PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Arcalyst Prior Authorization Policy
- Arcalyst® (rilonacept subcutaneous injection – Regeneron)

REVIEW DATE: 02/26/2025; selected revision 04/23/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Arcalyst, an interleukin-1 (IL-1) blocker, is indicated for the following uses:[1]
- **Cryopyrin-associated periodic syndromes** (CAPS), including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS), for treatment of patients ≥ 12 years of age.
- **Deficiency of interleukin-1 receptor antagonist** (DIRA), for maintenance of remission in adults and pediatric patients weighing at least 10 kg.
- **Pericarditis**, for treatment of recurrent disease and reduction in risk of recurrence in patients ≥ 12 years of age.

In the pivotal trial for CAPS, patients had significant improvement in symptom scores with Arcalyst through Week 6 which were maintained through Week 15.[1] The pivotal trial for DIRA enrolled patients with a loss of function *IL1RN* mutation who previously experienced a benefit with Kineret® (anakinra subcutaneous injection). All patients (n = 6) were in remission at Month 6 and sustained remission for the remainder of

the 2-year study. In the pivotal trial for pericarditis, patients had a mean of 4.7 total episodes of pericarditis (standard deviation, ± 1.7 episodes), including the current episode.[3] All patients who enrolled in the study were symptomatic despite treatment with standard treatment (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], colchicine, and/or systemic corticosteroids). Patients who responded to Arcalyst during the initial 12 weeks of treatment, defined as C-reactive protein ≤ 0.5 mg/dL with minimal or no pain (daily rating pain score), were eligible for continuation in the randomized withdrawal period.

Guidelines

Arcalyst is used for treatment of a variety of periodic fever syndromes and inflammatory conditions.

CAPS and DIRA

The European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) [2021] provide treatment guidelines for IL-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumor necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the IL-1 receptor antagonist.[4] Guidelines indicate IL-blocking therapy has become the preferred treatment and a therapeutic trial with IL-1 blocking agents may be started when strong clinical suspicious of a diagnosis of CAPS, TRAPS, MKD, or DIRA is suspected. The guidelines also provide additional diagnosis-specific treatment recommendations:

- **CAPS:** CAPS encompasses three rare genetic syndromes (familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal onset multisystem inflammatory disease formerly known as chronic infantile neurological cutaneous and articular syndrome) that are thought to be one condition along a spectrum of disease severity. IL-1 blockers are recommended as standard of care across the spectrum of disease for improved symptom control and reduced systemic and tissue/organ inflammation. The dose and/or frequency of administration should be adjusted to control disease activity, normalize markers of systemic inflammation, and for appropriate weight gain and development in the growing patient.
- **DIRA:** DIRA is caused by recessive loss-of-function pathogenic variants in the *IL1RN* gene. Treatment with agents that block both IL-α and IL-β is recommended and includes Arcalyst and Kineret.

Pericarditis

Guidelines for acute and chronic pericarditis are available from the American College of Cardiology (2020).[2] A symptom-free interval of 4 to 6 weeks and evidence of new pericardial inflammation are needed for a diagnosis of recurrent disease. For recurrent disease, controlled clinical trials support a remarkable reduction in recurrences with colchicine, which should be continued for at least 6 months. Additionally, low-dose corticosteroids are associated with a high treatment success rate. NSAIDs (e.g., aspirin, ibuprofen, indomethacin) are also listed as alternatives for recurrent disease. Immunosuppressive drugs, including azathioprine, methotrexate, and mycophenolate mofetil, are effective, well tolerated, and used as corticosteroid-sparing agents. There is also limited evidence suggesting efficacy of

intravenous immunoglobulins. Although Arcalyst was not yet approved for recurrent pericarditis, the guidelines note that benefit was shown in a Phase II study, demonstrated by a decrease in chest pain and C-reactive protein levels.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Arcalyst. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Arcalyst as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Arcalyst to be prescribed by or in consultation with a physician who specializes in the condition being treated.

- **Arcalyst® (rilonacept subcutaneous injection - Regeneron)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes (CAPS).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   Note: This includes familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and/or neonatal onset multisystem inflammatory disease (NOMID) formerly known as chronic infantile neurological cutaneous and articular syndrome (CINCA).
   A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
      i. Patient is ≥ 12 years of age; AND
      ii. The medication is prescribed by or in consultation with a rheumatologist, geneticist, allergist/immunologist, or dermatologist; OR
   B) Patient is Currently Receiving Arcalyst. Approve for 1 year if the patient meets BOTH of the following (i and ii):
      i. Patient has been established on this medication for at least 6 months; AND
      Note: For a patient who has not received 6 months of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.
      ii. Patient meets at least ONE of the following (a or b):
         a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
         Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, amyloid A), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
Note: Examples of improvement in symptoms include fewer cold-induced attacks; less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

2. Deficiency of Interleukin-1 Receptor Antagonist. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):

i. Patient is ≥ 10 kg (22 pounds); AND

ii. Genetic testing has confirmed bi-allelic pathogenic variants in the *IL1RN* gene; AND

iii. According to the prescriber, patient has demonstrated a clinical benefit with Kineret (anakinra subcutaneous injection); AND
Note: Examples of a clinical response with Kineret include normalized acute phase reactants; resolution of fever, skin rash, and bone pain; and reduced dosage of corticosteroids.

iv. The medication is prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory disorders; OR

B) Patient is Currently Receiving Arcalyst. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 6 months; AND
Note: For a patient who has not received 6 months of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
Note: Examples of objective measures include improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), reduction in proteinuria, and/or stabilization of serum creatinine.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.
Note: Examples of improvement of symptoms include an improvement of skin or bone symptoms; less joint pain/tenderness, stiffness, or swelling.

3. Pericarditis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets ALL of the following (i, ii, iii, iv, and v):

i. Patient is ≥ 12 years of age; AND

ii. Patient has recurrent pericarditis; AND

iii. Prior to starting treatment with Arcalyst, the patient had a history of at least three episodes of pericarditis; AND

iv. Patient meets ONE of the following (a or b):

a) For the current episode, the patient is receiving standard treatment; OR

b) Standard treatment is contraindicated; AND

Note: Standard treatments for pericarditis include nonsteroidal anti-inflammatory drug(s) [NSAIDs], colchicine, and/or systemic corticosteroids.

v. The medication is prescribed by or in consultation with a cardiologist or rheumatologist; OR

B) Patient is Currently Receiving Arcalyst. Approve for 1 year if the meets BOTH of the following (i and ii):

i. Patient has been established on this medication for at least 3 months; AND

Note: For a patient who has not received 90 days of therapy or who is restarting therapy with this medication, refer to Initial Therapy criteria above.

ii. Patient meets at least ONE of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR

Note: Examples of objective measures include normalization of inflammatory biomarkers such as erythrocyte sedimentation rate and/or C-reactive protein, continued resolution of fever.

b) Compared with baseline (prior to initiating the requested drug), patient experienced an improvement in at least one symptom.

Note: Examples of improvement of symptoms include resolution of chest pain or pericarditis pain.

CONDITIONS NOT COVERED

- **Arcalyst® (rilonacept subcutaneous injection - Regeneron)**

is(are) considered not medically necessary for ANY other use(s) including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Concurrent Biologic Therapy.** Arcalyst should not be administered in combination with another biologic agent for an inflammatory condition (see Appendix for examples).[1] Arcalyst has not been used in combination with tumor necrosis factor inhibitors (TNFis). An increased incidence of serious infections has been associated with another interleukin-1 blocker (Kineret® [anakinra subcutaneous injection]) when given in combination with TNFis.

REFERENCES

1. Arcalyst® subcutaneous injection [prescribing information]. Tarrytown, NY: Regeneron; November 2024.
2. Chiabrando JG, Bonaventura A, Vecchie A, et al. Management of acute and recurrent pericarditis. *J Am Coll Cardiol*. 2020;75(1):76-92.

3. Klein AL, Imazio M, Cremer P, et al. Phase 3 trial of interleukin-1 trap rilonacept in recurrent pericarditis. *N Engl J Med*. 2021;384(1):31-41.
4. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. *Ann Rheum Dis*. 2022;81(7):907-921.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	01/25/2023
Annual Revision	No criteria changes.	02/14/2024
Annual Revision	**Deficiency of Interleukin-1 Receptor Antagonist**: The term "mutation" was rephrased to "biallelic pathogenic variants". Updated Appendix.	02/26/2025
Selected Revision	**Policy Statement**: Removed "All reviews for COVID-19 and/or cytokine release syndrome associated with COVID-19 will be forwarded to the Medical Director." **COVID-19 (Coronavirus Disease 2019)**: Diagnosis removed from Conditions Not Covered.	04/23/2025

APPENDIX

	Mechanism of Action	Examples of Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, HS, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, JIA, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA, RA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Simponi®, Simponi Aria® (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Tocilizumab Products (Actemra® IV, biosimilar; Actemra SC, biosimilar)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Omvoh® (mirikizumab IV infusion, SC injection)	Inhibition of IL-23	UC
	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC

Stelara® (ustekinumab SC injection, ustekinumab IV infusion)		IV formulation: CD, UC
Siliq® (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection; secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, HS, nr-axSpA, PsO, PsA
		IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A/17F	AS, HS, nr-axSpA, PsO, PsA
Ilumya® (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO, UC
		IV formulation: CD, UC
Tremfya® (guselkumab SC injection, guselkumab IV infusion)	Inhibition of IL-23	SC formulation: PsA, PsO, UC
		IV formulation: UC
Entyvio® (vedolizumab IV infusion, vedolizumab SC injection)	Integrin receptor antagonist	CD, UC

* Not an all-inclusive list of indications. Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; HS – Hidradenitis suppurativa; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug.