Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION AND STEP THERAPY POLICY AND CRITERIA ORPTCOTH037.1024	**MISCELLANEOUS PRODUCTS** **INTERLEUKIN – 1 INHIBITORS** See Appendix A for medications covered by policy
Effective Date: 1/1/2025	**Review/Revised Date**: 02/10, 02/11, 12/11, 04/13, 04/14, 04/15, 06/15, 03/16, 03/17, 05/18, 02/19, 09/19, 08/20, 02/21, 05/21, 07/21, 09/22, 08/23, 12/23, 10/24 (MTW)
Original Effective Date: 10/08	**P&T Committee Meeting Date**: 10/08, 04/09, 02/10, 12/11, 04/13, 04/14, 04/15, 06/15, 04/16, 04/17, 06/18, 04/19, 10/19, 10/20, 02/21, 06/21, 08/21, 10/22, 10/23, 12/23, 10/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Medicare Part B

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:

1) For all requests, the patient must have an FDA labeled indication for the requested agent or use to treat the indication is supported in drug compendia (such as the American Hospital Formulary Service-Drug Information (AHFS-DI) or Truven Health Analytics' DRUGDEX® System).
   AND
2) The requested agent will not be given concurrently with another therapeutic immunomodulator agent
   AND
3) One of the following:
   a. For patients already established on the requested agent within the previous year (Note: Medications obtained as samples, coupons, or any other method of obtaining medications outside of an established health plan benefit are NOT considered established on therapy): Documentation of positive response to therapy (for example, an improvement or stabilization of clinical symptoms of disease).
   b. For patients not established on the requested agent, must meet ALL the following criteria according to their diagnosis:

i. Cryopyrin-Associated Periodic Syndrome (CAPS) including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) confirmed by both of the following:
    1) Laboratory evidence of genetic mutation NLRP-3 (Nucleotide-binding domain, leucine rich family (NLR) pyrin domain containing 3) or CIAS1 (Cold-Induced Auto-inflammatory Syndrome-1),
    2) Classic symptoms associated with Familial Cold Auto-Inflammatory Syndrome (FCAS) or Muckle-Wells Syndrome (MWS) – recurrent intermittent fever and rash typically associated with natural or artificial cold
ii. Familial Mediterranean Fever (FMF):
    1) Diagnosis confirmed by laboratory evidence of genetic mutation in Mediterranean fever gene, MEFV.
    2) Documented trial and failure, contraindication or intolerance to colchicine
    3) Classic symptoms associated with FMF (febrile episodes, pain in the abdomen, chest, or arthritis of large joints).
iii. Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD):
    1) Laboratory evidence of genetic mutation MVK (mevalonate kinase),
    2) Classic symptoms associated with HIDs (abdominal pain, lymphadenopathy, aphthous ulcers)
iv. Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS) confirmed by:
    1) Laboratory evidence of genetic mutation TNFRSF1A (tumor necrosis factor receptor super family)
    2) Classic symptoms associated with TRAPs (abdominal pain, skin rash, musculoskeletal pain, eye manifestations)
v. Still's Disease including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease, must meet ONE of the following criteria:
    1) Documentation of trial and failure, intolerance, or contraindication to non-steroidal anti-inflammatory drugs (NSAIDS) OR
    2) Presence of Macrophage Activation Syndrome
vi. Gout flares:
    1) Classic symptoms associated with gout flares (monoarticular inflammation, severe pain, redness, swelling)
    2) Confirmed diagnosis, defined as one of the following:

a. Presence of uric acid crystals in inflamed synovial fluid, joint, or tophus
b. Score greater or equal to 8 on gout clinical diagnostic rule

3) Documentation of inadequate response to therapy with all the following on contraindication/intolerance to all therapies:
   a. Colchicine (at least three days)
   b. Nonsteroidal anti-inflammatory drugs (NSAIDs) (at least one week)
   c. Corticosteroid therapy (at least one week) and provider attestation that repeat courses of corticosteroids are not appropriate (for example, osteoporosis, osteonecrosis, Cushing syndrome, diabetes mellitus, myopathy, glaucoma, congestive heart failure, or peptic ulcer disease)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:
Age must be appropriate based on FDA-approved indication

PRESCRIBER RESTRICTIONS:
- Cryopyrin-Associated Periodic Syndrome (CAPS), Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF): Must be prescribed by, or in consultation with, a rheumatologist or immunologist
- Systemic juvenile idiopathic arthritis (sJIA), Still's Disease including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease, gout flares: Must be prescribed by, or in consultation with, a rheumatologist

COVERAGE DURATION:
Gout flares: Initial authorization will be approved for three months, reauthorization will be approved for six months
All other indications: Initial authorization and reauthorization will be approved for one year.

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy

document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Canakinumab (Ilaris®) works by blocking the action of the inflammatory protein interleukin-1. Canakinumab is dosed based on body weight and must be administered by a healthcare professional.

FDA APPROVED INDICATIONS:

Canakinumab (Ilaris®):

- Cryopyrin-Associated Periodic Syndromes (CAPS): Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children four years of age and older.
- Periodic Fever Syndromes: Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF) in adults and children two years of age and older.
- Still's Disease: Active Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult Onset Still's Disease (AOSD) in patients aged two years and older.
- Gout flares: where non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are contraindicated, are not tolerated, or do not provide an adequate response, and repeated courses of corticosteroids are not appropriate in adults.

POSITION STATEMENT:

Cryopyrin-Associated Periodic Syndromes (CAPS)

CAPS are rare, genetic interleukin-1 associated autoinflammatory disorders that arise from mutations in the NLRP3 gene which encodes cryopyrin protein. CAPS includes the subtypes FCAS, MWS, and NOMID. Although these are three separate diagnoses, they are recognized as being the same disease, differentiated only by the severity of their severity with FCAS being the mildest and NOMID being the most severe phenotype. A combination of genetic analysis and clinical symptoms are recommended by the EULAR/American College of Rheumatology taskforce for the

differentiation of CAPS from other similar disorders. Characteristic signs/symptoms of CAPS include urticaria-like rash, cold/stress-triggered episodes, sensorineural hearing loss, chronic aseptic meningitis, and skeletal abnormalities.

Approximately 833 subjects have been treated with canakinumab in blinded and open-label clinical trials in CAPS and other diseases. The first trial included three phases, patients with the MWS phenotype of CAPS. The first phase was an 8-week open label period, 71% of patients had complete clinical response one week after initiation of treatment and 97% by week eight. Complete response was defined as ratings of minimal or better for physician's assessment of disease activity (PHY) and assessment of skin disease (SKD) and serum levels of C-Reactive Protein (CRP) and Serum Amyloid A (SAA) less than 10mg/l. Phase 2 was a 24 week randomized withdrawal period with canakinumab (n=15) or placebo (m=16). 81% of patients randomized to placebo experienced disease flare. Disease flare was defined as CRP and/or SAA values greater than 30mg/l and either a score of mild or worse PHY or a score of minimal or worse for PHY and SKD. All 15 canakinumab patients had absent or minimal disease activity. The third phase was a 16-week open label period where placebo patients were reintroduced to canakinumab and canakinumab patients were continued. A second study included patients four to 74 years of age with both MWS and FCAS. This was an open label study that showed clinically significant improvement of signs and symptoms and in normalization of high CRP and SAA in a majority of patients within 1 week. CRP and SAA normalized within eight days of treatment in most patients.

Periodic Fever Syndromes (PFS) (includes Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF))

A recent study has provided evidence to support canakinumab for the following Periodic Fever Syndromes: Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D (Hyper-IgD) Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF). The efficacy and safety of canakinumab for the treatment of TRAPS, HIDS/MKD, and FMF was demonstrated in a 4-Part study (TRAPS, HIDS/MKD, and FMF Study 1) consisting of three separate, disease cohorts (TRAPS, HIDS/MKD and FMF) which enrolled 185 patients aged greater than 28 days. Patients in each cohort entered a 12-week screening period (Part 1) during which they were evaluated for the onset of disease flare. Patients aged 2 to 76 years were then randomized at flare onset into a 16-week double-blind, placebo-controlled treatment period (Part 2) where they received either 150 mg canakinumab (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS,

HIDS/MKD, and FMF patients who resolved their index disease flare at Day 15 and had no new flare over the 16 weeks of treatment from the time of the resolution of the index flare.

Goals in FMF are to prevent acute attacks, minimize inflammation in between attacks, and to prevent the development and progression of amyloidosis. Colchicine is recommended as a prophylactic treatment in all patients with FMF. Interleukin-1 inhibitors are the preferred second-line therapy for patients who do not respond or do not tolerate colchicine.

Still's Disease (SD) (includes Adult-Onset Still's Disease (AOSD) and Systemic Juvenile Idiopathic Arthritis (SJIA)

SJIA is a unique type of JIA which manifests with fever and rash as well as visceral involvement. Approximately 40% of patients with SJIA present with Macrophage Activation Syndrome (MAS) which may be life-threatening. The American College of Rheumatology (ACR) recommends an interleukin-1 or interleukin-6 inhibitor as initial treatment of SJIA with or without MAS. For patients with SJIA without MAS, non-steroidal anti-inflammatory drugs (NSAIDs) may also be used for initial monotherapy.

Two phase III randomized controlled trials were performed to assess canakinumab in its treatment of SJIA in eligible patients aged 2 to 19 years with SJIA, including those with active systemic features and arthritis. A 29-day single-dose, randomized, double-blind, placebo-controlled study compared canakinumab group (n=43) to a placebo group (n=41). At baseline among 84 patients, a total of 53 (63%) were on methotrexate therapy, 48 (57%) patients had prior use of a biologic agent (i.e. anakinra, tocilzumab, and other biologics), and 59 (70%) patients were on stable prednisone therapy. By day 15 of the study, 36 (84%) of 43 patients from the canakinumab group compared to 4 (10%) of 41 patients in the placebo group achieved an endpoint of a JIA American College of Rheumatology (ACR) 30 response. These responses were sustained until the end of study.

A two-part (open-label and withdrawal phased) study initially treated 177 patients with canakinumab during the open label phase for 12 to 32 weeks. During the withdrawal phase, those who achieved JIA ACR 50 response (n=128) were randomized into either the canakinumab group (n=50) or placebo group (n=50). At baseline, a total of 93 (53%) of patients were on methotrexate therapy, 116 (66%) of patients had prior use of a biologic agent (i.e. anakinra, tocilzumab, and other biologics), and 128 (72%) of patients were on stable prednisone therapy. During the withdrawal phase, 39 (74%) patients form the canakinumab group compared to 24 (25%) patients in the placebo group achieved no flare of disease. By the end of the withdrawal phase, 31 of 50 (62%) patients form the canakinumab group compared to

17 of 50 (34%) patients in the placebo group achieved inactive disease. There was also an average reduction of glucocorticoid dose from 0.34mg to 0.05mg per kilogram per day. Additionally, 42 of 128 (33%) patients were able to discontinue glucocorticoids after tapering.

The efficacy of canakinumab in adults with AOSD is based on the pharmacokinetic exposure and extrapolation of the established efficacy in SJIA patients. Efficacy was also assessed in a randomized, double-blind, placebo-controlled study that enrolled 36 patients (22 to 70 years old) diagnosed with AOSD. The efficacy data were generally consistent with the results of a pooled efficacy analysis of SJIA patients.

Gout Flares
Gout flares are intensely painful and disabling. This condition affects a single joint and usually resolved completely within a few days to several weeks. However, symptoms may improve faster with treatment. The American College of Rheumatology (ACR) currently recommends colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic glucocorticoids as treatment options for gout flares, and should be started as soon as possible after the onset.

The efficacy of canakinumab was demonstrated in three 12-week, randomized, double-blind, active-controlled studies in patients with gout flares for whom NSAIDs and/or colchicine were contraindicated, not tolerated or ineffective, and who had experienced at least three gout flares in the previous year. In Study 1 (NCT01029652), patients were randomized to receive canakinumab 150 mg subcutaneous (N = 115) or triamcinolone acetonide 40 mg intramuscular (N = 115) at baseline and thereafter treated upon a new flare. In Study 2 (NCT01080131), patients were randomized to receive canakinumab 150 mg subcutaneous (N =112) or triamcinolone acetonide 40 mg intramuscular (N =114) at baseline and thereafter treated upon a new flare. In study 3 (NCT01356602), patients were randomized to receive canakinumab 150 mg subcutaneous (N =265) or triamcinolone acetonide 40 mg intramuscular (N =132) at baseline. All three studies' primary endpoints were: 1) patient's assessment of gout flare pain intensity at the most affected joint at 72 hours post-dose measured on a 0-100 mm visual analogue scale (VAS), 2) the time to first new gout flare. Results were consistent throughout the three studies, pain intensity of the most affected joint (0-100 mm VAS) at 72 hours post-dose was consistently lower for patients treated with canakinumab compared with triamcinolone acetonide in patients unable to use NSAIDs and colchicine. The pain intensity for patients unable to use NSAID and colchicine are presented in the following format, (mean canakinumab vs. mean triamcinolone; difference in 95% confidence interval in pain intensity 72 hours post dose): 21.4 vs. 38.4; -17.0 mm (-32.3, -1.6) [study 1], 24.1 vs. 33.1; -9.1 mm (-18.9, 0.8) [study 2], 20.8 vs. 40.3 19.5 mm (-28.6, -10.3) [study 3].

Canakinumab carries a safety warning for serious infections. Live vaccines should be avoided in patients receiving canakinumab. Other common adverse reactions include nasopharyngitis, diarrhea, influenza, headache, nausea, upper respiratory tract infections, abdominal pain and injection site reactions.

REFERENCE/RESOURCES:

1. Ilaris® (canakinumab) prescribing information. East Hanover, NJ: Novartis Pharmaceuticals, Inc. Aug 2023.
2. Canakinumab. In: DRUGDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically
3. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367(25):2396-2406.
4. Kastner DL. Familial Mediterranean Fever and Other Hereditary Autoinflammatory Diseases. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. Harrison's Principles of Internal Medicine, 19e. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com. Accessed October 13, 2016
5. Verbsky J. Hereditary Periodic Fever Syndromes and Other Systemic Autoinflammatory Diseases. In: Kliegman RM, St Geme JW, Blum NJ, eds. Nelson Textbook of Pediatrics. Philadelphia: Elsevier; 2002:1292-1304.e1 (Accessed September 10, 2022)
6. 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;81:907-921.
7. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. *Arthritis Rheum*. 2022;74(4):553-569.
8. Schlesinger N, Alten RE, Bardin T, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. Annals of the Rheumatic Diseases. 2012;71(11):1839-1848.

APPENDIX A

Brand Name	Generic Name	Procedure Code
Ilaris®	canakinumab injection	J0638