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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.

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).

RHEUMATOID DISORDERS

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is the most common inflammatory autoimmune arthritis in adults. The main goal of therapy is to achieve remission, but additional goals include decrease inflammation, relieve symptoms, prevent joint and organ damage, improve physical function/overall well-being, and reduce long term complications. 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 DMARD(s) chosen
- Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
    - csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
    - bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)
    - tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
- Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
- Biosimilars are considered equivalent to FDA-approved originator bDMARDs
- 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
- 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 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

Early use of DMARD, particularly MTX, is recommended as soon as possible following diagnosis of RA. Dosing of MTX for RA is once weekly dosing with starting doses at 7.5 mg or 15 mg once weekly. MTX dose is increased as tolerated and as needed to control symptoms and signs of RA disease. The usual target dose is at least 15 mg weekly and the usual maximum dose is 25 mg weekly. ACR defines optimal dosing for RA treatments as 1) dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities and 2) given for at least 3 months before therapy escalation or switching. For patients who are unable to take MTX, hydroxychloroquine, sulfasalazine, or leflunomide are other DMARD options. In patients resistant to initial MTX treatment, combination DMARD (e.g., MTX plus sulfasalazine or hydroxychloroquine or a TNF-inhibitor) is recommended.

For patients who are resistant to MTX after 3 months of treatment at optimal doses (usually 25 mg per week), it is recommended to either use DMARD triple therapy with MTX plus sulfasalazine and hydroxychloroquine or combination of MTX with TNF inhibitor. Triple therapy regimen has been found to be of similar clinical efficacy to MTX with biologics in several randomized trials, including in patients with high level of disease activity or with adverse prognostic features. The use of triple therapy has been shown to be highly cost-effective compared with combining a biologic with MTX, providing comparable or near comparable clinical benefit. The use of biologic with MTX combination is preferred when patients have high disease activity and clinical benefit from a more rapid response is needed and when patients who do not achieve satisfactory response within 3 months with non-biologic triple therapy following an inadequate response to MTX therapy.

OTHER DISORDERS

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

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 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), 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 do not include genetic confirmation, and therefore can be applied in places where genetic testing is not available. The diagnostic criteria for CAPS are as follows:

- Raised inflammatory markers (CRP/SAA)
- 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

FCAS is characterized by episodes of rash, fever, and joint pain following generalized exposure to cold. Attacks usually occur 1 to 2 hours after exposure and last less than 24 hours. Patients experience urticaria, arthralgia, fever with chills, severe thirst, red-eyes, and headache after a general cold exposure, including air conditioning. In MWS, inflammation can occur spontaneously as well as from triggers, such as stress, cold, or exercise, with episodes lasting from one to three days. MWS shares the same characteristics as FCAS, but is also characterized by renal amyloidosis, sensorineural hearing loss, and conjunctivitis. Hearing loss, partial or complete, often develop by teenage years.

NOMID is a rare chronic inflammatory disease. NOMID is characterized by fever, urticarial rash, aseptic meningitis, deforming arthropathy, hearing loss, and intellectual disability. An urticaria-like rash develops within the first six weeks of life, and a characteristic bony overgrowth predominantly involving the knees develops in most affected children. Therapies are aimed at suppressing inflammation and have included high-dose corticosteroids, disease-modifying antirheumatic drugs, and biologic agent targeting tumor necrosis factor (TNF). Selective blockade of interleukin-1B is effective in the pathophysiology and organ-specific manifestations of NMOSD, in particular the CNS manifestations of the disease.

Treatment aims are to suppress systemic inflammation, to improve functionality, to prevent organ damage, and to increase patient's quality of life. To achieve these aims, cytokine targeting drugs are

important and evidence-based treatment. Since IL-1 plays a central role in CAPS pathogenesis, the anti-IL1 treatments (anakinra, canakinumab, and rilonacept) are recommended for the whole CAPS spectrum.

Deficiency of the IL-1 Receptor Antagonist (DIRA)

Systemic autoinflammatory diseases (SAIDs) are a group of multisystem immunodysregulatory disorders caused primarily by the dysfunction of the innate immune system. Currently, SAIDs are comprised of a wide range of disorders with systemic and organ-specific inflammation in the absence of infections or autoimmunity. In a subset of genetically defined SAIDs, the pathogenesis is driven by increased release or signaling of the pro-inflammatory cytokine IL-1.

Patients with DIRA present with early-onset pustular rashes that can be triggered by mechanical stress (pathergy), with sterile osteomyelitis, and nail changes (onychomadesis). Although inflammatory markers are typically highly elevated, fever may be absent. Vertebral involvement can include odontoid osteomyelitis resulting in destruction and neck instability, vertebral block formation and gibbus-like spinal changes that need to be screened for by MRI or CT. The differential diagnosis for DIRA includes chronic recurrent multifocal osteomyelitis (CRMO), synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome and pustular psoriasis. Genetic testing for monogenic defects with overlapping clinical features should include *LPIN2*, *FGR*, *FBLIM1* for CRMO, *CARD14* for CARD14-Mediated Psoriasis (CAMPS), *IL36RN* for Deficiency of IL-36 Receptor Antagonist (DITRA), *AP1S3* for other pustular psoriasis and *MEFV* for Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND).

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. In absence of a consensus definition of remission or minimal disease activity for these diseases, remission has been defined for clinical studies and clinical monitoring as an absence of clinical symptoms and normal inflammatory markers. Anakinra and rilonacept both block IL-1α and IL-1β and should be used for DIRA patients.

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 (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (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 another 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** of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR**

	d. The member has an FDA labeled contraindication to **ALL** of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** e. The member's medication history indicates use of another biologic immunomodulator agent 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 at least **THREE** of the following preferred products after at least a 3-month trial per product: • Adalimumab-aaty • Adalimumab-adaz • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Xeljanz/Xeljanz XR (tofacitinib) **OR** b. 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** of the following: • Adalimumab-aaty • Adalimumab-adaz • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Xeljanz/Xeljanz XR (tofacitinib)

	OR c. The member has an FDA labeled contraindication to **ALL** of the following: • Adalimumab-aaty • Adalimumab-adaz • Enbrel (etanercept) • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Simlandi (adalimumab-ryvk) • Xeljanz/Xeljanz XR (tofacitinib) **OR** d. **ALL** of the following are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication: • 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)	**ALL** of the following: 1. Member is less than 18 years of age **AND**

Associated with SARS-CoV-2	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 (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (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.
- **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
D76.3	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 – M05.79	Rheumatoid arthritis with rheumatoid factor without organ or systems involvement
M05.80 – M05.89	Other rheumatoid arthritis with rheumatoid factor
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.00 – M06.09	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 – M06.89	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]
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.

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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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 11/13/24.

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.