy Committee review
01/12/2022	Medical Policy Implementation Committee approval. Added subcutaneous Actemra to the list of products than can be tried and failed prior to use of Kineret.

Next Scheduled Review Date: 01/2023

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

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would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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