# PDL DRUG REVIEW

**Proprietary Name: Arcalyst®**
**Common Name: rilonacept**
**PDL Category: Anti-Inflammatories, Non-NSAID**

| Comparable Products | Preferred Drug List Status |
|---|---|
| Ilaris | Non-Preferred with Conditions |

## Summary


**Pharmacology/Usage:** Rilonacept, the active ingredient of Arcalyst®, is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept is an interleukin-1 alpha (IL-1α) and interleukin-1 beta (IL-1β) cytokine trap. It blocks IL-1 signaling by acting as a soluble decoy receptor that binds both IL-1α and IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds interleukin-1 receptor antagonist (IL-1ra).

In most cases, inflammation in Cryopyrin-Associated Periodic Syndromes (CAPS) is associated with mutations in the NLRP-3 gene, which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1β). Mutations in the NLRP-3 result in an overactive inflammasome, resulting in excessive release of activated IL-1β that drives inflammation.

Deficiency of Interleukin-1 Receptor Antagonist (DIRA) is an autoinflammatory, autosomal recessive disorder caused by loss of function mutations in the *IL1RN* gene, which encodes IL-1 receptor antagonist (IL-1ra), resulting in unopposed signaling of the proinflammatory cytokines IL-1α and IL-1β through the IL-1 receptor.

Interleukin-1 (IL-1) is a key cytokine that mediates the pathophysiology of many inflammatory processes, and it has been implicated as a causative factor in pericarditis.

**Indication:** For:

- The treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and pediatric patients 12 years and older
- The maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adult and pediatric patients weighing at least 10kg
- The treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and pediatric patients 12 years and older.

There is no pregnancy category for this medication; however, the risk summary indicates that rare pregnancy outcomes reported post- marketing and from clinical trials, with very limited use of Arcalyst® in pregnant woman, are not sufficient to assess for a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There may be risks to the mother and fetus associated with CAPS. Clinical considerations include that

published data suggest that increased maternal levels of interleukin (IL)-1β, which induces inflammation that occurs in CAPS, may be associated with pre-term birth. The safety and efficacy of use have not been established in pediatric patients less than 12 years of age for CAPS and RP. The safety and efficacy of use have not been established in pediatric patients weighing less than 10kg for maintenance of remission of DIRA.

**Dosage Form:** For injection: 220mg of lyophilized powder for reconstitution in single-dose vials. Reconstitute each single-dose vial with 2.3ml of preservative-free Sterile Water for Injection (supplied separately) prior to administration of the drug. A volume of up to 2ml can be withdrawn, which is designed to deliver 160mg for SC administration only. Thus, after reconstitution, each vial contains rilonacept 80mg/ml. No preservatives are present.

**Recommended Dosage:** For subcutaneous use only. Rotate the sites for injection, such as the abdomen, thigh, or upper arm. Injections should never be administered at sites that are bruised, red, tender, or hard. Store in refrigerator. After reconstitution, may be kept at room temperature, but keep it protected from light and use the solution within 3 hours after reconstitution. Discard unused portions.

*With CAPS and recurrent pericarditis for adults*, start treatment with a loading dose of 320mg delivered as two, 2ml SC injections of 160mg each, administered on the same day at two different injection sites. Continue dosing with a once-weekly injection of 160mg administered as a single, 2ml subcutaneous injection. *For pediatric patients 12 to 17 years*, start treatment with a loading dose of 4.4mg/kg, up to a maximum dose of 320mg, administered as one or two SC injections, not to exceed single-injection volume of 2ml 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 2.2mg/kg, up to a maximum of 160mg, administered as a single SC injection, up to 2ml.

*With maintenance of remission of DIRA for adults*, the recommended dose is 320mg once weekly, administered as two SC injections on the same day at two different sites with a maximum single-injection volume of 2ml. Arcalyst® should not be given more often than once weekly. *For pediatric patients weighing 10kg or more*, the recommended dose is 4.4mg/kg (up to a maximum of 320mg) once weekly, administered as one or two SC injections with a maximum single-injection volume of 2ml. If the dose is given as two injections, administer both on the same day, each one at a different site. When switching from another IL-1 blocker, discontinue the IL-1 blocker and begin Arcalyst® treatment at the time of the next dose.

No studies have been conducted to evaluate the pharmacokinetics of rilonacept administered SC in patients with renal or hepatic impairment.

**Drug Interactions:** Specific drug interaction studies have not been conducted with Arcalyst®. Concomitant administration of another drug that blocks IL-1 with a TNF-blocking agent in another patient population has been associated with an increased risk of serious infections and an increased risk of neutropenia. The concomitant use of Arcalyst® with TNF-blocking agents may also result in similar toxicities and is not recommended. The concomitant use of Arcalyst® with other drugs that block IL-1 has not been studied. Based on the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of Arcalyst® and other agents that block IL-1 or its receptors is not recommended.

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g. IL-1) during chronic inflammation. Thus, it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g. warfarin). Upon initiation of Arcalyst® in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed, and the individual dose of the medicinal product may need to be adjusted.

**Box Warning:** There is no box warning associated with this product.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Arcalyst®) minus reported % incidence for placebo in patients with CAPS. Please note that an incidence of 0% means the incidence was the same as or less than the placebo.* The most frequently reported adverse events included

injection site reactions (35%), upper respiratory tract infection (22%), nausea (0%), diarrhea (0%), sinusitis (5%), abdominal pain upper (0%), cough (9%), hypoesthesia (9%), stomach discomfort (0%) and urinary tract infection (0%).

Interleukin-1 (IL-1) blockade may interfere with the immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking Arcalyst®. There was a greater incidence of infections in CAPS and RP patients on Arcalyst® compared with placebo. Arcalyst® is not recommended for use with TNF inhibitors because this may increase the risk of serious infections. In addition, drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as Arcalyst® that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Refer to current practice guidelines for evaluation and treatment of possible latent TB infections before starting therapy with Arcalyst®. Furthermore, treatment with Arcalyst® should not be started in patients with an active or chronic infection. Discontinue Arcalyst® if a patient develops a serious infection.

The impact of treatment with Arcalyst® on the development of malignancies is not known. Treatment with immunosuppressants, including Arcalyst®, may result in an increase in the risk of malignancies.

Hypersensitivity reactions associated with Arcalyst® occurred in clinical trials. If a hypersensitivity reaction occurs, discontinue Arcalyst® and start appropriate therapy.

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Increases in non-fasting lipid profile parameters occurred in patients treated with Arcalyst® in clinical trials. Monitor patient's lipid profiles and consider lipid-lowering therapies if needed, based on cardiovascular risk factors and current guidelines.

Since no data are available on the risks of secondary transmission of infection by live vaccines in patients receiving Arcalyst®, avoid administration of live vaccines during treatment with Arcalyst®. No data are available on the effectiveness of vaccines in patients receiving Arcalyst®. Since Arcalyst® may interfere with normal immune response to new antigens, vaccines may not be effective in patients receiving Arcalyst®. Furthermore, because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with Arcalyst®, adult and pediatric patients receive all recommended vaccinations, as per current immunization guidelines, including pneumococcal vaccine and inactivated influenza vaccine.

**Contraindications:** There are no contraindications listed with this product.

**Manufacturer:** By Kiniksa Pharmaceuticals (UK), Ltd. A registered trademark of Regeneron Pharmaceuticals

**Analysis:** *The safety and efficacy of Arcalyst® for the treatment of CAPS* was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS).

Part A was a 6-week, randomized, double-blind, parallel-group period comparing Arcalyst® to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all patients received Arcalyst® 160mg weekly, followed by a 9-week double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on Arcalyst® 160mg weekly or to receive placebo. Patients were then given an option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with Arcalyst® 160mg weekly.

Using a daily diary questionnaire, patients rated the following 5 signs and symptoms of CAPS, including 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.

The changes in mean symptom scores for the randomized parallel-group period (Part A) and the randomized withdrawal period (Part B) of the study can be seen in the table below, which was adapted from the prescribing information. 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®.

| Mean Symptom Scores | | | | | |
|---|---|---|---|---|---|
| Part A | Placebo (N=24) | Arcalyst® (N=23) | Part B | Placebo (N=23) | Arcalyst® (N=22) |
| Pre-treatment Baseline period (weeks -3 to 0) | 2.4 | 3.1 | Active Arcalyst® baseline period (weeks 13 to 15) | 0.2 | 0.3 |
| Endpoint Period (weeks 4 to 6) | 2.1 | 0.5 | Endpoint Period (weeks 22 to 24) | 1.2 | 0.4 |
| LS[2] mean change from baseline to endpoint | -0.5 | -2.4 | LS[2] mean change from baseline to endpoint | 0.9 | 0.1 |
| 95% CI for difference between treatments | (-2.4, -1.3)[1] | | 95% CI for difference between treatment groups | (-1.3, -0.4)[1] | |

[1] A confidence interval (CI) lying entirely below zero indicates a statistical difference favoring Arcalyst® versus placebo

[2] Least squares; differences are adjusted using an analysis of covariance model with terms for treatment and Part A baseline

Improvement in symptoms scores was noted within several days of initiation of Arcalyst® therapy in most patients.

In Part A, patients treated with Arcalyst® experienced more improvement in each of the 5 components of the composite endpoint (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) than placebo-treated patients.

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.

Serum Amyloid A (SAA) and C-Reactive Protein (CRP) levels are acute phase reactants that are typically elevated in patients with CAPS with active disease. During Part A, mean levels of CRP decreased versus baseline for the Arcalyst® treated patients, while there was no change for those on placebo. Arcalyst® also led to a decrease in SAA versus baseline to levels within the normal range. Results can be seen in the table below, which was adapted from the prescribing information.

| Part A | Arcalyst® | Placebo |
|---|---|---|
| SAA (normal range 0.7-6.4mg/L) | N=22 | N=24 |
| Pre-treatment baseline | 60 | 110 |
| Week 6 | 4 | 110 |
| CRP (normal range 0.0-8.4mg/L) | N=21 | N=24 |
| Pre-treatment baseline | 22 | 30 |
| Week 6 | 2 | 28 |

During the open-label extension, reductions in mean symptoms scores, serum CRP, and serum SAA levels were maintained for up to one year.

*The safety and efficacy of Arcalyst® for the maintenance of remission of Deficiency of Interluekin-1 Receptor Antagonist (DIRA)* were demonstrated in a 2-year, open-label study that included 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. Included patients had a median age at baseline of 4. 8 years (range 3.3 to 6.2) and stopped anakinra treatment 24 hours before Arcalyst® was initiated.

Remission was defined using the criteria of a diary score of <0.5 (reflecting no fever, skin rash, and bone pain), acute phase reactants (<0.5mg/dL CRP), absence of objective skin rash, and no radiological evidence of active bone lesions. After a loading dose of Arcalyst® 4.4mg/kg SC, patients received a once-weekly maintenance dose of 2.2mg/kg and were assessed for remission and possible dose escalation. During the first 3 months of Arcalyst® at the 2.2mg/kg dose, five of the 6 patients exhibited recurrence of pustular rash and thus the dose was escalated to 4.4mg/kg once weekly and the one patient remained on the 2.2mg/kg once-weekly dose. All patients met the primary endpoint 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.

*The safety and efficacy of Arcalyst® for recurrent pericarditis* were assessed in a phase 3, double-blind, placebo-controlled, randomized withdrawal, multinational study (RHAPSODY) that consisted of a 12-week run-in followed by a double-blind, placebo-controlled, randomized withdrawal period. In the run-in period, adults received a loading dose of Arcalyst® 320mg followed by 160mg weekly. Patients between 12 and 17 years of age received a loading dose of 4.4mg/kg followed by 2.2mg/kg weekly. During the run-in period, patients tapered and discontinued standard-of-care therapies. In the withdrawal period, patients were randomized to remain on Arcalyst® 160mg weekly or to receive placebo. The randomized withdrawal period continued until the pre-specified number of primary efficacy endpoint events (pericarditis recurrence) had accrued.

Patients recorded scores for pericarditis pain in a daily dairy using the 0 to 10 numeric rating scale (NRS) score. Measurements of CRP, electrocardiograms, and echocardiograms were conducted at intervals during study visits and to assess pericarditis recurrence. Patients who experienced pericarditis recurrence were eligible for open-label Arcalyst® (bailout).

A total of 86 patients (mean age 45 years, 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 NRS ≥4 and CRP ≥1mg/dL). Mean qualifying NRS pain score was 6.2 and mean qualifying CRP level was 6.2mg/dl. During the run-in period, daily NRS pain scores and CRP levels decreased.

Time to treatment response (NRS ≤2 and CRP ≤0.5mg/dl) can be seen in the table below, which was adapted from the prescribing information. The median time to treatment response was 5.0 days. All patients were required to taper off standard-of-care pericarditis medications before randomization, and median time to rilonacept monotherapy was 7.9 weeks during the run-in period. Of the 86 patients enrolled, 41 (48%) were on treatment with corticosteroids at baseline (mean treatment duration of 20 weeks).

| Time to Treatment Response: Run-in Period | Arcalyst® (N=86) |
|---|---|
| Subjects with baseline NRS score >2 or CRP >0.5mg/dl | 79 |
| Subjects achieving treatment response | 77 (97%) |
| Days to treatment response | 5 |
| Time to monotherapy | 8 weeks |

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 patients 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 on placebo with a hazard ratio of 0.04 ($p<0.0001$); rilonacept reduced the risk of recurrence by 96%.

The two recurrence events in the rilonacept group happened in association with temporary interruptions of the trial-drug regimen, of one to three weekly doses. In the placebo group, all 23 patients who had pericarditis recurrence received bailout rilonacept, with resolution of the episodes.

Secondary efficacy endpoints were the proportion of patients with maintenance of clinical response and the percentage of trial days with none/minimal pericarditis pain (NRS ≤2), each measured at week 16 of the withdrawal period. Results can be seen in the table below, which was adapted from the prescribing information.

| | Arcalyst® (N=21) | Placebo (N=20) | Increase (%) | p-value |
|---|---|---|---|---|
| # of patients who maintained response at week 16 | 17 | 4 | 61 | 0.0002 |
| Percentage of days with NRS ≤2 | 92 | 40 | 52 | <0.0001 |

**Place in Therapy:** Arcalyst® is a subcutaneous interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and pediatric patients 12 years and older. It is also indicated for the maintenance of remission of Deficiency of Interleukin-1 Receptor Antagonist (DIRA) in adults and pediatric patients weighing at least 10kg and for the treatment of recurrent pericarditis and reduction in risk of recurrence in adults and pediatric patients 12 years and older. It is recommended that prior to initiation of therapy with Arcalyst®, adult and pediatric patients receive all recommended vaccinations, as per current immunization guidelines, including pneumococcal vaccine and inactivated influenza vaccine. Clinical trials were performed to assess the safety and efficacy of Arcalyst® and it was proven to be effective as compared with placebo for patients with CAPS and recurrent pericarditis for the corresponding primary endpoints. A small open-label study of 6 pediatric patients for the maintenance of remission of DIRA resulted in all patients meeting the primary endpoint of remission at 6 months, with sustained remission for the 2 year study.

It is recommended that Arcalyst® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

**PDL Placement:** ☐ **Preferred**
☒ **Non-Preferred**

## References

[1] Arcalyst [package insert]. London, UK: Kiniksa Pharmaceuticals; 2021.