Drug Coverage Policy

Effective Date.....9/1/2024
Coverage Policy Number.....IP0437
Policy Title.....Arcalyst

Inflammatory Conditions – Arcalyst

- Arcalyst® (rilonacept subcutaneous injection - Regeneron)

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 and have discretion in making individual coverage determinations. 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 Healthcare Coverage Policy

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 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. 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 a variety of periodic fever syndromes and inflammatory conditions. The European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) [2021] provide treatment guidelines for interleukin-1 mediated autoinflammatory diseases and 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.[4] The guidelines also provide additional diagnosis-specific treatment recommendations:

- **CAPS:** 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:** Treatment with agents that block both IL-α and IL-β is recommended and includes Kineret® (anakinra subcutaneous injection) and Arcalyst.

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.

Medical Necessity Criteria

Arcalyst is considered medically necessary when ONE of the following is met:

FDA-Approved Indications

1. **Cryopyrin-Associated Periodic Syndromes.** 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 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 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.
   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 a mutation 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.
   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 in 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.
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 in improvement of symptoms include resolution of chest pain or pericarditis pain.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, 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.

2. **COVID-19 (Coronavirus Disease 2019).** Note: This includes requests for cytokine release syndrome associated with COVID-19.

References

1. Arcalyst® subcutaneous injection [prescribing information]. Tarrytown, NY: Regeneron; March 2021.
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.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	Updated title of the policy from Rilonacept to Inflammatory Conditions – Arcalyst. **All Indications:** Criteria were updated to clarify "Initial Therapy" versus "Patient is Currently Receiving Arcalyst". **Cryopyrin-Associated Periodic Syndromes.** "Treatment of ONE of the following: Chronic infantile neurological cutaneous and articular (CINCA) syndrome, Familial Cold Autoinflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), or Neonatal-Onset Multisystem Inflammatory Disease (NOMID)" was relocated to a Note with all of the conditions included as examples of CAPS. Updated the initial approval duration from 12 months to 6 months. Added "Patient is ≥ 12 years of age." **Deficiency of Interleukin-1 Receptor Antagonist**. Updated the initial approval duration from 12 months to 6 months. Added "According to the prescriber, patient has demonstrated a clinical benefit with Kineret (anakinra subcutaneous injection)" with examples of a clinical response included in a Note. **Pericarditis.** Removed "Pericarditis secondary to the following etiologies has been ruled out: systemic autoimmune disease, infection (e.g.	9/1/2024

	tuberculosis), myocarditis, trauma, radiation or cancer." **Conditions Not Covered.** Removed Adult Onset Still's Disease, Gout, Juvenile Idiopathic Arthritis, Schnitzler Syndrome, and Type 1 or 2 Diabetes for list maintenance and simplification. This does not imply a change in coverage status, and all remain conditions not covered.	

The policy effective date is in force until updated or retired.

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Zymfentra® (infliximab-dyyb SC injection)	Inhibition of TNF	CD, UC
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA, PMR
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	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
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	IV formulation: CD, UC

Siliq™ (brodalumab SC injection)	Inhibition of IL-17RA	PsO
Bimzelx® (bimekizumab-bkzx SC injection)	Inhibition of IL-17A and IL-17F	PsO
Cosentyx® (secukinumab SC injection, secukinumab IV infusion)	Inhibition of IL-17A	SC formulation: AS, ERA, nr-axSpA, PsO, PsA
Skyrizi® (risankizumab-rzaa SC injection)	Inhibition of IL-23	IV formulation: AS, nr-axSpA, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). 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; 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.