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Rilonacept

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Overview

This policy supports medical necessity review for rilonacept (Arcalyst®).

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

Medical Necessity Criteria

Rilonacept (Arcalyst) is considered medically necessary when ONE of the following is met (1, 2, or 3):

1. **Cryopyrin-Associated Periodic Syndromes (CAPS).** Individual meets **BOTH** of the following criteria (A and B):
   A. The medication is being used for treatment of **ONE** of the following (i, ii, iii or iv):
      i. Chronic infantile neurological cutaneous and articular (CINCA) syndrome
      ii. Familial Cold Autoinflammatory Syndrome (FCAS)
      iii. Muckle-Wells Syndrome (MWS)
      iv. Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

B. Medication is being prescribed by, or in consultation with, a rheumatologist, geneticist, allergist/immunologist, or dermatologist

2. **Deficiency of Interleukin-1 Receptor Antagonist (DIRA).** Individual meets **ALL** of the following criteria (A, B, and C):
   A. Individual is greater than or equal to 10 kg (22 pounds)
   B. Genetic testing has confirmed a mutation in the IL1RN gene
   C. The medication is prescribed by or in consultation with a rheumatologist, geneticist, dermatologist, or a physician specializing in the treatment of autoinflammatory disorders

3. **Pericarditis, Recurrent.** Individual meets **ALL** of the following criteria (A, B, C, D, E and F):
   A. Individual is 12 years of age or older
   B. Documentation supporting a diagnosis of pericarditis [for example, pericarditic chest pain, pericardial rub, new widespread ST-segment elevation or PR-segment depression according to ECG findings, pericardial effusion (new or worsening)]
   C. Prior to starting treatment with Arcalyst, the individual has recurrent pericarditis defined as a history of at least three distinct treated episodes
   D. Pericarditis secondary to the following etiologies has been ruled out: systemic autoimmune disease, infection (e.g. tuberculosis), myocarditis, trauma, radiation or cancer
   E. Individual meets **ONE** of the following (i or ii):
      i. For the current episode, individual has acute signs and symptoms of pericarditis despite standard treatment [nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and/or systemic corticosteroids)
      ii. Individual has a contraindication or intolerance for standard treatment

   F. Medication is prescribed by, or in consultation with, a cardiologist or rheumatologist

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.

Reauthorization Criteria

Rilonacept (Arcalyst) is considered medically necessary for continued use when initial criteria are met AND there is documentation of beneficial response.

Examples of beneficial response include:

1. **Cryopyrin-Associated Periodic Syndromes (CAPS) [including Familial Cold Autoinflammatory Syndrome {FCAS}, Muckle-Wells Syndrome {MWS}, and Neonatal Onset Multisystem Inflammatory Disease {NOMID} or Chronic Infantile Neurological Cutaneous and Articular {CINCA} Syndrome]:** 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, stabilization of serum creatinine, 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:** 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, stabilization of serum creatinine, improvement of skin or bone symptoms, or less joint pain/tenderness, stiffness, or swelling.

3. **Pericarditis, Recurrent**: normalization of inflammatory biomarkers such as erythrocyte sedimentation rate and/or C-reactive protein, continued resolution of fever, or resolution of chest pain or pericarditis pain.

Authorization Duration

Initial approval duration:

1. **Cryopyrin-associated periodic syndromes (CAPS)**: up to 12 months
2. **Deficiency of interleukin-1 receptor antagonist (DIRA):** up to 12 months
3. **Pericarditis, Recurrent:** up to 3 months

Reauthorization approval duration: up to 12 months.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

1. **Adult Onset Still's Disease.** Rilonacept is not indicated for use in the treatment of Adult Onset of Still's Disease.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[4]

2. **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.

3. **COVID-19 (Coronavirus Disease 2019).** This includes requests for cytokine release syndrome and pericarditis associated with COVID-19.

4. **Gout**. Rilonacept is not indicated for use in the treatment of gout.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[5]

5. **Juvenile Idiopathic Arthritis**. Rilonacept is not indicated for use in the treatment of Juvenile Idiopathic Arthritis.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[6]

6. **Schnitzler Syndrome**. Rilonacept is not indicated for use in the treatment of Schnitzler.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[7]

7. **Type 1 or 2 Diabetes**. Rilonacept is not indicated for use in the treatment of Type 1 or 2 Diabetes.[1] At this time, there is insufficient safety and efficacy data to support its use for this condition.[6]

Background

OVERVIEW

Arcalyst, an interleukin-1 blocker, is indicated for the following uses:[1]

1. **Cryopyrin-associated periodic syndromes (CAPS)**, including familial cold autoinflammatory syndrome and Muckle-Wells syndrome, for treatment of patients ≥ 12 years of age.
2. **Deficiency of interleukin-1 receptor antagonist (DIRA),** for maintenance of remission in patients weighing at least 10 kg.
3. **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. 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.

Dosage and Administration

Cryopyrin-Associated Periodic Syndromes, Familial Cold AutoInflammatory Syndrome, Muckle-Wells Syndrome and Recurrent Pericarditis

- Adults: Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg each, administered on the same day at two different injection sites. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection.

- Pediatric patients 12 years to 17 years: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum dose of 320 mg, administered as one or two subcutaneous injections, not to exceed single-injection volume of 2 mL per injection site. If the initial dose is given as two injections, administer on the same day at two different sites. 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.

Deficiency of IL-1 Receptor Antagonist

- Adults: The recommended dose of Arcalyst is 320 mg, once weekly, administered as two subcutaneous injections on the same day at two different sites with a maximum single-injection volume of 2 mL. ARCALYST should not be given more often than once weekly.

- Pediatric patients weighing 10 kg or more: The recommended dose of Arcalyst is 4.4 mg/kg (up to a maximum of 320 mg), once weekly, administered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. If the dose is given as two injections, administer both on the same day, each one at a different site.

Clinical Efficacy

- Cryopyrin-Associated Periodic Syndromes, Familial Cold Auto-Inflammatory Syndrome and Muckle-Wells Syndrome
  - The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study (NCT00288704) with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS. Part A was a 6-week, randomized, double-blind, parallel-group period comparing ARCALYST at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all patients received ARCALYST 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on ARCALYST 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with ARCALYST 160 mg weekly.
  - Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment.
  - ARCALYST-treated patients had a larger reduction in the mean symptom score in Part A compared to placebo-treated patients. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on ARCALYST.
  - In Part A, a higher proportion of patients in the ARCALYST group experienced improvement from baseline in the composite score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%) and by at least 75% (70% vs. 0%) compared to the placebo group.

- Deficiency of IL-1 Receptor Antagonist

- The safety and efficacy of ARCALYST for the maintenance of remission of DIRA was demonstrated in a 2-year, open label study (NCT01801449) of 6 pediatric patients who previously experienced clinical benefit from daily injections of an IL-1 receptor antagonist, anakinra. The study population included patients with a loss-of-function IL1RN mutations. Patients had a median age at baseline of 4.8 years (range 3.3 to 6.2), and stopped anakinra treatment 24 hours before initiation of ARCALYST.
- Remission was defined using the following criteria: diary score of < 0.5 (reflecting no fever, skin rash and bone pain), acute phase reactants (<0.5 mg/dL CRP), absence of objective skin rash, and no radiological evidence of active bone lesions.
- Following an ARCALYST loading dose of 4.4 mg/kg subcutaneously, patients received a once-weekly maintenance dose of 2.2 mg/kg (up to a maximum 160 mg), and were assessed for remission and possible dose escalation. During the first 3 months of ARCALYST administration at the 2.2 mg/kg dose, five of 6 patients exhibited recurrence of pustular rash and therefore the dose was escalated to 4.4 mg/kg once-weekly (up to a maximum of 320 mg). One patient remained on the 2.2 mg/kg once-weekly dose.
- All patients met the primary end point of the study, remission at 6 months and sustained the remission for the remainder of the 2-year study. No patient required steroid use during the study.

- Recurrent Pericarditis
  - The efficacy and safety of ARCALYST was evaluated in the Phase 3 study RHAPSODY (NCT03737110), a double-blind, placebo-controlled, randomized withdrawal, multinational study. The study consisted of a 12-week run-in followed by a double-blind, placebo-controlled, randomized withdrawal period.
  - A total of 86 patients (mean age 45 years [range 13-78], 57% females) with symptomatic pericarditis recurrence were enrolled and received study treatment. Of these, 73 (85%) had a diagnosis of “idiopathic” pericarditis, and the remainder post-cardiac injury pericarditis. The mean duration of disease was 2.4 years with a mean of 4.4 pericarditis events per year including the qualifying pericarditis event (0-10 point Numerical Rating Scale [NRS] ≥ 4 and CRP ≥ 1 mg/dL). Mean qualifying NRS pain score was 6.2, and mean qualifying CRP level was 6.2 mg/dL. The primary efficacy endpoint was time to first adjudicated pericarditis recurrence (based on pain, CRP and clinical signs) in the event-driven withdrawal period.
  - Of 61 randomized, 23 patients (74%) in the placebo arm had a recurrence compared with 2 patients (7%) in the rilonacept arm who temporarily discontinued treatment for 1 – 3 doses. The median time-to recurrence on rilonacept could not be estimated because too few events occurred and was 8.6 weeks (95% CI 4.0, 11.7) on placebo with a hazard ratio of 0.04 ($p < 0.0001$);Rilonacept reduced the risk of recurrence by 96%.

Guidelines

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.

References

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Appendix

Table 1. Approved TNFis for Targeted Indications.

	Rheumatology					Dermatology	Gastroenterology	
	RA	JIA	AS	nr-axSpA	PsA	PsO	CD	UC
Tumor Necrosis Factor Inhibitors								
Cimzia	√	--	√	√	√	√	√	--
Enbrel	√	√	√	--	√	√	--	--
Humira	√	√	√	--	√	√	√	√
Infliximab Products	√	--	√	--	√	√	√	√
Simponi Subcutaneous	√	--	√	--	√	--	--	√
Simponi Aria	√	√	√	--	√	--	--	--

TNFis – Tumor necrosis factor inhibitors; RA – Rheumatoid arthritis; JIA – Juvenile idiopathic arthritis; AS – Ankylosing spondylitis; nr-axSpA – Non-radiographic spondyloarthritis; PsA – Psoriatic arthritis; PsO – Plaque psoriasis; CD – Crohn's disease; UC – Ulcerative colitis.

Table 2. Approved IL-17, IL-23, and IL-12/23 Blockers for Targeted Indications.

	Rheumatology			Dermatology	Gastroenterology	
	Ankylosing Spondylitis	nr-axSpA	Psoriatic Arthritis	Plaque Psoriasis	Crohn's Disease	Ulcerative Colitis
Interleukin-17 Blockers						
Cosentyx	√	√	√	√	--	--
Siliq	--	--	--	√	--	--
Taltz	√	√	√	√	--	--
Interleukin-23 Blockers						
Ilumya	--	--	--	√	√	--
Skyrizi Intravenous	--	--	--	--	√[#]	--
Skyrizi Subcutaneous	--	--	√	√	√[^]	--
Tremfya	--	--	√	√	--	--
Interleukin-12/23 Blockers						
Stelara Subcutaneous	--	--	√	√	√[^]	√[^]
Stelara Intravenous	--	--	--	--	√[#]	√[#]

IL – Interleukin; nr-axSpA – Non-radiographic spondyloarthritis; [^] Maintenance dosing only; [#] Induction dosing only.

Table 3. Approved Oral tsDMARDs for Targeted Indications.

	Rheumatology				Dermatology	Gastro-enterology
	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Ankylosing Spondylitis	Psoriatic Arthritis	Plaque Psoriasis	Ulcerative Colitis
Janus Kinases Inhibitors						
Olumiant	√	--	--	--	--	--
Rinvoq	√	--	√	√	--	√
Xeljanz tablets	√	√[#]	√	√	--	√
Xeljanz oral solution	--	√[#]	--	--	--	--
Xeljanz XR	√	--	√	√	--	√
Phosphodiesterase Type 4 Inhibitor						
Otezla	--	--	--	√	√	--
Sphingosine 1-Phosphate Receptor Modulator						
Zeposia	--	--	--	--	--	√

tsDMARDs – Targeted synthetic disease-modifying antirheumatic drugs; [#] Indicated in polyarticular JIA.

Table 4. Other Approved Biologics for Targeted Indications.

	Rheumatology

	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Psoriatic Arthritis
Interleukin-6 Blockers			
Actemra Intravenous	√	√^	--
Actemra Subcutaneous	√	√^	--
Kevzara	√	--	--
Interleukin-1 Blocker			
Kineret	√	--	--
T-Cell Costimulation Modulator			
Orencia Intravenous	√	√#	√
Orencia Subcutaneous	√	√#	√
CD20-Directed Cytolytic Antibody			
Rituximab Intravenous Products	√	--	--

^ Indicated in polyarticular and systemic JIA; # Indicated in polyarticular JIA.