09-J0000-45

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Subject: Anakinra (Kineret®) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Anakinra (Kineret) is a recombinant, non-glycosylated form of the human Interleukin-1 receptor antagonist (IL-1Ra) that differs from the naturally occurring human interleukin-1 (IL-1) receptor antagonist by the addition of one N-terminal methionine. IL-1, a dominant cytokine associated with rheumatoid arthritis, is produced in response to inflammatory stimuli and mediates inflammatory and immunological responses. IL-1 causes cartilage degradation by its induction of the rapid loss of proteoglycans, stimulation of bone resorption, and inflammation due to prostaglandin and cyclooxygenase-2 production. In normal joints, endogenous IL-1Ra adheres to the IL-1 receptor on target cells and blocks the binding of IL-1 thus inhibiting the effects of IL-1. In joints effected by rheumatoid arthritis (RA), there is an over-expression of IL-1 that cannot be sufficiently countered by endogenous IL-1Ra. Anakinra exerts its action in the same manner as endogenous IL-1Ra by blocking the biologic activity of interleukin-1 (IL-1) due to competitive inhibition of IL-1 binding to the IL-1 type I receptor (IL-1RI).

Anakinra was approved by the US Food and Drug Administration (FDA) in 2001 for treatment of RA in persons 18 years of age or older who have failed one or more disease-modifying anti-rheumatic drugs (DMARDs). While anakinra can be used in combination with DMARDs, it should not be used concomitantly with tumor necrosis factor (TNF) antagonists. In 2012, the FDA expanded the approval of anakinra to include treatment of cryopyrin-associated periodic syndromes (CAPS), specifically neonatal-onset multisystem inflammatory disease (NOMID). NOMID was previously designated by the FDA as an orphan indication in 2010. In December 2020, the FDA again expanded the approval of anakinra to include treatment of Deficiency of Interleukin-1 Receptor Antagonist (DIRA). Anakinra, as sponsored by the innovator drug company, also has an orphan drug designation for “treatment of Still's disease including systemic juvenile idiopathic arthritis and adult-onset Still's disease” (2015). The American College of Rheumatology Clinical Guidance for Pediatric Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2 and Hyperinflammation in COVID-19 recommend anakinra for the treatment of MIS-C Associated with SARS-CoV-2 in certain situations. In November 2022, the FDA issued an emergency use authorization (EUA) for anakinra for the treatment of COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 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).

In 2018 the National Comprehensive Cancer Network (NCCN) began publishing its guideline Management of Immunotherapy-Related-Toxicities. The NCCN eventually separated this guideline into two separate guidelines - Management of Immune Checkpoint Inhibitor-Related Toxicities and Management of CAR T-Cell and Lymphocyte Engager-Related Toxicities. The NCCN recommend anakinra in a variety of scenarios for CAR T-cell-related toxicities and the management of immunotherapy-related hemophagocytic lymphohistiocytosis (HLH)-like syndrome if no response to corticosteroids after 5 days. The NCCN Guidelines for Castleman Disease, recommend anatakinra as subsequent therapy as a single agent for multicentric CD that has progressed following treatment of relapsed/refractory or progressive disease. The NCCN Guidelines for Histiocytic Neoplasms, recommend anakinra as first-line or subsequent therapy, irrespective of mutation, as a single agent for Erdheim-Chester Disease (ECD) with symptomatic disease or relapsed/refractory disease.

RHEUMATOID DISORDERS

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that primarily affects the joints but can also damage extra-articular organs. The main goal of therapy is to achieve remission, but additional goals include decreased disease activity, prevention of systemic complications, and improved physical functioning. The choice of therapy depends on several factors, including the severity of disease activity when therapy is initiated and the response of the patient to prior therapeutic interventions. American College of Rheumatology (ACR) guidelines list the following guiding principles in the treatment of RA:

- RA requires early evaluation, diagnosis, and management
- Treatment decisions should follow a shared decision-making process
- Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the disease-modifying antirheumatic drug(s) (DMARDs) chosen
- Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
    - Conventional synthetic DMARDs (csDMARDs): hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
    - Biologic DMARDs (bDMARDs): Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (e.g., abatacept), Interleukin (IL)-6 receptor inhibitors (e.g., tocilizumab, sarilumab), anti-CD20 antibody* (e.g., rituximab)

        *Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy
    - Targeted synthetic DMARDs (tsDMARDs): Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib, upadacitinib)
- Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
- Biosimilars are considered equivalent to FDA-approved originator bDMARDs
- Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modifications of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission)

ACR guidelines (2021) are broken down by previous treatment and disease activity:

- DMARD-naïve patients with moderate-to-high disease activity initial treatment:
    - MTX monotherapy is strongly recommended over hydroxychloroquine, sulfasalazine, bDMARDs monotherapy, tsDMARD monotherapy, or combination of MTX plus a non-TNF bDMARD or tsDMARD

    - MTX monotherapy is conditionally recommended over leflunomide, dual or triple csDMARD therapy, or combination MTX plus a TNF inhibitor
- DMARD-naïve patients with low disease activity initial treatment
    - Hydroxychloroquine is conditionally recommended over other csDMARDs
    - Sulfasalazine is conditionally recommended over MTX
    - MTX is conditionally recommended over leflunomide
- Initial therapy in csDMARD-treated patients, but MTX naïve, with moderate-to high disease activity:
    - MTX monotherapy is conditionally recommended over combination MTX and a bDMARD or tsDMARD
- Treatment modifications in patients treated with DMARDs who are not at target:
    - Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of MTX who are not at target
    - Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.

The European Alliance of Associations for Rheumatology (EULAR) guidelines for RA (2022 update) also recommend a treat-to-target approach in therapy. MTX is recommended as first line therapy and should be initiated as soon as the diagnosis of RA is made. If MTX is not clinically appropriate, then an alternative csDMARD should be used as part of the (first) treatment strategy. If initial csDMARD therapy does not produce adequate improvement after 3 months, another csDMARD may be added or switched to as long as poor prognosis factors are absent. In the presence of poor prognosis factors, a bDMARD or JAK inhibitor should be added to csDMARD therapy. If treatment failure occurs with the initial bDMARD or JAK inhibitor, another bDMARD or JAK inhibitor should be considered. If a TNF- or IL-6 receptor inhibitor therapy was initially failed, patients may receive an agent with another mode of action or a second TNF- or IL-6 receptor inhibitor.

Initial dosing of MTX for RA should optimally be 15 mg once weekly, with the dose increased as tolerated and as needed to control signs and symptoms. A fast dose escalation of 5 mg/month to 25-30 mg/week has been associated with higher efficacy, but toxicity with this dosing regimen is a limiting factor. In the presence of sufficient folic acid supplementation, the MTX dose can be rapidly escalated to 25 mg once weekly. The MTX target dose is 25 mg weekly, or the highest tolerable dose.

OTHER DISORDERS

Cryopyrin-Associated Periodic Syndromes (CAPS)/Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominant hereditary autoimmune disorder associated with a defect in the cryopyrin protein. CAPS syndrome is caused by a gain of function mutation in the NLRP3 gene leading to over secretion of fever causing cytokine interleukin (IL)-1B. The CAPS spectrum includes mild, moderate, and severe phenotypes. The mild phenotype is called familial cold autoinflammatory syndrome (FCAS), the moderate phenotype is also known as Muckle-Wells syndrome (MWS), and the neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous articular syndrome (CINCA) describes the severe phenotype. CAPS is diagnosed clinically and genetically. There are more than 240 sequence variants of the NLRP3 gene and mutations in this gene are not inclusive of a CAPS diagnosis. The diagnostic criteria of CAPS recognize that all but a few patients with CAPS have detectable systemic inflammation and use unique CPS-specific clinical features along the whole disease spectrum to achieve reasonable specificity and sensitivity to aid clinicians in making the CAPS diagnosis. These diagnostic criteria does not include genetic confirmation and can be applied to all CAPS subtypes regardless of NLRP3 mutation. The diagnostic criteria for CAPS are as follows:

- Raised inflammatory markers (C-reactive protein [CRP]/serum amyloid A [SAA]), AND
- The presence of at least two of the following signs/symptoms:
    - Urticaria-like rash
    - Cold/stress triggered episodes
    - Sensorineural hearing loss
    - Musculoskeletal symptoms of arthralgia/arthritis/myalgia
    - Chronic aseptic meningitis
    - Skeletal abnormalities of epiphyseal overgrowth/frontal bossing

Goals of treatment include suppressing systemic inflammation, improving functionality, preventing organ damage, and improving quality of life. IL-1 blocking therapy is the preferred treatment for CAPS and is the recommended standard of care. IL-1 blocking therapies control inflammation in the absence of corticosteroids. Current IL-1 blocking therapies include anakinra, canakinumab, and rilonacept. Each of these drugs blocks the effect of IL-1B on the IL-1 receptor and downstream signaling.

Deficiency of the IL-1 Receptor Antagonist (DIRA)

Deficiency of interleukin (IL)-1 receptor antagonist (DIRA) is a very rare, autosomal recessive inflammatory disease caused by biallelic deleterious loss-of-function mutations in the *IL1RN* gene, which encodes the IL-1 receptor antagonist (IL-1Ra). These mutations lead to the absence of IL-1Ra, which allows unopposed action of IL-1 and an increased response to proinflammatory cytokines IL-1α and IL-1β stimulation. This results in life-threatening systemic inflammation and marked skin and bone involvement.

DIRA presents in early childhood, sometimes at birth, with pustular rashes, osteomyelitis, and/or nail changes (onychomadesis). Which features a patient may present with is dependent on the domain affected by the mutation, with some patients presenting primarily with skin involvement and minimal bone involvement, or vice versa. Although inflammatory markers are typically highly elevated, patients rarely present with flare-associated fever unless an infection is present. The diagnosis of DIRA is typically suspected based on clinical features and confirmed on subsequent genetic testing. DIRA can only be diagnosed by genetic analysis and detection of mutations in the *IL1RN* gene. If untreated, DIRA can result in multiorgan failure and death in early childhood.

Aims of therapy are early control of disease activity, prevention of disease and treatment related damage, and optimal health-related quality of life. The ultimate goal of a treat-to-target approach is complete remission, with remission defined as an absence of clinical symptoms and normal inflammatory markers. In patients with DIRA, treatment with agents that block both IL-1α and IL-1β is recommended and includes anakinra and rilonacept. Both drugs have shown benefit in controlling disease flares and in preventing long-term complications. Anakinra is typically used initially in all patients with DIRA to achieve disease control, while rilonacept is used to maintain remission.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

NOTE: The list of self-administered products with prerequisites for certain indications can be found at Preferred Agents and Drug List.

Initiation of anakinra (Kineret) meets the definition of medical necessity when **ALL** of the following are met ("1" to "5"):

1. **ONE** of the following ("a", "b", or "c"):
    a. The member has been treated with anakinra (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with anakinra (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
    c. **BOTH** of the following ('i" and "ii"):
        i. Anakinra will be used for the treatment of an indication listed in Table 1, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following if the member has an FDA-approved indication ("I" or "II")
            I. The member's age is within FDA labeling for the requested indication for anakinra
            II. The prescriber has provided information in support of using anakinra for the member's age for the requested indication
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for RA) or the prescriber has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to anakinra
4. Member will **NOT** be using anakinra in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
5. **ANY** of the following ("a", "b", "c", or "d"):
    a. The dosage does not exceed 100 mg once daily
        - QL: 100 mg syringe - 28 syringes (18.76 mL)/28 days
    b. The member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
        ii. **ALL** of the following ("1", "2", and "3"):
            1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication
            2. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)
            3. **EITHER** of the following ("a" or "b"):
                a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
                b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, **AND** there is

support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
    i. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
    ii. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)
d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):
    i. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
    ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Approval duration: 12 months [except COVID-19 treatment and MIS-C Associated with SARS-CoV-2, approve for 1 month]

Table 1

Diagnosis	Criteria
Moderately to severely active rheumatoid arthritis (RA)	**BOTH** of the following: 1. **ONE** of the following: a. The member has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) after at least a 3-month duration of therapy **OR** b. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA after at least a 3-month duration of therapy **OR** c. The member has an intolerance or hypersensitivity to **ONE** conventional agent (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** d. The member has an FDA labeled contraindication to **ALL** conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR**

	e. The member's medication history (excluding samples) indicates use of another biologic immunomodulator agent **OR** a systemic targeted synthetic small molecule drug (e.g., oral JAK inhibitor) that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of RA **AND** 2. **ANY** of the following (submitted medical records/chart notes are required for confirmation): a. The member has tried and had an inadequate response to **THREE** preferred products after at least a 3-month trial per product **OR** b. The member has tried and had an inadequate response to **TWO** preferred products after at least a 3-month duration of therapy per product, **AND** an intolerance or hypersensitivity to **ONE** preferred product **OR** c. The member has tried and had an inadequate response to **ONE** preferred product after at least a 3-month duration of therapy, **AND** an intolerance or hypersensitivity to **TWO** preferred products **OR** d. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to **THREE** preferred products **OR** e. The member has an FDA labeled contraindication to **ALL** preferred products **OR** f. **ALL** preferred products are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried preferred products for the requested indication **The preferred RA products are:** • Adalimumab-aaty • Adalimumab-adaz • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Xeljanz/Xeljanz XR (tofacitinib)
Deficiency of Interleukin-1 Receptor Antagonist (DIRA)	Diagnosis only

Neonatal-Onset Multisystem Inflammatory Disease (NOMID)	Diagnosis only
Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with SARS-CoV-2	**ALL** of the following: 1. Member is less than 18 years of age **AND** 2. Member has been previously infected with SARS-CoV-2 **AND** 3. Member's symptoms are severe enough that hospitalization is required **AND** 4. **ANY** of the following: a. Member is refractory to IVIG **AND** glucocorticoids **OR** b. Member has contraindications to long-term use of glucocorticoids **OR** c. Member has features of macrophage activation syndrome (MAS)
Coronavirus disease 2019 (COVID-19) treatment [per FDA emergency use authorization (EUA)]	**ALL** of the following: 1. Member is hospitalized **AND** 2. Diagnosis has been confirmed by positive results of direct SARS-CoV-2 viral testing **AND** 3. Member has pneumonia requiring supplemental oxygen (low- or high-flow oxygen) **AND** 4. Member is at risk of progressing to severe respiratory failure **AND** 5. Member is likely to have an elevated plasma soluble urokinase plasminogen activator receptor (suPAR) **AND** 6. Dosage does not exceed 100 mg daily for a maximum of 10 days
Other indications	The member has another FDA labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a

Continuation of anakinra **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "6"):

1. An authorization or reauthorization for anakinra has been previously approved by Florida Blue (except COVID-19 treatment and MIS-C Associated with SARS – see initiation criteria) [Note: members not previously approved for the requested agent will require initial evaluation review]
2. Member has had clinical benefit with anakinra therapy
3. The prescriber is a specialist in the area of the member's diagnosis (e.g., rheumatologist for RA) or the prescriber has consulted with a specialist in the area of the member's diagnosis
4. Member does **NOT** have any FDA labeled contraindications to anakinra
5. Member will **NOT** be using anakinra in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Leqselvi (deuruxolitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq/Rinvoq LQ (upadacitinib), and Xeljanz/Xeljanz XR (tofacitinib)]; Otezla/Otezla XR (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
6. **ANY** of the following ("a", "b", "c", or "d"):
    a. The dosage does not exceed 100 mg once daily
        - QL: 100 mg syringe - 28 syringes (18.76 mL)/28 days
    b. The member has an FDA labeled indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum FDA labeled dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
        ii. **ALL** of the following ("1", "2", and "3"):
            1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication
            2. The member has tried and had an inadequate response to at least a 3-month trial of the maximum FDA labeled dose for the requested indication (medical records required)
            3. **EITHER** of the following ("a" or "b"):
                a. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
                b. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)
    c. The member has a compendia supported indication for the requested agent, **AND EITHER** of the following ("i" or "ii"):
        i. The requested quantity (dose) does **NOT** exceed the maximum compendia supported dose for the requested indication, AND the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does not exceed the program quantity limit
        ii. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication, **AND** there is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

d. The member does **NOT** have an FDA labeled indication **NOR** a compendia supported indication for the requested agent, **AND BOTH** of the following ("i" and "ii"):

   i. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit

   ii. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: anakinra is indicated for - (1) reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis in persons 18 years of age and older who have failed 1 or more disease-modifying anti-rheumatic drugs (DMARDs), (2) Neonatal-Onset Multisystem Inflammatory Disease (NOMID), and (3) Deficiency of Interleukin-1 Receptor Antagonist (DIRA). The recommended dose of anakinra for rheumatoid arthritis is 100 mg/day administered as subcutaneous (SQ) injection. The dose should be administered at approximately the same time every day. The recommended starting dose of anakinra for NOMID and DIRA is 1 to 2 mg/kg daily. The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation. Adjust doses in 0.5 to 1 mg/kg increments. Each syringe is intended for a single use. A new syringe must be used for each dose. Any unused portion after each dose should be discarded.

Dose Adjustments

- **Renal Impairment:** Physicians should consider administration of the prescribed dose every other day in persons with severe renal insufficiency or end stage renal disease (defined as creatinine clearance [CrCl] less than 30 ml/min)

Drug Availability: anakinra is available as a 100 mg/0.67 mL prefilled glass syringe

PRECAUTIONS:

Contraindication

Persons with a known hypersensitivity to E. coli-derived proteins or in those known to have a hypersensitivity to the active or inactive ingredients

Warnings/Precautions

- **Serious infections:** discontinue in RA patients if serious infection develops. In NOMID and DIRA patients the risk of a disease flare when discontinuing treatment should be weighed against the potential risk of continued treatment. Do no initiate therapy in persons with active infections.
- **Concomitant TNF-antagonist therapy:** do not use in combination with TNF-antagonist therapy (e.g., adalimumab, etanercept, infliximab, certolizumab, golimumab).
- **Hypersensitivity:** hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported.
- **Amyloidosis**: post-marketing cases of injection site amyloid deposits have been reported in NOMID patients after receiving high doses of anakinra injected subcutaneously into the same area of skin

over long periods of time. Recommend patients to rotate their injection sites. In patients with confirmed injection site amyloid deposits, monitor proteinuria for systemic amyloidosis.

- **Immunosuppression:** the impact of treatment with anakinra on active and/or chronic infections and the development of malignancies is unknown.
- **Neutrophil count:** assess neutrophil counts prior to therapy initiation, monthly for 3 months following initiation, and quarterly thereafter for a period up to 1 year.
- **Vaccinations:** do not administer live vaccines in members receiving anakinra.

BILLING/CODING INFORMATION:

HCPCS Coding:

J3590	Unclassified biologics

ICD-10 Diagnosis Codes That Support Medical Necessity:

D47.2	Monoclonal gammopathy [for Schnitzler syndrome only]
D47.Z2	Castleman disease
D76.1	Hemophagocytic lymphohistiocytosis
D76.3	Other histiocytosis syndromes
G03.1	Chronic meningitis [for neonatal-onset multisystem inflammatory disease (NOMID) only]
L50.8	Other urticaria [for NOMID and Schnitzler syndrome only]
M04.8	Other autoinflammatory syndromes [for DIRA only]
M05.00 – M05.09	Felty's syndrome
M05.10 – M05.19	Rheumatoid lung disease with rheumatoid arthritis
M05.20 – M05.29	Rheumatoid vasculitis with rheumatoid arthritis
M05.30 – M05.39	Rheumatoid heart disease with rheumatoid arthritis
M05.40 – M05.49	Rheumatoid myopathy with rheumatoid arthritis
M05.50 – M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis
M05.60 – M05.69	Rheumatoid arthritis with involvement of other organs and systems
M05.70 – M05.7A	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.8A	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M05.A	Abnormal rheumatoid factor and anti-citrullinated protein antibody with rheumatoid arthritis
M06.00 – M06.0A	Rheumatoid arthritis without rheumatoid factor
M06.1	Adult-onset Still's disease
M06.20 – M06.29	Rheumatoid bursitis
M06.30 – M06.39	Rheumatoid nodule
M06.80 – M06.8A	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.20 – M08.29	Juvenile rheumatoid arthritis with systemic onset
Q87.89	Other specified congenital malformation syndromes, not elsewhere classified [for NOMID only]
T80.82XA	Complication of immune effector cellular therapy, initial encounter
T80.82XD	Complication of immune effector cellular therapy, subsequent encounter
T80.82XS	Complication of immune effector cellular therapy, sequela
U07.1	COVID-19

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

DMARDs: An acronym for disease-modifying antirheumatic drugs. These are drugs that modify the rheumatic disease processes, and slow or inhibit structural damage to cartilage and bone. These drugs are unlike symptomatic treatments such as NSAIDs that do not alter disease progression. DMARDs can be further subcategorized. With the release of biologic agents (e.g., anti-TNF drugs), DMARDs were divided into either: (1) conventional, traditional, synthetic, or non-biological DMARDs; or as (2) biological DMARDs. However, with the release of newer targeted non-biologic drugs and biosimilars, DMARDs are now best categorized as: (1) conventional synthetic DMARDs (csDMARD) (e.g., MTX, sulfasalazine), (2) targeted synthetic DMARDs (tsDMARD) (e.g., tofacitinib, apremilast), and (3) biological DMARDs (bDMARD), which can be either a biosimilar DMARD (bsDMARD) or biological originator DMARD (boDMARD).

Neonatal-onset multisystem inflammatory disease (NOMID): also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome, is a rare, congenital, systemic, inflammatory condition distinguished by fever, rash, joint disease, and central nervous system (CNS) disease. The hallmark of NOMID is onset during infancy or early childhood. NOMID is the most severe form of the cryopyrin associated periodic syndromes (CAPS) caused by mutations in the CIAS1/NLRP3 gene.

Rheumatoid arthritis: An inflammatory disease of the synovium, or lining of the joint which results in pain, stiffness, and swelling of multiple joints. The inflammation may extend to other joints and cause bone and cartilage erosion, joint deformities, movement problems, and activity limitations.

RELATED GUIDELINES:

Abatacept (Orencia), 09-J0000-67
Adalimumab Products, 09-J0000-46
Apremilast (Otezla) Tablet, 09-J2000-19
Baricitinib (Olumiant), 09-J3000-10
Canakinumab (Ilaris) Injection, 09-J1000-14
Certolizumab Pegol (Cimzia), 09-J0000-77
Etanercept (Enbrel), 09-J0000-38
Golimumab (Simponi, Simponi Aria), 09-J1000-11
Infliximab Products, 09-J0000-39
Rilonacept (Arcalyst), 09-J0000-89
Rituximab Products, 09-J0000-59
Sarilumab (Kevzara), 09-J2000-87

Tocilizumab Products (Actemra, Tofidence, Tyenne) Injection, 09-J1000-21
Tofacitinib (Xeljanz, Xeljanz XR) Oral Solution, Tablet and Extended-Release Tablet, 09-J1000-86
Upadacitinib (Rinvoq), 09-J3000-51
Vedolizumab (Entyvio), 09-J2000-18

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

Table 2: Conventional Systemic DMARDs

Generic Name	Brand Name
Auranofin (oral gold)	Ridaura
Azathioprine	Imuran
Cyclosporine	Neoral, Sandimmune
Hydroxychloroquine	Plaquenil
Leflunomide	Arava
Methotrexate	Rheumatrex, Trexall
Sulfasalazine	Azulfidine, Azulfidine EN-Tabs

Table 3: Grading of Severity of Rheumatoid Arthritis

Severity	Criteria
Mild	Joint pain Inflammation of at least 3 joints No inflammation in tissues other than the joints Usually, a negative result on a rheumatoid factor test An elevated erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) level No evidence of bone or cartilage damage on x-rays
Moderate	Between 6 and 20 inflamed joints Usually no inflammation in tissues other than the joints An elevated ESR or CRP levels A positive rheumatoid factor test or anti-cyclic citrullinated peptide (anti-CCP) antibodies Evidence of inflammation but no evidence of bone damage on x-rays
Severe	More than 20 persistently inflamed joints or a rapid loss of functional abilities Elevated ESR or CRP levels Anemia related to chronic illness Low blood albumin level A positive rheumatoid factor test, often with a high level Evidence of bone and cartilage damage on x-ray Inflammation in tissues other than joints

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Diseases: Cryopyrin-Associated Periodic Syndromes, Tumour Necrosis Factor Receptor-Associated Periodic Syndrome, Mevalonate Kinase Deficiency, and Deficiency of the Interleukin-1 Receptor Antagonist. Arthritis Rheumatol. 2022 Jul;74(7):1102-1121.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/11/25.

GUIDELINE UPDATE INFORMATION:

01/01/05	New Medical Coverage Guideline.
08/15/05	Revised and Updated: added description, when services are covered, dose/administration, deleted precautions, updated when services are not covered, other, references, and related internet links.
01/01/06	CPT code update: deleted expired code 90782 and added new code 90772.
09/15/06	Biennial review: updated references and added related guidelines.
01/01/07	MCG revised to include Medicare Part D as a program exception.
07/15/07	Reviewed: maintain current coverage and limitations. Reformatted guideline, updated internet links and references.
07/15/08	Reviewed with no changes in coverage. Added related MCG and updated references and links.
01/01/09	Annual HCPCS coding update: deleted code 90772; added code 96372.
07/15/09	Review and revision; consisting of review of product information, added PRECAUTIONS section and updated the references.
08/15/10	Review and revision; consisting of rewording description, updating precautions and references.
01/15/11	Revision; consisting of adding ICD-10 codes.
04/01/11	Revision; consisting of adding dosage limitations.
08/15/11	Review and revision to guideline; consisting of updating references.
08/15/12	Review and revision to guideline; consisting of reformatting the position statement, updating coding and references.
09/15/12	Revision to guideline; consisting of modifying continuation criteria.
04/15/13	Revision to guideline; consisting of revising and reformatting position statement to include treatment of chronic infantile neurological cutaneous articular syndrome and orphan drug indications; reformatted and revised description, dosage/administration, and precautions sections; updated references and coding; added pertinent definitions.

09/15/13	Review and revision to guideline; consisting of updating position statement, description, program exceptions, and references.
01/01/14	Revision to guideline; consisting of updating position statement.
04/15/14	Revision to guideline; consisting of updating and reformatting position statement.
09/15/14	Review and revision to guideline; consisting of updating position statement, references, and related guidelines.
09/15/15	Review and revision to guideline; consisting of updating description section, position statement, billing/coding, and references.
12/15/15	Revision to guideline consisting of updating description and position statement based on a new orphan indication.
09/15/16	Review and revision to guideline consisting of updating description, position statement, coding/billing, definitions, and references.
10/01/16	Revision: ICD-10 code updates
10/15/17	Review and revision to guideline consisting of updating description, position statement, coding/billing, definitions, related guidelines, and references
01/01/18	Revision to guideline consisting of updating the preferred self-administered biologic products according to indication for use. Tofacitinib (Xeljanz, Xeljanz XR) added as prerequisite therapy for rheumatoid arthritis indication.
07/01/18	Revision to guideline consisting of updating the position statement.
10/15/18	Review and revision to guideline consisting of updating the position statement, related guidelines, and references.
10/15/19	Review and revision to guideline consisting of updating the description, position statement, billing/coding, and references.
01/01/20	Revision to guideline consisting of updating the position statement due to changes in preferred and non-preferred products.
07/01/20	Revision to guideline consisting of updating the description, position statement, and billing/coding.
01/01/21	Review and revision to guideline consisting of updating the position statement and references.
03/15/21	Revision to guideline consisting of updating Table 1 in the position statement.
06/15/21	Revision to guideline consisting of updating the description, position statement, dosage/administration, billing/coding, and references based on a new FDA-approved indication.
09/15/21	Update to Table 1 in Position Statement.
11/15/21	Revision to guideline consisting of updating the position statement.
01/01/22	Review and revision to guideline consisting of updating the position statement and references.
02/15/22	Update to Table 1 in Position Statement.
03/15/22	Revision to guideline consisting of updating the position statement and other sections.
05/15/22	Update to Table 1 in Position Statement.
07/15/22	Update to Table 1 in Position Statement.
09/15/22	Update to Table 1 in Position Statement.
01/01/23	Review and revision to guideline consisting of updating the description section, position statement, other section, billing/coding, and references. New EUA for the treatment of hospitalized patients with COVID-19. New drugs were added to the list of drugs that are not permitted for use in combination.
04/15/23	Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/23	Revision to guideline consisting of updating the position statement and other section. Amjevita and Hadlima added as Step 1a agents. Humira biosimilar products added to list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/24	Review and revision to guideline consisting of updating the description section (CAPS and DIRA info), position statement, other section, and references. Amjevita low-concentration [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] clarified as the

	preferred prerequisite product. Update to Table 1 in Position Statement. New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/24	Revision to guideline consisting of updating the position statement, related guidelines, and other section. Amjevita low-concentration removed as a required prerequisite agent. Updates to the positioning of agents in Table 1. Removal of latent TB testing requirement. New drugs added to the list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
10/01/24	Revision to guideline consisting of updating the position statement. Updates to Table 1. Simlandi added among the required prerequisite agents for RA.
01/01/25	Review and revision to guideline consisting of updating the position statement, other section, and references. Kineret for RA moved from a Step 3a agent (double step) to a Step 3c agent (triple step). Adalimumab-aaty and Adalimumab-adaz added among the prerequisite therapies for RA. Update to original Table 1 which is now a link out from the Position Statement. Table titles updated. Revised wording regarding maximum dosage exceptions. New drugs were added to the list of drugs that are not permitted for use in combination.
10/01/25	Revision: Added ICD-10 code M05.A. Updated ICD-10 code ranges for RA.
01/01/26	Review and revision to guideline consisting of updating the description, position statement, billing/coding, and references.
07/01/26	Revision: Modified the prerequisite requirement that bypasses the conventional agent step to exclude sample use and include systemic targeted synthetic small molecule drugs as an option.