



**BlueCross BlueShield  
of Alabama**

## **Interleukin (IL)-1 Inhibitors Prior Authorization with Quantity Limit Program Summary**

This prior authorization program applies to Commercial, GenPlus, Blue Partner, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

### **OBJECTIVE**

The intent of the Interleukin (IL)-1 Inhibitors prior authorization (PA) with Quantity Limit program is to ensure appropriate therapy based on FDA approved product labeling and/or clinical guidelines and/or clinical studies. The PA defines appropriate use as the FDA labeled indication. Criteria will limit the approved dose to at or below the maximum FDA labeled dose. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized.

### **TARGETED AGENTS**

**Arcalyst®** (rilonacept)

**Ilaris®** (canakinumab)

### **QUANTITY LIMIT FOR PRIOR AUTHORIZATION**

<b>Brand (generic)</b>	<b>GPI</b>	<b>Multisource Code</b>	<b>Quantity Limit</b>
<b>Arcalyst (rilonacept)</b>			
220 mg single-use vial	66450060002120	M, N, O, or Y	4 vials/28 days
<b>Ilaris (canakinumab)</b>			
150 mg/mL single-use vial	66460020002015	M, N, O, or Y	2 vials/28 days
150 mg single-use vial	66460020002115	M, N, O, or Y	2 vials/28 days

### **PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

#### **Initial Evaluation**

Arcalyst (rilonacept) will be approved when ALL of the following are met:

1. The patient has ONE of the following diagnoses
  - a. Cryopyrin Associated Periodic Syndrome (CAPS)
  - b. Familial Cold Auto-Inflammatory Syndrome (FCAS)
  - c. Muckle-Wells Syndrome (MWS)
  - d. Another FDA approved diagnosis

#### **AND**

2. The patient is 12 years of age and over

#### **AND**

3. The prescriber is a specialist in the area of the patient's requested indication or has consulted with a specialist in the area of the patient's requested indication (e.g. allergist, autoimmune specialist, immunologist, pediatrician)

#### **AND**

4. ONE of the following:

- a. The patient is NOT currently being treated with another biologic immunomodulator

#### **OR**

- b. The patient is currently being treated with another biologic immunomodulator AND it will be discontinued prior to starting the requested agent

- AND**
5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent
- AND**
6. ONE of the following:
- a. The quantity (dose) requested is less than or equal to the program quantity limit
- OR**
- b. ALL of the following:
    - i. The requested quantity (dose) is greater than the program quantity limit**AND**
    - ii. The requested quantity (dose) is less than or equal to the FDA labeled dose**AND**
    - iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
- OR**
- c. ALL of the following:
    - i. The requested quantity (dose) is greater than the program quantity limit**AND**
    - ii. The requested quantity (dose) is greater than the FDA labeled dose**AND**
    - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

**Length of Approval:** 12 months

NOTE: approve loading dose 320 mg once; then maximum 160mg maintenance dose weekly

**Ilaris (canakinumab)** will be approved when ALL of the following are met:

- 1. The patient has ONE of the following diagnoses:
  - a. Cryopyrin Associated Periodic Syndrome (CAPS)**OR**
  - b. Familial Cold Auto-Inflammatory Syndrome (FCAS)**OR**
  - c. Muckle-Wells Syndrome (MWS)**OR**
  - d. Familial Mediterranean Fever (FMF) **AND** ONE of the following:
    - i. The patient has tried and had an inadequate response to colchicine for at least 6 months**OR**
    - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to colchicine**OR**
  - e. Hyperimmunoglobulin D Syndrome (HIDS) or Mevalonate Kinase (MKD) **AND** ONE of the following:
    - i. The patient has tried and had an inadequate response to BOTH NSAIDs and glucocorticosteroids (e.g. prednisone, prednisolone)**OR**
    - ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH NSAIDs and glucocorticosteroids**OR**
  - f. Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)**OR**
  - g. Active systemic Juvenile Idiopathic Arthritis (SJIA) **AND** BOTH of the following:

- i. The patient has documented active systemic features (e.g. ongoing fever for at least 2 weeks, anemia, rash, C-Reactive Protein levels >50 mg/L, ≥1 joint with active arthritis, hepatomegaly, splenomegaly, etc)  
**AND**
- ii. ONE of the following:
  - 1. The patient has tried and had an inadequate response to TWO of the following: methotrexate, leflunomide, systemic glucocorticoids (oral or IV), or NSAIDs for at least 3 month trial each, except NSAID 1 month trial is accepted  
**OR**
  - 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL prerequisite agents
- OR**
- h. Another FDA approved diagnosis  
**AND**
- 2. The patient is within the FDA labeled age for the requested indication  
**AND**
- 3. The prescriber is a specialist in the area of the patient's requested indication or has consulted with a specialist in the area of the patient's requested indication (e.g. immunologist, pediatrician, rheumatologist)  
**AND**
- 4. ONE of the following:
  - a. The patient is NOT currently being treated with another biologic immunomodulator  
**OR**
  - b. The patient is currently being treated with another biologic immunomodulator AND it will be discontinued prior to starting the requested agent
- AND**
- 5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent  
**AND**
- 6. ONE of the following:
  - a. The quantity (dose) requested is less than or equal to the program quantity limit  
**OR**
  - b. ALL of the following:
    - i. The requested quantity (dose) is greater than the program quantity limit  
**AND**
    - ii. The requested quantity (dose) is less than or equal to the FDA labeled dose  
**AND**
    - iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit
  - OR**
  - c. ALL of the following:
    - i. The requested quantity (dose) is greater than the program quantity limit  
**AND**
    - ii. The requested quantity (dose) is greater than the FDA labeled dose  
**AND**
    - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

**Length of approval:** 12 months

### **Renewal Evaluation**

The targeted agent will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through Prime Therapeutics Prior Authorization process  
**AND**
2. The patient has shown clinical improvement with the requested agent (i.e. improvement in serum levels of C-Reactive Protein (CRP), improvement in Serum Amyloid A (SAA), slowing of disease progression, decrease in symptom severity and/or frequency)  
**AND**
3. The prescriber is a specialist in the area of the patient's requested indication or has consulted with a specialist in the area of the patient's requested indication (e.g. immunologist, pediatrician, rheumatologist)  
**AND**
4. ONE of the following:
  - a. The patient is NOT currently being treated with another biologic immunomodulator agent **OR**
  - b. The patient is currently being treated with another biologic immunomodulator agent AND it will be discontinued prior to starting the requested agent**AND**
5. The patient does NOT have any FDA labeled contraindication(s) to the requested agent  
**AND**
6. ONE of the following:
  - a. The quantity (dose) requested is less than or equal to the program quantity limit **OR**
  - b. ALL of the following:
    - i. The requested quantity (dose) is greater than the program quantity limit **AND**
    - ii. The requested quantity (dose) is less than or equal to the FDA labeled dose **AND**
    - iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the limit**OR**
  - c. ALL of the following:
    - i. The requested quantity (dose) is greater than the program quantity limit **AND**
    - ii. The requested quantity (dose) is greater than the FDA labeled dose **AND**
    - iii. The prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis (must be reviewed by the Clinical Review pharmacist)

**Length of approval: 12 months**

*This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.*

*The purpose of pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.*

*Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.*

**FDA APPROVED INDICATIONS AND DOSAGE<sup>1-3</sup>**

<b>Agent</b>	<b>Indication</b>	<b>Dosage and Administration</b>
<b>Arcalyst®</b> (rilonacept)  subcutaneous injection	Treatment of Cryopyrin Associated Periodic Syndrome (CAPS), including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 years and older	≥18 years old: initial loading dose of 320 mg, then continue 160 mg once weekly 12-17 years old: initial loading dose of 4.4mg/kg (max of 320 mg), then continue 2.2mg/kg (up to 160 mg) once weekly
<b>Ilaris®</b> (canakinumab)  subcutaneous injection	Periodic Fever Syndromes: <ul style="list-style-type: none"> <li>• Treatment of CAPS including FCAS and MWS, in adults and children 4 years of age and older</li> <li>• Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients</li> <li>• Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase (MKD) in adult and pediatric patients</li> <li>• Familial Mediterranean Fever (FMF) in adult and pediatric patients</li> </ul> Active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients aged 2 years and older	CAPS/FCAS/MWS: ≥15-40 kg: 2 mg/kg every 8 weeks (inadequate response can increase to 3 mg/kg every 8 weeks) >40 kg: 150 mg every 8 weeks  TRAPS/HIDS/MKD/FMF: ≤40 kg: 2 mg/kg every 4 weeks (inadequate response can increase to 4 mg/kg every 4 weeks) >40 kg: 150 mg every 4 weeks (inadequate response can increase to 300 mg every 4 weeks)  SJIA: 4mg/kg (maximum of 300mg) for body weight ≥7.5kg every 4 weeks

**CLINICAL RATIONALE****Periodic Fever Syndromes**

Periodic fever syndromes include cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean Fever (FMF), hyperimmunoglobulin D syndrome (HIDS), and tumor necrosis factor (TNF) receptor-1 associated periodic syndrome (TRAPS),

**Cryopyrin-Associated Periodic Syndromes (CAPS)**

Cryopyrin- associated periodic syndromes (CAPS) consists of three very rare diseases related to a defect in the same protein – cryopyrin. All 3 cryopyrinopathies arise from mutations in a single gene, *NLRP3*, encoding a protein called cryopyrin. These diseases differ in the systems involved and in the severity of the disease. Familial cold autoinflammatory syndrome (FCAS) is more common in the United States. and Muckle-Wells syndrome (MWS) is more common in Europe. Neonatal-onset multisystem inflammatory disease (NOMID) is the least common disease, usually starting shortly after birth, and is the most severe form.<sup>5,6</sup>

FCAS, formerly called familial cold urticaria, is the mildest of the cryopyrin-associated disorders. Exposure to cold, such as air-conditioned room, results in stereotyped systemic inflammatory response, including fever, an urticarial rash, conjunctival injection, and substantial arthralgias. Symptoms develop with the first year of life, occasionally in the newborn period upon exposure to cold in the delivery room. Attacks resolve within 24 hours, though considerable variability is observed between individuals and depends on the extent and

duration of cold exposure. The presence of conjunctivitis and triggering by cold help to discriminate FCAS from other periodic fever disorders. Diagnosis of CAPS is confirmed by genetic testing for *NALP3* mutation and two of the six parameters: urticaria-like rash, cold-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis, and skeletal abnormalities.<sup>6</sup>

MWS is a rare condition characterized by intermittent episodes of fever, headache, urticarial rash, and joint pain (arthralgia or arthritis); progressive sensorineural hearing loss; and secondary amyloidosis with nephropathy. Febrile episodes occur at irregular intervals every few weeks, lasting 12 to 36 hours before resolving spontaneously. Age of onset is variable. Precipitating factors vary and cannot be identified, but they may include both heat and cold. Sensorineural hearing loss, presumably related to inflammation within the cochlea or the leptomeninges, begins in childhood and maybe profound. *NLRP3* mutations implicated in MWS maybe distinct or overlap those causing FCAS.<sup>6</sup>

NOMID usually presents as fever with inflammation in multiple organs. Other signs and symptoms include erythematous rash resembling urticaria, chronic meningitis, which can result in headache, blindness, hearing loss or other neurologic problems, uveitis, and hepatosplenomegaly.<sup>5,6</sup> After 1 year of age, 50% of patients develop joint pain and swelling of the bones surrounding the large joints, especially the knees. Growth delay can occur in NOMID.<sup>6</sup>

Interleukin (IL)-1- beta inhibitors (anakinra, rilonacept, and canakinumab) have shown effectiveness in preventing and alleviating symptoms of CAPS and reducing levels of inflammatory indices, including serum amyloid A. Treatment with non-steroidal anti-inflammatory drugs, disease modifying antirheumatic drugs, and glucocorticoids was only partially effective.<sup>6</sup>

### **Familial Mediterranean Fever (FMF)**

FMF is the most common of the monogenic periodic fever syndromes. FMF is an autosomal recessive disorder in which there is a mutation in the FMF gene (*MEFV*) encoding the protein pyrin, which regulates the production of interleukin-1 beta, a mediator also implicated in several other autoinflammatory disorders. FMF is characterized by episodic attacks of fever lasting one to three days. Most patients also experience abdominal pain, pleurisy, and arthralgias or arthritis.<sup>4</sup> Its major complication is the insidious development of secondary amyloidosis with eventual renal failure in uncontrolled patients.<sup>7</sup>

Goals of therapy for FMF are to prevent acute attacks, minimize subclinical inflammation in between attacks, and prevent the development and progression of amyloidosis. Initial treatment of FMF is with colchicine. Colchicine is recommended in all patients regardless of the frequency and intensity of attacks. Use of intermittent high-dose colchicine only for treatment of acute attacks of FMF does not protect against the development of amyloidosis resulting from low-grade inflammation that can occur during asymptomatic intervals. Colchicine has demonstrated efficacy in preventing acute inflammatory episodes as well as preventing or slowing the progression toward amyloidosis.

Patients who fail to respond to colchicine fall into one of the following: patients whose symptoms are not due to FMF; patients who are non-adherent or incompletely adherent with therapy; or colchicine resistant FMF. Colchicine-resistant FMF is defined as frequent attacks despite the maximal tolerable dose of colchicine (up to 3 mg daily in adults and 2 mg in children). Further consensus recommendations have defined it as the occurrence of one or more attacks each month despite receiving the maximally tolerated dose for at least 6 months. Patients with elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or serum amyloid A (SAA) between attacks despite maximal or tolerable dose of colchicine are also considered colchicine resistant FMF because of their risk of developing amyloidosis.

Approximately 5-10% of FMF patients are non-responders to colchicine and 2-5% do not tolerate it due to gastrointestinal side effects. Interleukin-1 inhibition is the preferred second line therapy for these patients. In patients who do not respond to IL-1 inhibition, TNF inhibitors or tocilizumab are tried.<sup>7</sup>

### **Hyperimmunoglobulin D Syndrome (HIDS)**

HIDS is a periodic fever syndrome usually associated with mutations in the *MVK* gene that encodes mevalonate kinase, a key enzyme in the nonsterol isoprenoid biosynthesis pathway.<sup>4</sup> Recurrent febrile episodes typically associated with lymphadenopathy, abdominal pain, and an elevated serum polyclonal immunoglobulin D (IgD) level.<sup>8</sup> More than two-thirds of patients with HIDS present within the first year of life with episodic attacks of fever lasting 3-7 days, accompanied in most cases by chills, cervical lymphadenopathy, abdominal pain, and vomiting or diarrhea. Some patients experience headache, arthralgias or arthritis, aphthous ulceration, a pleomorphic rash, and occasionally splenomegaly. Attacks may be precipitated by vaccination, viral infection, trauma, and stress.<sup>4</sup>

Goal of treatment is to alleviate the immediate symptoms to improve quality of life and avoiding unnecessary therapies. Amyloidosis is rare. NSAIDs are recommended first-line therapy for fever and pain associated with HIDS episodes with a duration of 4-7 days, based on the child's pattern. There is no role for NSAID therapy between episodes. Glucocorticoids is the recommended second line recommendation for patients who fail treatment with NSAIDs. Treatment with a biologic agent is reserved for patients who fail both NSAIDs and glucocorticoids or who respond to glucocorticoids but require frequent and/or higher doses and would benefit from a steroid-sparing agent.<sup>8</sup>

### **TNF Receptor-1 Associated Periodic Syndrome (TRAPS)**

TRAPS, formerly known as familial Hibernian fever or familial periodic fever, is an inherited genetic defect in the *TNFR1* gene, that encodes the 55 kDa receptor for tumor necrosis factor. Patients may present with TRAPS from age of infancy to 40s years and beyond, though more than half develop symptoms in the first decade of life.<sup>4</sup> Recurrent fevers over months or years despite the absence of associated viral or bacterial infections are characteristics of TRAPS.<sup>8</sup> Flares commonly last for at least 5 days and often continue for more than 2 weeks. Accompanying symptoms include conjunctivitis and periorbital edema, focal migratory myalgias, rash, abdominal pain, and occasionally monoarthritis. Approximately 10-15% of patients develop clinical manifestations of secondary amyloidosis.<sup>4</sup>

Goals of treatment for TRAPS are to control symptoms, prevent recurrent attacks, and reduce the risk of amyloidosis associated with multiple cycles of fever and inflammation. NSAIDs may help to control fever, but glucocorticoids are typically required to terminate other clinical features of an attack. Initial dose of 1 mg/kg of prednisone or prednisolone at the start of onset of an attack, followed by a gradual taper and discontinuation after 7-10 days is recommended. Patients with ongoing inflammation from frequent and/or severe attacks are at increased risk of developing amyloidosis. Efficacy data favors the use of IL-1 blockade over anti-TNF therapy in TRAPS, even though there are no head to head studies. IL-1 antagonists are the preferred first-line biologic treatment for TRAPS. Anakinra is a possible alternative to canakinumab that could be given on demand rather than as a standing dose due to its much shorter half-life.<sup>9</sup>

### **Systemic Juvenile Idiopathic Arthritis (SJIA)**

Systemic juvenile idiopathic arthritis (SJIA) was formerly called Still's disease or juvenile rheumatoid arthritis. It is a subset of JIA that is characterized by daily quotidian fever, rash, and arthritis.<sup>10</sup> The American College of Rheumatology (ACR) defines SJIA as arthritis in  $\geq 1$  joint for at least 6 weeks' duration in a child age  $< 16$  years with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days and

accompanied by one or more of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly or splenomegaly, and serositis.<sup>11</sup>

Goals of therapy for SJIA includes control of active inflammation and symptoms and the prevention of a number of disease and/or treatment related morbidities, such as growth disturbances, joint damage, and functional limitations. SJIA initial therapy treatment update for active systemic features includes NSAIDs, systemic glucocorticoids (oral or intravenous) and anakinra (IL-1). Many children with SJIA have refractory disease, in which agents targeting interleukins IL-1 and IL-6 are used. ACR suggests continued disease activity be managed with calcineurin inhibitors, canakinumab (IL-1), tocilizumab (IL-6), TNF- $\alpha$  inhibitors, methotrexate, leflunomide or options included in initial therapy not yet utilized. Treatment suggestions/decisions are based on the patient's physician global assessment (MD global) and active joint count (AJC).<sup>11</sup>

Treatment with NSAID as monotherapy is effective for some children with treatment length of no more than a few weeks. Glucocorticoids along with DMARD, methotrexate, were traditionally used in patients who failed NSAID therapy. Biologic DMARDs, IL-1 and IL-6, were initially reserved for patients refractory to conventional therapy (NSAIDs followed by the addition of glucocorticoids with or without methotrexate).<sup>10</sup>

## REFERENCES

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