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

This program applies to MN Medicaid.

The BCBS MN Step Therapy Supplement also applies to this program for Medicaid.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

### FDA APPROVED INDICATIONS AND DOSAGE

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Indication(s)</th>
<th>Dosage and Administration</th>
</tr>
</thead>
</table>
| **Arcalyst®** (rilonacept) | 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 |
| **Ilaris®** (canakinumab) | Periodic Fever Syndromes:  
• Treatment of CAPS including FCAS and MWS, in adults and children 4 years of age and older  
• Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) in adult and pediatric patients  
• Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD) in adult and pediatric patients  
• Familial Mediterranean Fever (FMF) in adult and pediatric patients  
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).²
Cryopyrin-Associated Periodic Syndromes (CAPS)\textsuperscript{3,7}

Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominant hereditary autoimmune disorder associated with a defect in the cryopyrin protein. There are three distinct phenotypes related to a defect in the same gene, but differ in the organs involved and disease severity. Familial cold autoinflammatory syndrome (FCAS) is the mildest form and more common in the United States. Muckle-Wells syndrome (MWS) is the intermediate phenotype and more common in Europe. Neonatal-onset multisystem inflammatory disease (NOMID) is the least common disease and is the most severe form.

FCAS is characterized by a hive-like rash that is associated with exposure to cold and other environmental triggers and with symptoms lasting up to 24 hours. Patients experience urticaria, arthralgia, fever with chills, severe thirst, red-eyes, and headache after a general cold exposure, including air conditioning. In MWS, inflammation can occur spontaneously as well as from triggers, such as stress, cold, or exercise, with episodes lasting from one to three days. MWS shares the same characteristics as FCAS, but is also characterized by renal amyloidosis, sensorineural hearing loss, and conjunctivitis. Hearing loss, partial or complete, often develop by teenage years.

NOMID is characterized by neonatal onset of cutaneous symptoms along with fever with inflammation in multiple organ systems. NOMID shares most of the same characteristics with FCAS and MWS, but also has more severe arthropathy, chronic urticaria, and CNS involvement. CNS manifestations range from hearing loss to aseptic meningitis and mental disabilities. Arthropathy typically affects the large joints, resulting in joint enlargement and functional disability.

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 were offered only some patients partial symptom control.

Familial Mediterranean Fever (FMF)

Familial Mediterranean Fever (FMF) is an inherited disorder that causes episodic fevers with pain in the abdomen, joints, or chest. Episodic attacks typically last one to three days, and often resolve without treatment. Children with severe disease can have such frequent episodes they do not fully recover and do not grow properly. The most severe complication is the development of secondary amyloidosis with eventual renal failure in uncontrolled patients. FMF results from a mutation in the MEFV gene, which creates the protein pyrin. Pyrin plays a role in the control of the inflammatory system. Mutations lead to uncontrolled inflammation, often triggered by infection, trauma, exercise, menstrual cycles, and psychological stress.\textsuperscript{8}

Initial treatment of FMF is with colchicine. Colchicine is recommended in all patients regardless of the frequency and intensity of attacks. Colchicine only prevents acute attacks, and does not treat an episode that has already started. Colchicine has demonstrated efficacy in preventing acute inflammatory episodes as well as preventing or slowing the progression toward amyloidosis.\textsuperscript{8}

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. Approximately 10\% of FMF patients are non-responders to colchicine or do not tolerate it. Interleukin-1 inhibitions is the preferred second line therapy for these patients.\textsuperscript{8,10}
Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD)
Hyperimmunoglobulin D Syndrome (HIDS), now known as Mevalonate Kinase Deficiency (MKD), is a genetic syndrome that results in episodes of high fever with skin rash, swollen lymph nodes in the neck, mouth sores, abdominal pain, vomiting, diarrhea, and joint pain with swelling. Fevers tend to be the main symptom lasting 3 to 7 days, and recur anywhere from 2 to 12 weeks. MKD is an autosomal recessive disease and results from an abnormality in the mevalonate kinase protein, leading to an increase in the amount of immunoglobulin (especially D). MKD typically develops in early childhood and tends to ease over time. Attacks may be precipitated by vaccination, viral infection, trauma, and stress.

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.

TNF Receptor-1 Associated Periodic Syndrome (TRAPS)
Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), formerly known as familial Hibernian fever or familial periodic fever, is a rare genetic disease that causes recurrent episodes of fever that last more than a week and are associated with severe muscle pain in the torso and arms. Other symptoms include red and swollen eyes, a red and painful rash, and abdominal pain with nausea, vomiting, and diarrhea. TRAPS develops as a result from a defect in the TNFRI gene, that encodes the 55 kDa receptor for tumor necrosis factor, leading to an increase in a patient’s normal inflammatory response. Persistent, uncontrolled inflammation may lead to the development of amyloidosis.

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.

Systemic Juvenile Idiopathic Arthritis (SJIA)
Systemic juvenile idiopathic arthritis (SJIA) is a subset of JIA. The ACR defines SJIA as arthritis in ≥1 joint for at least 6 weeks’ duration in a child age less than 16 years of age with or preceded by a 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. 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 treatment depends on the presence of active systemic features and physician global assessment score (MD global) and active joint count (AJC):

- Active systemic features and varying degrees of synovitis:
  - Initial therapy: Anakinra, glucocorticoids (oral or IV) monotherapy, or NSAID monotherapy
  - Continued disease activity despite initial therapy:
    - 1 month of Anakinra: canakinumab, tocilizumab, MTX, leflunomide, or TNF inhibitor
    - 2 weeks of glucocorticoids (GC): anakinra, canakinumab, tocilizumab, MTX, or leflunomide
- 1 month of NSAIDs: GC monotherapy, anakinra, canakinumab, or tocilizumab
- Without active systemic features and varying degrees of synovitis:
  - Initial therapy: MTX, leflunomide, NSAID monotherapy, or intra-articular GC
  - Continued disease activity despite initial therapy:
    - 3 months of MTX or leflunomide: abatacept, anakinra, TNF inhibitor, or tocilizumab
    - 1 month of NSAIDs: anakinra, MTX, or leflunomide
    - Following initial intra-articular GC joint injection: anakinra, MTX, or leflunomide
  - Continued disease activity despite second line therapy:
    - 1 month of anakinra: abatacept, MTX, leflunomide, TNF inhibitor, or tocilizumab
    - 3 months of MTX or leflunomide: abatacept, anakinra, TNF inhibitor, or tocilizumab

REFERENCES
Interleukin (IL)-1 Inhibitors Prior Authorization with Quantity Limit

TARGETED AGENTS
Arcalyst® (rilonacept)
Ilaris® (canakinumab)

QUANTITY LIMIT FOR PRIOR AUTHORIZATION

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>Arcalyst (rilonacept)</td>
<td>66450060002120</td>
<td>M, N, O, or Y</td>
<td>4 vials/28 days</td>
</tr>
<tr>
<td>220 mg single-use vial</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ilaris (canakinumab)</td>
<td>66460020002015</td>
<td>M, N, O, or Y</td>
<td>2 vials/28 days</td>
</tr>
<tr>
<td>150 mg/mL single-use</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg single-use vial</td>
<td>66460020002115</td>
<td>M, N, O, or Y</td>
<td>2 vials/28 days</td>
</tr>
</tbody>
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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 indications:
   a. Cryopyrin Associated Periodic Syndrome (CAPS)
      OR
   b. Familial Cold Auto-Inflammatory Syndrome (FCAS)
      OR
   c. Muckle-Wells Syndrome (MWS)
      OR
   d. Another FDA approved indication for the requested agent
      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 diagnosis or has consulted with a specialist in the area of the patient’s diagnosis (e.g., allergist, immunologist, pediatrician)
   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 contraindications to the requested agent
      AND
6. ONE of the following:
   a. The requested quantity (dose) does NOT exceed 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) does NOT exceed the maximum FDA labeled dose for the requested indication
         AND
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity 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 maximum FDA labeled dose for the requested indication
      AND
   iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

**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 indications:
   a. Cryopyrin Associated Periodic Syndrome (CAPS) AND the patient is 4 years of age and over
      OR
   b. Familial Cold Auto-Inflammatory Syndrome (FCAS) AND the patient is 4 years of age and over
      OR
   c. Muckle-Wells Syndrome (MWS) AND the patient is 4 years of age and over
      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 Deficiency (MKD) AND ONE of the following:
      i. The patient has tried and had an inadequate response to BOTH NSAIDs and corticosteroids (e.g., prednisone, prednisolone)
      OR
      ii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to BOTH NSAIDs and corticosteroids
      OR
   f. Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS)
      OR
   g. Active systemic juvenile idiopathic arthritis (SJIA) AND ALL of the following:
      i. The patient is 2 years of age and over
      AND
      ii. The patient has documented active systemic features (e.g., ongoing fever for at least 2 weeks, evanescent erythematosus rash, generalized lymphadenopathy, ≥1 joint with active arthritis, hepatomegaly, splenomegaly, serositis)
      AND
      iii. ONE of the following:
         1. The patient has tried and had an inadequate response to TWO of the following drug classes:
a. DMARDs (i.e., methotrexate, leflunomide) for at least a 3-month trial
   OR
b. systemic glucocorticoids (oral or IV) for at least a 3-month trial
   OR
c. NSAIDs for at least a 1-month trial

2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to ALL prerequisite agents
   OR
3. The patient’s medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of SJIA
   OR

h. Another FDA approved indication for the requested agent

AND

2. The prescriber is a specialist in the area of the patient’s diagnosis or has consulted with a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, pediatrician, rheumatologist)

AND

3. 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

4. The patient does NOT have any FDA labeled contraindications to the requested agent

AND

5. ONE of the following:
   a. The requested quantity (dose) does NOT exceed 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) does NOT exceed the maximum FDA labeled dose for the requested indication
         AND
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity 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 maximum FDA labeled dose for the requested indication
         AND
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

Length of approval: 12 months
Renewal Evaluation

**Target 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 had clinical benefit with the requested agent
   **AND**
3. The prescriber is a specialist in area of the patient’s diagnosis or has consulted with a specialist in the area of the patient’s diagnosis (e.g., allergist, 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 continuing the requested agent
   **AND**
5. The patient does NOT have any FDA labeled contraindications to the requested agent
   **AND**
6. ONE of the following:
   a. The requested quantity (dose) does NOT exceed 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) does NOT exceed the maximum FDA labeled dose for the requested indication
         **AND**
      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity 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 maximum FDA labeled dose for the requested indication
         **AND**
      iii. The prescriber has submitted documentation in support of therapy with a higher dose for the requested indication

**Length of approval:** 12 months
Step Therapy Supplement Program Summary

This program applies to Medicaid.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT
OBJECTIVE
The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL
The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
   AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

2. BOTH of the following
   a. The patient’s medication history includes the required prerequisite/preferred agent(s) or a drug in the same pharmacological class with the same mechanism of action as indicated by ONE of the following:
      i. Evidence of a paid claim(s) within the past 999 days
      OR
      ii. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days
   AND
   b. ONE of the following:
      i. The required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
      OR
      ii. The prescriber has submitted an evidence-based and peer-reviewed clinical practice guideline supporting the use of the requested agent over the prerequisite/preferred agent(s)

OR

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria