09-J2000-04

Original Effective Date: 10/15/13

Reviewed: 03/12/25

Revised: 04/15/25

Subject: Rilonacept (Arcalyst®) 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:

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 type I receptor (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human immunoglobulin G1. The drug is an interleukin-1 (IL-1) receptor antagonist (IL-1Ra) FDA-approved for the management of cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) in adults and children 12 years of and older.

Cryopyrin-associated periodic syndromes are rare genetic syndromes generally caused by mutations in the NLRP-3 gene. Inflammation in CAPS is usually associated with mutations in the NLRP-3 gene that encodes the protein cryopyrin, which is an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1b). Mutations in the NLRP-3 gene result in an overactive inflammasome, which causes excessive release of activated IL-1b. Rilonacept blocks IL-1b signaling by acting as a soluble decoy receptor that binds IL-1b and prevents its interaction with cell surface receptors. The drug also binds interleukin-1 alpha (IL-1a) and interleukin-1 receptor antagonist (IL-1Ra) to a lesser extent.

Rilonacept is also FDA-approved for the maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing at least 10 kg and for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and children 12 years and older.

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.

I. Initiation of rilonacept (Arcalyst) **meets the definition of medical necessity** for members meeting **ONE** of the following criteria:

1. Member is diagnosed with Cryopyrin-Associated Periodic Syndrome (CAPS) or Cold Induced Auto-inflammatory Syndrome (CAIS) including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) and meets **ALL** of the following:
    a. There is clinical documentation of functional impairment resulting in limitations of activities of daily living
    b. Rilonacept is **NOT** being administered 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), 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)]
    c. The loading dose does not exceed 320 mg, and subsequent dosing does not exceed 160 mg weekly
    d. The member is 12 years of age and older.
2. Member is diagnosed with deficiency of interleukin-1 receptor antagonist (DIRA) and **ALL** of the following:
    a. Rilonacept will be used for the maintenance of remission of DIRA
    b. The member has a IL1RN genetic mutation – documentation must be submitted
    c. The member has previously experienced a clinical benefit with anakinra (Kineret)
    d. Rilonacept is **NOT** being administered 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), 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)]
    e. The dose does not exceed 4.4 mg/kg (max of 320 mg) weekly
3. Member is diagnosed with symptomatic recurrent pericarditis and **ALL** of the following:
    a. **BOTH** of the following – documentation must be submitted:
        i. The member had an inadequate response, intolerance, or contraindication to a sufficient trial of an NSAID (e.g., aspirin, ibuprofen,

indomethacin) in combination with colchicine for the treatment of recurrent pericarditis

ii. The member had an inadequate response, intolerance, or contraindication to a corticosteroid for the treatment of recurrent pericarditis

b. Rilonacept is **NOT** being administered 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), 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)]

c. The loading dose does not exceed 320 mg, and subsequent dosing does not exceed 160 mg weekly

d. The member is 12 years of age and older

Approval duration: 12 months

II. Rilonacept meets the definition of **medical necessity** when used as a single agent for the following designated Orphan Drug indication (http://www.fda.gov/orphan/designat/list.htm) when the dose does not exceed 160 mg weekly:

1. Treatment of familial Mediterranean fever (FMF)

Approval duration: 12 months

III. Continuation of rilonacept (Arcalyst) injection **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. Member has a history of beneficial clinical response with rilonacept therapy for the treatment of **ONE** of the following indications:

   a. Cryopyrin-Associated Periodic Syndrome (CAPS) or Cold Induced Auto-inflammatory Syndrome (CAIS) including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)

   b. Familial Mediterranean fever

   c. Deficiency of interleukin-1 receptor antagonist (DIRA)

   d. Recurrent pericarditis

2. The member has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), **OR** the member has previously met all indication-specific criteria.

3. Rilonacept is **NOT** being administered 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), 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)]

4. The dose does not exceed the following:
    a. DIRA: 4.4 mg/kg (max of 320 mg) weekly
    b. All other indications:160 mg weekly

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

Cryopyrin-Associated Periodic Syndrome (CAPS) or Cold Induced Auto-inflammatory Syndrome (CAIS) including Familial Cold Auto-inflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and recurrent pericarditis (RP):

Age 18 years or older

- Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg on the same day at two different sites
- Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection
- Do not administer more often than once weekly

Age 12 to 17 years

- Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL
- Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL
- If the initial dose is given as two injections, they should be given on the same day at two different sites
- Do not administer more often than once weekly

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

Adults and Pediatric Patients weighing at least 10 kg:

- 4.4 mg/kg up to a maximum of 320 mg, delivered as 1 or 2 injections (2 mL/injection) once weekly
- When switching from another IL-blocker, discontinue the IL-1 blocker and begin treatment at the same time of the next dose

Dose Adjustments

- None

Drug Availability

- 220 mg single-use, glass vial

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Interleukin-1 blockade may interfere with immune response to infections; discontinue treatment if serious or active infection; do not initiate treatment in patients with active or chronic infections. Do not take with TNF inhibitors because of increased risk of serious infections.
- It is unknown if treatment with immunosuppressants such as rilonacept result in an increased risk of malignancy.
- Hypersensitivity
- Live vaccines should not be given concurrently
- May cause elevations in lipid concentrations

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J2793	Injection, rilonacept, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

E85.0	Non-neuropathic heredofamilial amyloidosis
I30.0	Acute nonspecific idiopathic pericarditis
I30.9	Acute pericarditis, unspecified
L50.2	Urticaria due to cold and heat
M04.1	Periodic fever syndromes
M04.2	Cryopyrin-associated periodic syndromes
M04.8	Other autoinflammatory syndromes
M04.9	Autoinflammatory syndrome, unspecified

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: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time this guideline was drafted.

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:

Cryopyrin-Associated Periodic Syndrome (CAPS) aka Cold Induced Auto-inflammatory Syndrome (CAIS1): is a spectrum of autoinflammatory syndromes including familial cold autoinflammatory syndrome (FCAS, formerly termed familial cold-induced urticaria), the Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID, also called chronic infantile neurologic cutaneous and articular syndrome or CINCA).

Deficiency of Interleukin-1 Receptor Antagonist (DIRA): a rare autoinflammatory disease caused by a *IL1RN* gene mutation that presents with severe skin and bone inflammation,

Familial cold autoinflammatory syndrome (FCAS): is an autosomal dominant condition characterized by rash, conjunctivitis, fever/chills and arthralgias elicited by exposure to cold.

Familial Mediterranean fever (FMF): is an inherited autosomal recessive disease characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints. These episodes are often accompanied by fever and sometimes a rash.

Muckle-Wells syndrome (MWS): is a rare autosomal dominant disease which causes sensorineural deafness, recurrent hives, and can lead to amyloidosis.

RELATED GUIDELINES:

Canakinumab (Ilaris®) Injection, 09-J2000-03

OTHER:

NOTE: The list of biologic immunomodulator agents not permitted as concomitant therapy can be found at 09-J9000-02, Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.

REFERENCES:

1. Arcalyst® [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; May 2021.
2. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 2025 February 26].
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025 February 26].
4. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2025 February 26].
5. Garg M, de Jesus AA, Chapelle D, et al. Rilonacept maintains long-term inflammatory remission in patients with deficiency of the IL-1 receptor antagonist. JCI Insight. 2017;2(16):e94838. Published 2017 Aug 17. doi:10.1172/jci.insight.94838.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Coverage Committee on 03/12/25.

GUIDELINE UPDATE INFORMATION:

10/15/13	New Medical Coverage Guideline.
10/15/14	Review and revision to guideline; consisting of updating position statement, dosage/administration, precautions, references.
10/15/15	Review and revision to guideline; consisting of updating position statement, precautions, coding, references.
11/01/15	Revision: ICD-9 Codes deleted.
10/01/16	Update to ICD-10 codes.
10/15/16	Review and revision to guideline; consisting of updating position statement and references.
11/15/16	Revision to guideline consisting of updating position statement and coding.
03/15/21	Review and revision to guideline; consisting of updating position statement, description, dosing and references.
05/15/21	Revision to guideline consisting of updating position statement and coding.
08/15/21	Revision to guideline consisting of updating the position statement.
04/15/23	Review and revision of the guideline, consisting of updating the position statement to include additional interleukin blockers that are not permitted as concomitant therapy and to require documentation from other health plans for continuation and updating the references.
04/15/24	Review and revision of the guideline, consisting of revising the list of biologic agents not permitted as concomitant therapy within the position statement and updating the references.
04/15/25	Revision to the guideline consisting of revising the position statement to add Leqselvi (deuruxolitinib) to the JAK inhibitor list not to use in combination with rilonacept (Arcalyst), adding the policy that lists the biologics not permitted as concomitant therapy in the Other section, and updating the references.