Canakinumab

Indications/Dosage

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Labeled

- cryopyrin-associated periodic syndromes (CAPS)
- familial mediterranean fever
- hyperimmunoglobulin D syndrome
- systemic juvenile idiopathic arthritis
- tumor necrosis factor receptor associated periodic syndrome

Off-Label

- coronavirus disease 2019 (COVID-19) †
- severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection †

† Off-label indication

For the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)

Subcutaneous dosage

- **Adults, Adolescents, and Children 4 years and older and weight more than 40 kg**

  150 mg subcutaneously every 8 weeks.[41378] The efficacy of canakinumab was evident in most patients during the pivotal clinical trial after only 1 dose; symptoms of Cryopyrin-Associated Periodic Syndromes (CAPS) diminished within 24 hours in responding patients. The median C-reactive protein (CRP) and serum amyloid A protein (SAA) concentrations fell to within the normal range. Most (81%) of patients who stopped receiving canakinumab experienced a disease flare; the median time until the disease flare was 100 days. All patients who continued therapy with canakinumab maintained normal CRP and SAA concentrations. Upon reinitiation canakinumab, patients who experienced a disease flare responded again. At the end of the 48-week trial, 30 of 31 patients had no or minimal disease activity, according to the physician's assessment.[41379]

- **Adults, Adolescents, and Children 4 years and older and weight 15 to 40 kg**

  2 mg/kg subcutaneously every 8 weeks. If response is inadequate in children in this weight range, may consider dose increase to 3 mg/kg subcutaneously every 8 weeks.[41378]

For the treatment of active systemic juvenile idiopathic arthritis (SJIA)

Subcutaneous dosage

- **Children and Adolescents 2 years and older and weight 7.5 kg or more**

  4 mg/kg (Max: 300 mg/dose) subcutaneously every 4 weeks.[41378]

For the treatment of tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), and familial mediterranean fever (FMF)

Subcutaneous dosage

- **Adults, Adolescents, and Children 2 years and older and weight more than 40 kg**

  150 mg subcutaneously every 4 weeks. The dose can be increased to 300 mg subcutaneously every 4 weeks if the clinical response is not adequate. During clinical trials, canakinumab was superior to placebo in the proportion of patients who resolved their disease flare by Day 15 and had no new flare over the next 16 weeks of treatment.[41378]

- **Adults, Adolescents, and Children 2 years and older and weight less than 40 kg**

  2 mg/kg subcutaneously every 4 weeks. May increase to 4 mg/kg subcutaneously every 4 weeks if the clinical response is not adequate. During clinical trials, canakinumab was superior to placebo in the proportion of patients who resolved their disease flare by Day 15 and had no new flare over the next 16 weeks of treatment.[41378]

INVESTIGATIONAL USE: For adjunctive use in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection†, the virus that causes coronavirus disease 2019 (COVID-19)†

Intravenous dosage

- **Adults**

  Efficacy has not been established. Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of IL-1 antagonists, such as canakinumab.[65314] Dosing regimens being evaluated include: 4 mg/kg and 8 mg/kg IV once for patients 40 kg or less; 300 mg and 600 mg IV once for patients more than 40 kg; 450 mg IV once for patients 40 to 59 kg; 600 mg IV once for patients 60 to 80 kg; 750 mg IV once for patients more than 80 kg. All doses are to be diluted in 250 mL of 5% dextrose and infused over 2 hours.[65390] [65393]

Subcutaneous dosage

- **Adults**

  Efficacy has not been established. Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of IL-1 antagonists, such as canakinumab.[65314] A single 150 mg subcutaneous injection is being evaluated in a retrospective and prospective observational study.[65392]

Maximum Dosage Limits

- Adults

  CAPS

  more than 40 kg: 150 mg/dose subcutaneously every 8 weeks.

  40 kg or less: 3 mg/kg/dose subcutaneously every 8 weeks.

  TRAPS, HIDS/MKD, FMF

  more than 40 kg: 300 mg/dose subcutaneously every 4 weeks.

  40 kg or less: 4 mg/kg/dose subcutaneously every 4 weeks.

- Geriatric

  CAPS

  more than 40 kg: 150 mg/dose subcutaneously every 8 weeks.

  40 kg or less: 3 mg/kg/dose subcutaneously every 8 weeks.

  TRAPS, HIDS/MKD, FMF

more than 40 kg: 300 mg/dose subcutaneously every 4 weeks.

40 kg or less: 4 mg/kg/dose subcutaneously every 4 weeks.

- Adolescents

  CAPS

  more than 40 kg: 150 mg/dose subcutaneously every 8 weeks.

  15 to 40 kg: 3 mg/kg/dose subcutaneously every 8 weeks.

  TRAPS, HIDS/MKD, FMF

  more than 40 kg: 300 mg/dose subcutaneously every 4 weeks.

  40 kg or less: 4 mg/kg/dose subcutaneously every 4 weeks.

  SJIA

  7.5 kg or more: 4 mg/kg/dose (Max: 300 mg/dose) subcutaneously every 4 weeks.

- Children

  CAPS

  4 years and older and more than 40 kg: 150 mg/dose subcutaneously every 8 weeks.

  4 years and older and 15 to 40 kg: 3 mg/kg/dose subcutaneously every 8 weeks.

  Less than 4 years: Safety and efficacy have not been established.

  TRAPS, HIDS/MKD, FMF

  2 years and older and more than 40 kg: 300 mg/dose subcutaneously every 4 weeks.

  2 years and older and 40 kg or less: 4 mg/kg/dose subcutaneously every 4 weeks.

  Less than 2 years: Safety and efficacy have not been established.

  SJIA

  2 years and older and 7.5 kg or more: 4 mg/kg/dose (Max: 300 mg/dose) subcutaneously every 4 weeks.

  Less than 2 years: Safety and efficacy have not been established.

- Infants

  Safety and efficacy have not been established.

- Neonates

  Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

No formal studies have been conducted in patients with hepatic impairment.[41378]

Patients with Renal Impairment Dosing

No formal studies have been conducted in patients with renal impairment.[41378]

† Off-label indication

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References

41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

41379 – Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009: 360:2416 to 2425.

65314 – COVID-19 Treatment Guidelines Panel. Coronavirus Diseases 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Accessed May 12, 2020. Available at on the World Wide Web at: https://covid19treatmentguidelines.nih.gov/.

65390 – The Cleveland Clinic. Canakinumab to reduce deterioration of cardiac and respiratory function due to COVID-19. Retrieved May 11, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04365153?term=canakinumab&cond=COVID&draw=2&rank=3.

65392 – AUSL Romagna Rimini. Observational study, use of canakinumab administered subcutaneously in the treatment COVID-19 pneumonia. Retrieved May 11, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04348448?term=canakinumab&cond=COVID&draw=2&rank=2.

65393 – Novartis Pharmaceuticals. Study of efficacy and safety of canakinumab treatment for CRS in participants with COVID-19-induced pneumonia (CAN-COVID). Retrieved May 11, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04362813?term=canakinumab&cond=COVID&draw=2&rank=1.

How Supplied

Canakinumab Lyophilisate for solution for injection
ILARIS 180mg (150mg/mL) Powder for Injection (00078-0582) (Novartis Pharmaceuticals Corporation) (off market)

Canakinumab Solution for injection
ILARIS 150mg/mL Solution for Injection (00078-0734) (Novartis Pharmaceuticals Corporation)

Description/Classification

Description

Canakinumab (Ilaris) is a human monoclonal antibody against interleukin (IL)-1 beta approved for the treatment of 2 forms of cryopyrin-associated periodic syndromes (CAPS), Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in patients 4 years of age and older. Canakinumab is also approved for adult and pediatric patients for Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF). In addition, canakinumab is approved for active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years of age and older. Most patients with FCAS and MWS respond positively to canakinumab. For example, 34 of 35 patients who received a single 150 mg canakinumab subcutaneous dose had a complete response, which was defined as a physician global assessment of no or minimal disease activity, an assessment of no or minimal rash, and a C-reactive protein and serum amyloid A protein concentration less than 10 mg/L. The patient without a complete response had self-injected the drug and had substantially lower than expected canakinumab concentrations. Continued remission was achieved by all patients who received canakinumab every 8 weeks through week 24.[41379]

Updates for coronavirus disease 2019 (COVID-19):

Due to a lack of clinical data, the National Institutes of Health (NIH) COVID-19 treatment guidelines do not give recommendations for or against the use of IL-1 antagonists, such as canakinumab.[65314] Based on preliminary data from other anti-interleukin medications, studies have begun to evaluate the use of canakinumab for COVID-19.[65390][65392][65393]

Classifications

- Antineoplastic and Immunomodulating Agents
  - Agents that Suppress the Immune System
    - Interleukin-1 Beta (IL-1 Beta) Inhibitors
- Musculo-Skeletal System
  - Antiinflammatory Agents and Antirheumatic Agents
    - Specific Anti-Rheumatic Agents
      - Anti-Rheumtic Monoclonal Antibodies

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References

41379 – Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009: 360:2416 to 2425.

65314 – COVID-19 Treatment Guidelines Panel. Coronavirus Diseases 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Accessed May 12, 2020. Available at on the World Wide Web at:

https://covid19treatmentguidelines.nih.gov/.

65390 – The Cleveland Clinic. Canakinumab to reduce deterioration of cardiac and respiratory function due to COVID-19. Retrieved May 11, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04365153?term=canakinumab&cond=COVID&draw=2&rank=3.

65392 – AUSL Romagna Rimini. Observational study, use of canakinumab administered subcutaneously in the treatment COVID-19 pneumonia. Retrieved May 11, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04348448?term=canakinumab&cond=COVID&draw=2&rank=2.

65393 – Novartis Pharmaceuticals. Study of efficacy and safety of canakinumab treatment for CRS in participants with COVID-19-induced pneumonia (CAN-COVID). Retrieved May 11, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04362813?term=canakinumab&cond=COVID&draw=2&rank=1.

Administration Information

General Administration Information

For storage information, see the specific product information within the How Supplied section.

Route-Specific Administration

Injectable Administration

- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.

Subcutaneous Administration

- Health care providers should perform administration of canakinumab.[41378]

Reconstitution:

- Using aseptic technique, slowly inject 1 mL of preservative-free sterile water for injection with a syringe and an 18-gauge, 2-inch needle.
- Slowly swirl the vial at a 45-degree angle for approximately 1 minute; allow to stand for 5 minutes.
- Gently turn the vial upside down and back again 10 times. Do NOT shake. Avoid touching the rubber stopper with your fingers.
- Allow the reconstituted solution to stand for about 15 minutes at room temperature to obtain a clear solution. Tap the side of the vial to remove any residual liquid from the stopper.
- The reconstituted solution has a final concentration of 150 mg/mL.
- The reconstituted solution should be essentially free from particulates, and should be clear to opalescent; do not use if particulate matter is present in the solution. The solution should be colorless or may have a slight brownish-yellow tint; do not use if the solution has a distinctly brown discoloration. It is not unusual to have slight foaming of the product upon reconstitution.
- *Storage:* If not used within 60 minutes of reconstitution, the solution should be stored in the refrigerator at 2 to 8 degrees C (36 to 46 degrees F) and used within 4 hours. Protect from light.

[41378]

Subcutaneous injection:

- Using a sterile 1-mL syringe and needle, carefully withdraw the required volume depending on the dose to be administered.
- Discard any unused product; the vial is for single-use and does not contain any preservatives.
- Subcutaneously inject using a 27-gauge, 0.5-inch needle. Avoid injection into scar tissue as this may result in insufficient exposure to canakinumab.[41378]

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References

41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

Adverse Reactions

- abdominal pain
- antibody formation
- cough
- diarrhea
- elevated hepatic enzymes
- headache
- hyperbilirubinemia
- hypotension
- immunosuppression
- infection
- influenza
- injection site reaction
- leukopenia
- macrophage activation syndrome
- musculoskeletal pain
- nausea
- neutropenia
- new primary malignancy
- palpitations
- pharyngitis
- pruritus
- rash
- rhinitis
- sinusitis
- thrombocytopenia
- urticaria
- vertigo
- weight gain

Diarrhea (20%), nausea (14%), and gastroenteritis (11%) were among the most commonly reported adverse reactions associated with canakinumab during clinical trials in 35 patients with Cryopyrin-Associated Periodic Syndromes (CAPS). Gastroenteritis was reported in 3% of canakinumab patients in a Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD), and Familial Mediterranean Fever (FMF) trial. Among patients with systemic juvenile idiopathic arthritis, 7% to 16% of canukinumab recipients had upper abdominal pain as compared with 2.4% to 12% of placebo recipients.[41378]

During clinical trials with canakinumab, mean values decreased for white blood cells and neutrophils. Thus, canakinumab may cause immunosuppression (including leukopenia and neutropenia) and resultant increased risk of infection including serious infections or activation of latent infections (e.g., tuberculosis). Of 50 canakinumab recipients for systemic juvenile idiopathic arthritis (SJIA), 10.4% had a WBC less than or equal to 0.8 times the

lower limit of normal as compared with 4% of the 50 placebo recipients. In the same study, transient decreases in absolute neutrophil counts (ANC) to less than 1,000 cells/mm^3 were reported in 6% of canakinumab recipients as compared with 2% of placebo recipients. Further, 1 case of ANC counts less than 500 cells/mm^3 was observed in the canakinumab group versus none in the placebo group. Infections, predominately upper respiratory tract infections, have been reported with the use of canakinumab. Some of these infections were reported as serious and generally responded to standard therapy. Isolated cases of opportunistic or rare infections (e.g., aspergillosis, atypical mycobacterial infections, cytomegalovirus, herpes zoster) also have been reported with canakinumab therapy; a causal relationship with canakinumab cannot be excluded.[41378] An increased incidence of serious infections has been associated with the administration of IL-1 blockers in combination with tumor necrosis factor inhibitors. One patient experienced a recurrent antibiotic-resistant lower urinary tract infection and sepsis (requiring hospital admission and study withdrawal).[41379] In 1 patient who received canakinumab, an intra-abdominal abscess after appendectomy was reported. However, most infections reported in clinical trials involved the upper respiratory tract. In a phase 3 clinical trial of 35 patients with Cryopyrin-Associated Periodic Syndromes (CAPS), adverse events included nasopharyngitis (34%), influenza (17%), rhinitis (17%), bronchitis (11%), and pharyngitis (11%). Among patients with SJIA, 30.2% to 54.8% of canakinumab recipients had an infection; the rates were higher in treated patients than in those receiving placebo. Approximately 4% to 5% of canakinumab patients developed serious infections (e.g., pneumonia, varicella, gastroenteritis, measles, sepsis, otitis media, sinusitis, adenovirus, lymph node abscess, pharyngitis) during SJIA clinical trials.[41378] The following infections were reported in the Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase (HIDS/MKD), and Familial Mediterranean Fever (FMF) trial, nasopharynigitis (10.7%), upper respiratory tract infection (7.1%), rhinitis (5.3%), and pharyngitis (3%). Serious infection (e.g., conjunctivitis, pneumonia, pharyngitis, pharyngotonsillitis) occurred in 2.4% of canakinumab recipients. Decreases in neutrophil count that were grade 2 or greater occurred in 6.5% of canakinumab patients in the TRAPS, HIDS/MKD and FMF trial. Persistent cough could be a symptom of tuberculosis; instruct patients to seek care for a persistent cough, weight loss, or subfebrile temperature. If a serious infection occurs during treatment, discontinue canakinumab.[41378]

Vertigo was noted in 9% to 14% of canakinumab recipients in studies of Cryopyrin-Associated Periodic Syndromes (CAPS) and was reported as a serious event in 2 cases. Vertigo occurred exclusively in Muckle-Wells Syndrome (MWS) patients. Cases of vertigo resolved with continued canakinumab receipt. Headache was noted in 14% of 35 patients receiving canakinumab for CAPS.[41378]

A subcutaneous injection site reaction to canakinumab was observed in 7% to 9% of patients enrolled in the Cryopyrin-Associated Periodic Syndromes (CAPS) clinical trials, and all cases were mild or moderate local tolerability reactions. No severe reactions were reported, and none led to discontinuation of treatment. Among patients with systemic juvenile idiopathic arthritis (SJIA), 12% or fewer patients had a mild injection site reaction, and moderate reactions occurred in 2% or less. Injection site reactions may include pain, erythema, swelling, itching, bruising, mass, inflammation, dermatitis, edema, hives, vesicles, warmth, and local hemorrhage. Avoid injecting canakinumab into an area that is already swollen or red. In the Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase (HIDS/MKD), and Familial Mediterranean Fever (FMF) trial, mild to moderate injection-site reactions occurred in 10.1% of canakinumab patients.[41378] [41379]

Weight gain was reported in 11% of 35 patients during clinical trials of canakinumab for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS).[41378]

Musculoskeletal pain was reported with the use of canakinumab during clinical trials in 11% of 35 patients with Cryopyrin-Associated Periodic Syndromes (CAPS).[41378]

Elevated hepatic enzymes have been observed among canakinumab recipients. Transaminases (ALT and/or AST) greater than 3 times the upper limit of normal (ULN) were noted in 2 (4.1%) of 50 canakinumab recipients and in 1 of 50 placebo recipients with systemic juvenile idiopathic arthritis (SJIA); all patients had normal values at the next visit. In addition to elevated hepatic enzymes, hyperbilirubinemia may occur. Asymptomatic

and mild elevations of serum bilirubin have been observed without concomitant elevations of liver transaminases.[41378]

Hypersensitivity reactions have been reported with canakinumab; anaphylactic reactions were not reported during clinical trials. Only one patient with Cryopyrin-Associated Periodic Syndromes (CAPS) discontinued a trial due to hypersensitivity reactions whereas 0% of the patients with systemic juvenile idiopathic arthritis (SJIA, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase (HIDS/MKD), or Familial Mediterranean Fever (FMF) discontinued trials because of a hypersensitivity reaction. Instruct patients to get immediate medical help if they develop signs of an allergic reaction such as difficulty breathing or swallowing, nausea, dizziness, skin rash (unspecified), pruritus, urticaria, palpitations, or hypotension. Do not readminister the drug if a hypersensitivity reaction occurs: canakinumab is contraindicated for use by patients with confirmed hypersensitivity to canakinumab or to any of its excipients. Of note, some symptoms of Cryopyrin-Associated Periodic Syndromes (CAPS) may be similar to symptoms of hypersensitivity. In patients with CAPS, excessive amounts of interleukin-1 beta may lead to symptoms such as an urticaria-like skin rash.[41378]

Canakinumab may cause thrombocytopenia. In clinical trials for Cryopyrin-Associated Periodic Syndromes (CAPS), mean values decreased for platelets. Of 50 canukinumab recipients for systemic juvenile idiopathic arthritis, 6.3% had transient decreases in platelet counts that were less than the lower limit of normal but greater than 75,000 cells/mm^3 compared to 2% of placebo recipients. In the Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase (HIDS/MKD), and Familial Mediterranean Fever (FMF) trial, 0.6% of canakinumab patients had decreased platelet counts that were grade 2 or greater.[41378]

Among patients who received canakinumab for Cryopyrin-Associated Periodic Syndromes (CAPS), 1.5% had antibody formation to the drug, which was detected by a biosensor binding assay. Antibodies to canakinumab were also detected mostly via a bridging immunoassay among 3.1% of patients with systemic juvenile idiopathic arthritis who received canakinumab. No neutralizing antibodies were detected, and no apparent correlation of antibody development to clinical response or adverse events was observed. In the Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase (HIDS/MKD), and Familial Mediterranean Fever (FMF) trial, no patients tested positive for anti-canakinumab antibodies. Several factors strongly affect the data obtained in an assay including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, underlying disease, and the number of patients tested. For these reasons, it may be misleading to compare the incidence of antibodies to canakinumab with the incidence of antibodies to other products.[41378]

Macrophage activation syndrome (MAS) is a life-threatening disorder that may develop in patients with rheumatic conditions, especially systemic juvenile idiopathic arthritis (SJIA), and it has been reported in SJIA patients treated with canakinumab in clinical trials. Based on limited data, canakinumab does not appear to increase the incidence of MAS; 11 cases were observed in 201 patients who received canakinumab for SJIA. However, infection is a trigger for MAS, and canakinumab is associated with an increased risk of serious infections. Clinicians should be attentive to symptoms of infection or worsening arthritis symptoms; SJIA worsening is also a trigger for MAS.[41378] The diagnostic criteria for MAS developed through a collaborative initiative between the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR), and Pediatric Rheumatology International Trials Organization are the presence of any two of the following in a febrile patient with known or suspected SJIA and ferritin greater than 684 ng/mL: platelet count less than 181,000 cells/mm^3, AST greater than 48 units/L, triglycerides greater than 156 mg/dL, and fibrogen 360 mg/dL or less.[65453]

The effect of anti-interleukin-1 (IL-1) therapy with canakinumab on the development of malignancies is not known. However, treatment with immunosuppressants, including canakinumab, may result in an increase in the risk of new primary malignancy.[41378]

References

41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

41379 – Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009: 360:2416 to 2425.

65453 – Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/ Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol 2016;68:566-576.

Contraindications/Precautions

Absolute contraindications are italicized.

- breast-feeding
- children
- hepatic disease
- hepatitis
- human immunodeficiency virus (HIV) infection
- immunosuppression
- infants
- infection
- neonates
- neoplastic disease
- pregnancy
- renal impairment
- tuberculosis
- vaccination

Canakinumab is contraindicated for use in patients with *a confirmed hypersensitivity to canakinumab*. Hypersensitivity reactions have been reported with canakinumab therapy. During clinical trials, no anaphylactic reactions have been reported. It should be recognized that symptoms of the underlying disease being treated may be similar to symptoms of hypersensitivity.[41378]

Patients who receive canakinumab are at an increased risk of developing serious infections. Canakinumab should not be initiated in patients with an active infection requiring medical intervention and therapy should be discontinued if a patient develops a serious infection. Infections, primarily of the upper respiratory tract, in some instances serious, have been reported with the drug. Generally, the observed infections responded to standard therapy. Isolated cases of unusual or opportunistic infections (e.g., aspergillosis, atypical mycobacterial infections, cytomegalovirus, herpes zoster) have been reported with canakinumab therapy. Canakinumab is an IL-1 blocker that may cause immunosuppression and use is associated with an increased risk of serious infections. Canakinumab use may also increase the risk of tuberculosis (TB) or other atypical or opportunistic infections. Prior to initiation of canakinumab, evaluate patients for tuberculosis risk factors and test them for active or latent tuberculosis. The drug has not been studied in patients with a positive tuberculosis screen. Patients with positive tuberculosis screening or with known active or latent tuberculosis should be treated before canakinumab receipt, following the current Centers for Disease Control (CDC) guidelines. Use caution in patients with infection, including human immunodeficiency virus (HIV) infection, hepatitis B or hepatitis C, history of recurring infections, or underlying conditions that may predispose them to infections.[41378]

The impact of anti-interleukin-1 therapy with canakinumab on the development of neoplastic disease is not known. However, treatment with immunosuppressants, including canakinumab, may result in an increase in the

risk of certain malignancies.[41378]

Live vaccines should not be given to patients taking canakinumab; other forms of vaccination should be completed prior to initiation of therapy. Data are lacking on the efficacy of live vaccines and on the risks of secondary transmission of infection by live vaccines in patients receiving canakinumab. In addition, limited data are available on the effectiveness of vaccinations in patients receiving canakinumab; it is possible the drug may interfere with normal immune response to vaccine antigens. Interleukin-1 blockade may also interfere with immune response to infections. It is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive all recommended vaccinations (including pneumococcal vaccine and inactivated influenza vaccine; consult current recommendations of the Centers for Disease Control).[41378] [43236]

Use canakinumab with caution in patients with hepatic disease or renal impairment. No formal studies have been conducted to examine the pharmacokinetics or use of canakinumab in patients with renal or hepatic impairment. [41378]

Pregnancy exposure data is insufficient to inform regarding drug-associated risk with canakinumab. Monoclonal antibodies, such as canakinumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential fetal effects are likely to be greater during the second and third trimesters. Canakinumab has been studied in marmoset monkeys using doses 11-fold the maximum recommended human dose (MRHD) and greater (based on a plasma area under the time-concentration curve, AUC comparison); delays in fetal skeletal development were reported. Doses producing exposures within the clinical exposure range at the MRHD were not evaluated.[41378]

No information is available regarding the presence of canakinumab in breast-milk, the effects on milk production, or the effects on the breast-fed infant. Excretion of the drug into mature breast milk is considered unlikely due to the drugs high molecular weight (145,157). Absorption is unlikely because canakinumab is a protein that will likely be destroyed in the infant's gastrointestinal tract. Because maternal antibodies are known to be present in colostrum, there is a potential of exposing a nursing infant to the drug during the first few days after birth. Thus, health care providers are advised to monitor nursing babies for signs of infection as well as other drug associated adverse effects including nasopharyngitis, diarrhea, rhinitis, nausea, headache, bronchitis, and gastroenteritis. The FDA-approved product label recommends considering the developmental and health benefits of breast-feeding, the mother's need for canakinumab therapy, and potential adverse effects of the drug or an inadequately treated condition on the breast-fed infant.[41378] [61034]

The safety and effectiveness of canakinumab in neonates, infants, and children less than 2 years old have not been established for Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD), Familial Mediterranean Fever (FMF), and Systemic Juvenile Idiopathic Arthritis (SJIA). The safety and effectiveness of canakinumab in neonates, infants, and children less than 4 years old have not been established in Cryopyrin-Associated Periodic Syndrome (CAPS). Clinical trials with canakinumab included a total of 23 pediatric patients with CAPS, ages 4 years to 17 years (11 adolescents were treated with 150 mg subcutaneously, and 12 children were treated with 2 mg/kg based on body weight 15 kg to 40 kg). Overall, the efficacy and safety of canakinumab in pediatric and adult patients were comparable. In the TRAPS, HIDS/MKD, and FMF clinical trial, 102 pediatric patients, ages 2 to 17 years were treated with canakinumab 2 mg/kg subcutaneously every 4 weeks. No clinically meaningful differences in efficacy, safety, and tolerability were found between adult and pediatric patients.[41378]

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References

41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

43236 – National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(2):1-64.

61034 – National Institutes of Health (NIH). Canakinumab monograph. LactMed: Drugs and Lactation Database. Available at: https://toxnet.nlm.nih.gov. Accessed July 29, 2016.

Mechanism of Action

Canakinumab is a human monoclonal antibody against interleukin (IL)-1 beta. Binding of canakinumab to IL-1 beta blocks the interaction with IL-1 receptors. Excessive release of IL-1 beta drives inflammation in patients with cryopyrin-associated periodic syndromes (CAPS), which is a rare, genetic-based disease. Patients with the disease have mutations in the NLRP-3 (CIAS1) gene that encodes the protein cryopyrin.[41378] Cryopyrin binds with an intrinsic inhibitor and controls the activation of caspase-1. Caspase-1 cleaves pro-interleukin-1 beta and IL-18 into the biologically active forms.[33840] Patients with CAPS have increased caspase activity and thus, increased biologically active IL-1 beta.

Canakinumab has a disease-modifying effect through autocrine down-regulation of IL-1 beta production.[41379] IL-1 beta has been shown both *in vivo* and *in vitro* to stimulate its own production. Unbound IL-1 beta in the tissue stimulates production of C-reactive protein (CRP) and serum amyloid A protein (SAA), leading to an increased probability of a disease flare. Canakinumab binds to IL-1 beta and suppresses free IL-1 beta; this disrupts this feedback mechanism and hence reduces IL-1 production to a rate of that seen in healthy subjects.[41419]

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References

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41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

41379 – Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009: 360:2416 to 2425.

41419 – Lachmann HJ,Lowe P, Felix SD, et al. In vivo regulation of interleukin 1 beta in patients with cryopyrin-associated periodic syndromes. J Exp Med 2009;206:1029—1036.

Pharmacokinetics

Canakinumab is administered subcutaneously. Canakinumab binds to serum interleukin (IL)-1 beta. The volume of distribution at steady-state varied with body weight and was estimated to be 6.01 L in a typical patient with cryopyrin-associated periodic syndromes (CAPS) weighing 70 kg, 3.2 L in a patient weighing 33 kg with systemic juvenile idiopathic arthritis (SJIA), and 6.34 L for a patient weighing 70 kg with periodic fever syndrome. Clearance of the drug also varied according to body weight and was estimated to be 0.174 L/day in a

typical 70 kg patient with CAPS, 0.11 L/day in a SJIA patient weighing 33 kg, and 0.17 L/day in a periodic fever syndrome patient weighing 70 kg. After repeated administration, there was no indication of accelerated clearance or time-dependent change. The expected accumulation ratio was 1.3-fold for CAPS patients and 1.6-fold for SJIA patients after 6 months of 150 mg canakinumab subcutaneously every 8 weeks and 4 mg/kg subcutaneously every 4 weeks, respectively. The mean terminal half-life was 26 days in adults with CAPS receiving subcutaneous dosing.[41378]

Affected cytochrome P450 (CYP450) isoenzymes and drug transporters: various CYP isoenzymes

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 canakinumab, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index (NTI), where the dose is individually adjusted (e.g., warfarin). Upon initiation of canakinumab, in patients being treated with drugs with an NTI, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.[41378]

Route-Specific Pharmacokinetics

- **Intravenous Route**

  Canakinumab has been investigated as an intravenous infusion. Exposure parameters (such as AUC and Cmax) increased in proportion to dose over the dose range of 0.30 to 10 mg/kg given as intravenous infusion.[41378]

- **Subcutaneous Route**

  The peak serum canakinumab concentration (Cmax) of 16 +/- 3.5 mcg/mL occurred approximately 7 days after subcutaneous administration of a single, 150 mg dose in adult patients with cryopyrin-associated periodic syndromes (CAPS). The absolute bioavailability of subcutaneous canakinumab was estimated to be 66%. Exposure parameters (such as AUC and Cmax) increased in proportion to dose over the dose range of 150 to 300 mg as a subcutaneous injection.[41378]

Special Populations

- **Hepatic Impairment**

  No formal studies have been conducted to examine the pharmacokinetics or use of canakinumab in patients with hepatic impairment.[41378]

- **Renal Impairment**

  No formal studies have been conducted to examine the pharmacokinetics or use of canakinumab in patients with renal impairment.[41378]

- **Pediatrics**

Peak concentrations of canakinumab occurred between 2 to 7 days after single subcutaneous administration of canakinumab 150 mg or 2 mg/kg in pediatric patients with cryopyrin-associated periodic syndromes (CAPS). The terminal half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties observed in adults. Pharmacokinetic properties of canakinumab are similar among pediatric patients with CAPS or systemic juvenile idiopathic arthritis (SJIA). Among patients with SJIA who received 4 mg/kg subcutaneously every 4 weeks, canakinumab exposure parameters such as AUC and Cmax were comparable across age groups from 2 years of age and older. Following subcutaneous administration of canakinumab 2 mg/kg every 4 weeks in patients 2 years to less than 20 years of age, trough concentrations were similar among patients with tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), and familial mediterranean fever (FMF).[41378]

- **Geriatric**

  No age-related pharmacokinetic differences were observed between geriatric adults and younger adults after correction for body weight.[41378]

- **Gender Differences**

  No pharmacokinetic differences were observed between males and females after correction for body weight.[41378]

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References

41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

Pregnancy/Breast-feeding

Pregnancy

Pregnancy exposure data is insufficient to inform regarding drug-associated risk with canakinumab. Monoclonal antibodies, such as canakinumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential fetal effects are likely to be greater during the second and third trimesters. Canakinumab has been studied in marmoset monkeys using doses 11-fold the maximum recommended human dose (MRHD) and greater (based on a plasma area under the time-concentration curve, AUC comparison); delays in fetal skeletal development were reported. Doses producing exposures within the clinical exposure range at the MRHD were not evaluated.[41378]

Breast-Feeding

No information is available regarding the presence of canakinumab in breast-milk, the effects on milk production, or the effects on the breast-fed infant. Excretion of the drug into mature breast milk is considered unlikely due to the drugs high molecular weight (145,157). Absorption is unlikely because canakinumab is a protein that will likely be destroyed in the infant's gastrointestinal tract. Because maternal antibodies are known to be present in colostrum, there is a potential of exposing a nursing infant to the drug during the first few days after birth. Thus, health care providers are advised to monitor nursing babies for signs of infection as well as other drug associated adverse effects including nasopharyngitis, diarrhea, rhinitis, nausea, headache, bronchitis,

and gastroenteritis. The FDA-approved product label recommends considering the developmental and health benefits of breast-feeding, the mother's need for canakinumab therapy, and potential adverse effects of the drug or an inadequately treated condition on the breast-fed infant.[41378] [61034]

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References

41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

61034 – National Institutes of Health (NIH). Canakinumab monograph. LactMed: Drugs and Lactation Database. Available at: https://toxnet.nlm.nih.gov. Accessed July 29, 2016.

Interactions

Level 1 (Severe)

- Rilonacept
- Tumor Necrosis Factor modifiers

Level 2 (Major)

- Anakinra
- Bacillus Calmette-Guerin Vaccine, BCG
- Baricitinib
- Encorafenib
- Influenza Virus Vaccine
- Intranasal Influenza Vaccine
- Live Vaccines
- Measles Virus; Mumps Virus; Rubella Virus; Varicella Virus Vaccine, Live
- Measles/Mumps/Rubella Vaccines, MMR
- Rotavirus Vaccine
- Rubella Virus Vaccine Live
- Sarilumab
- Smallpox and Monkeypox Vaccine, Live, Nonreplicating
- Smallpox Vaccine, Vaccinia Vaccine
- Tocilizumab
- Tofacitinib
- Typhoid Vaccine
- Upadacitinib
- Varicella-Zoster Virus Vaccine, Live
- Yellow Fever Vaccine, Live

Level 3 (Moderate)

- Carbamazepine
- Cyclosporine
- Ethosuximide
- Fosphenytoin
- Phenytoin
- Tacrolimus
- Theophylline, Aminophylline
- Warfarin

Anakinra: (Major) Concomitant use of anakinra with other drugs that also block interleukin (IL)-1, such as canakinumab, is not recommended; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [27940] [41378]

Bacillus Calmette-Guerin Vaccine, BCG: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab

treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Baricitinib: (Major) Concomitant use of baricitinib with biologic DMARDs, such as canakinumab, is not recommended because of the possibility of additive immunosuppression and increased infection risk. [63229]

Carbamazepine: (Moderate) If canakinumab is initiated or discontinued in a patient taking carbamazepine, monitor carbamazepine concentrations; carbamazepine dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as carbamazepine. [41378]

Cyclosporine: (Moderate) If canakinumab is initiated or discontinued in a patient taking cyclosporine, monitor cyclosporine concentrations; cyclosporine dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as cyclosporine. [41378]

Encorafenib: (Major) Avoid coadministration of encorafenib and canakinumab due to increased encorafenib exposure. If concurrent use cannot be avoided, reduce the encorafenib dose to one-half of the dose used prior to the addition of canakinumab. If canakinumab is discontinued, the original encorafenib dose may be resumed after 3 to 5 elimination half-lives of canakinumab. Encorafenib is a CYP3A4 substrate; canakinumab is a moderate CYP3A4 inhibitor. Coadministration of a moderate CYP3A4 inhibitor with a single 50 mg dose of encorafenib (0.1 times the recommended dose) increased the encorafenib AUC and Cmax by 2-fold and 45%, respectively. [41378] [63317]

Ethosuximide: (Moderate) If canakinumab is initiated or discontinued in a patient taking ethosuximide, monitor ethosuximide concentrations; ethosuximide dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as ethosuximide. [41378]

Fosphenytoin: (Moderate) If canakinumab is initiated or discontinued in a patient taking fosphenytoin, monitor phenytoin concentrations; fosphenytoin dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as fosphenytoin. [41378]

Influenza Virus Vaccine: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is

recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Intranasal Influenza Vaccine: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Live Vaccines: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Measles Virus; Mumps Virus; Rubella Virus; Varicella Virus Vaccine, Live: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Measles/Mumps/Rubella Vaccines, MMR: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Phenytoin: (Moderate) If canakinumab is initiated or discontinued in a patient taking phenytoin, monitor phenytoin concentrations; phenytoin dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as phenytoin. [41378]

Rilonacept: (Severe) The concomitant administration of canakinumab with other drugs that block interleukin (IL)-1, such as rilonacept, has not been studied; however, based upon the potential for serious infection

associated with the use of both drugs, concomitant administration of canakinumab with rilonacept is not recommended. [41378]

Rotavirus Vaccine: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Rubella Virus Vaccine Live: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Sarilumab: (Major) Avoid using sarilumab with other biological DMARDs including interleukin-1 receptor antagonists such as canakinumab; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [61976]

Smallpox and Monkeypox Vaccine, Live, Nonreplicating: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Smallpox Vaccine, Vaccinia Vaccine: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Tacrolimus: (Moderate) If canakinumab is initiated or discontinued in a patient taking tacrolimus, monitor tacrolimus concentrations; tacrolimus dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as tacrolimus. [41378]

Theophylline, Aminophylline: (Moderate) If canakinumab is initiated or discontinued in a patient taking aminophylline, monitor theophylline concentrations; aminophylline dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as aminophylline. [41378] (Moderate) If canakinumab is initiated or discontinued in a patient taking theophylline, monitor theophylline concentrations; theophylline dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as theophylline. [41378]

Tocilizumab: (Major) Avoid using tocilizumab with other biological DMARDs including interleukin-1 receptor antagonists such as canakinumab; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [38283]

Tofacitinib: (Major) Concomitant use of tofacitinib with biologic DMARDs, such as canakinumab, is not recommended because of the possibility of additive immunosuppression and increased infection risk. Tofacitinib may be used as monotherapy or concomitantly with methotrexate or other nonbiologic DMARDs. [52315]

Tumor Necrosis Factor modifiers: (Severe) The concomitant administration of tumor necrosis factor (TNF) modifiers with other drugs that block interleukin (IL)-1, such as canakinumab, has not been studied; however, an increased incidence of serious infections and an increased risk of neutropenia have been associated with administration of another IL-1 blocker in combination with TNF inhibitors. Based upon the potential for similar interactions, concomitant administration of TNF inhibitors and canakinumab is not recommended. [41378]

Typhoid Vaccine: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Upadacitinib: (Major) Concomitant use of upadacitinib with biologic DMARDs, such as canakinumab, is not recommended because of the possibility of increased immunosuppression and increased infection risk. Upadacitinib may be used as monotherapy or concomitantly with methotrexate or other nonbiologic DMARDs. [64572]

Varicella-Zoster Virus Vaccine, Live: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Warfarin: (Moderate) If canakinumab is initiated or discontinued in a patient taking warfarin, monitor the INR; warfarin dose adjustments may be needed. The formation of CYP450 enzymes may be altered by increased concentrations of cytokines during chronic inflammation. Thus, the formation of CYP450 enzymes could be

normalized during canakinumab administration. In theory, clinically relevant drug interactions may occur with CYP450 substrates that have a narrow therapeutic index such as warfarin. [28549] [41378]

Yellow Fever Vaccine, Live: (Major) Do not administer live vaccines to a patient who is receiving canakinumab; other vaccination schedules should be complete as recommended prior to initiating canakinumab treatment. No data are available regarding the risk of secondary transmission of infection by live vaccines, and the efficacy and safety of live vaccines have not been established in patients receiving canakinumab. The immune response to vaccines or toxoids may be decreased, as canakinumab may interfere with normal immune response to new antigens. Limited data are available on the effectiveness of vaccination with inactivated antigens in patients receiving canakinumab. Because interleukin-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with canakinumab, adult and pediatric patients receive any recommended vaccination (including pneumococcal vaccine and inactivated influenza vaccines). [41378] [43236]

Revision Date: 05/07/2020 02:26:00 AM

References

27940 – Kineret (anakinra) package insert. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2018 Jun.

28549 – Coumadin (warfarin tablets) package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2017 Aug.

38283 – Actemra (tocilizumab) injection package insert. South San Francisco, CA: Genentech, Inc.; 2019 Jun.

41378 – Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Sep.

43236 – National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60(2):1-64.

52315 – Xeljanz and Xeljanz XR (tofacitinib) package insert. New York, NY: Pfizer, Inc.; 2019 Dec.

61976 – Kevzara (sarilumab) package insert. Bridgewater, NJ: Sanofi-Aventis US. LLC; 2018 Apr.

63229 – Olumiant (baricitinib) tablets package insert. Indianapolis, IN: Lilly USA, LLC; 2019 Oct.

63317 – Braftovi (encorafenib) capsules package insert. Boulder, CO: Array BioPharma Inc.; 2020 April.

64572 – Rinvoq (upadacitinib) package insert. North Chicago, IL: Abbvie Inc.; 2019 Aug.

Monitoring Parameters

- tuberculin skin test

US Drug Names

- Ilaris

Global Drug names

Argentina

- Ilaris - (Novartis)

Australia

- Ilaris - (Novartis)

Austria

- Ilaris - (Novartis)

Belgium

- Ilaris - (Novartis)

Brazil

- Ilaris - (Novartis)

Canada

- Ilaris - (Novartis)

Czech Republic

- Ilaris - (Novartis)

Denmark

- Ilaris - (Novartis)

Finland

- Ilaris - (Novartis)

France

- Ilaris - (Novartis)

Germany

- Ilaris - (Novartis)

Greece

- Ilaris - (Novartis)

Hong Kong

- Ilaris - (Novartis)

Hungary

- Ilaris - (Novartis)

Ireland

- Ilaris - (Novartis)

Israel

- Ilaris - (Novartis)

Italy

- Ilaris - (Novartis)

Japan

- Ilaris - (Novartis)

Netherlands

- Ilaris - (Novartis)

New Zealand

- Ilaris - (Novartis)

Norway

- Ilaris - (Novartis)

Philippines

- Ilaris - (Novartis)

Poland

- Ilaris - (Novartis)

Portugal

- Ilaris - (Novartis)

Russian Federation

- Ilaris - (Novartis)

Spain

- Ilaris - (Novartis)

Sweden

- Ilaris - (Novartis)

Switzerland

- Ilaris - (Novartis)

Turkey

- Ilaris - (Novartis)

Ukraine

- Ilaris - (Novartis)

United Kingdom

- Ilaris - (Novartis)
