Anakinra

Indications/Dosage

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Labeled

- cryopyrin-associated periodic syndromes (CAPS)
- rheumatoid arthritis

Off-Label

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

† Off-label indication

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 receptor inhibitors, such as anakinra.[65314] 100 mg via intravenous infusion given every 6 hours for 15 days is being evaluated. In SARS-CoV-2 infected patients with macrophage activation syndrome (MAS) or immune dysregulation, one study is evaluating 200 mg intravenously every 8 hours for 7 days. For patients with renal impairment, the dose is to be reduced to 100 mg intravenously every 8 hours for 15 days. [65233] [65234]

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 receptor inhibitors, such as anakinra.[65314] 100 mg once daily via subcutaneous injection for 28 days or until hospital discharge, whichever is first, is being evaluated.[65194]

For the treatment of moderately to severely active rheumatoid arthritis in patients who have failed 1 or more disease-modifying antirheumatic drugs (DMARDs)

Subcutaneous dosage

- **Adults**

  100 mg subcutaneously once daily, every 24 hours, at approximately the same time each day. Higher doses do not result in increased response. Anakinra may be given alone or in combination with DMARDs other than tumor necrosis factor (TNF) inhibitors.[27940]

For the treatment of cryopyrin-associated periodic syndromes (CAPS), specifically Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

Subcutaneous dosage

- **Adults**

  1 to 2 mg/kg subcutaneously once daily, initially. If needed, increase by 0.5 to 1 mg/kg increments. In a clinical trial, the average maintenance dose was 3 to 4 mg/kg/day. Usually given as a single daily dose. However, splitting the daily dose into twice daily administrations may result in better symptom control for some patients. Max: 8 mg/kg/day.[27940]

- **Infants, Children, and Adolescents**

  1 to 2 mg/kg subcutaneously once daily, initially. If needed, increase by 0.5 to 1 mg/kg increments. In a clinical trial, the average maintenance dose was 3 to 4 mg/kg/day. Usually given as a single daily dose. However, splitting the daily dose into twice daily administrations may result in better symptom control for some patients. Max: 8 mg/kg/day. The NOMID premarket clinical trial included 36 pediatric patients, 13 of which were younger than 2 years; the youngest patient studied was 8 months of age.[27940] In a retrospective study of 10 patients (2 months to 20 years of age), the 8 oldest patients

(ages 6 to 20 years) required dosages of 1 to 3 mg/kg/day, whereas the 2 youngest patients (3 and 4 months) had severe disease and required 6 and 10 mg/kg/day to control symptoms.[56308]

Therapeutic Drug Monitoring

Check the patient's neutrophil count before anakinra initiation, followed by monthly for the first 3 months of therapy, and then quarterly for up to 1 year.[27940]

Maximum Dosage Limits

- Adults

  100 mg/day subcutaneously for RA; 8 mg/kg/day subcutenously for NOMID.

- Geriatric

  100 mg/day subcutaneously for RA.

- Adolescents

  8 mg/kg/day subcutaneously for NOMID.

- Children

  8 mg/kg/day subcutaneously for NOMID.

- Infants

  8 mg/kg/day subcutaneously. Limited data available in young infants; up to 10 mg/kg/day subcutaneously has been used off-label in an infant with severe NOMID.

- Neonates

  Safety and efficacy have not been established.

Patients with Hepatic Impairment Dosing

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Patients with Renal Impairment Dosing

CrCl 30 mL/minute or more: No dosage adjustment needed.

CrCl less than 30 mL/minute: Increased risk of adverse reactions; consider administration of the prescribed dose every other day instead of daily for both RA and NOMID.

† Off-label indication

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References

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

56308 – Neven B, Marvillet I, Terrada C, et al. Long-term efficacy of the interleukin-1 receptor antagonist anakinra in ten patients with neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous, articular syndrome. Arthritis & Rheumatism. 2010; 62 (1): 258-267.

65194 – University Hospital Ghent. Treatment of COVID-19 patients With anti-interleukin drugs (COV-AID). Retrieved April 2, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04330638?cond=Coronavirus&intr=Tocilizumab&draw=2&rank=4.

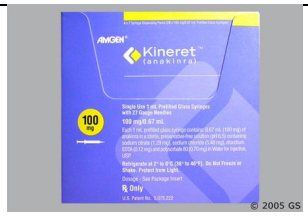
65233 – Swedish Orphan Biovitrum. Efficacy and safety of emapalumab and anakinra in reducing hyperinflammation and respiratory distress in patients with COVID-19 infection. Retrieved April 9, 2020. Available on the World Wide Web: https://clinicaltrials.gov/ct2/show/NCT04324021

65234 – Hellenic Institute for the study of sepsis. Personalized immunotherapy for SARS-CoV-2 (COVID-19) associated with organ dysfunction (ESCAPE). Retrieved April 9, 2020. Available on the World Wide Web: https://clinicaltrials.gov/ct2/show/NCT04339712?term=anakinra&cond=covid&draw=2&rank=2

65314 – COVID-19 treatment guidelines panel. COVID-19 treatment guidelines. National Institutes of Health Web site. Accessed April 22, 2020. Available at: https://covid19treatmentguidelines.nih.gov/.

How Supplied

Anakinra Solution for injection	
Kineret 100mg/0.67ml Solution for Injection (55513-0177) (Amgen Inc) (off market)	

Anakinra Solution for injection	
Kineret 100mg/0.67ml Solution for Injection (55513-0177) (SOBI ab) (off market)	
Kineret 100mg/0.67ml Solution for Injection (66658-0234) (SOBI ab)	

Description/Classification

Description

Anakinra is a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). The drug is produced by recombinant DNA technology using an *E. coli* bacterial expression system. Anakinra is useful for treating rheumatoid arthritis (RA) and some other inflammatory conditions. In adults with moderately to severely active RA, anakinra improves signs and symptoms of the disease and slows the progression of structural damage. Anakinra was considered but not included in the American College of Rheumatology 2015 guidelines due to its infrequent use at that time in RA compared to other available treatments and lack of new data since 2012; however, tumor necrosis factor (TNF) inhibitors are usually first-line choices in the biologic treatment categories due to the long-term safety data and the amount of experience associated with the TNF biologics.[65215] For adult RA, anakinra may be used as monotherapy; the drug may also be used with other disease-modifying antirheumatic drugs (DMARDs). The ideal combination of therapy for individual RA patients is determined by treat to target strategies and severity of disease.[56233] [65215] While anakinra has been studied in pediatric patients 2 years and older with polyarticular juvenile rheumatoid arthritis (JRA)/juvenile idiopathic arthritis (JIA), the study data were insufficient to establish efficacy for this condition, and use for JRA/JIA is not recommended. Anakinra is helpful for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) such as Muckle-Wells Syndrome (MWS), Familial Cold Auto-Inflammatory Syndrome (FCAS), and Neonatal-Onset Multisystem Inflammatory Disease (NOMID), which is also called Chronic Infantile Neurological, Cutaneous and Articular Syndrome (CINCA). Of all the forms of CAPS, NOMID/CINCA has the highest severity of chronic inflammation. Among patients with NOMID, disease symptoms and serum markers of inflammation usually worsened within 5 days of anakinra withdrawal and promptly responded to anakinra re-initiation.[27940] [33464] [33465] [33468] [33469]

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 receptor inhibitors, such as anakinra.[65314] Based on preliminary data from other anti-interleukin medications, studies have begun to evaluate the use of anakinra for COVID-19.[65194] [65233] [65234]

Classifications

- Antineoplastic and Immunomodulating Agents
  - Agents that Suppress the Immune System
    - Interleukin-1 (IL-1) Inhibitors

- Musculo-Skeletal System
  - Antiinflammatory Agents and Antirheumatic Agents
    - Specific Anti-Rheumatic Agents
      - Other Specific Antirheumatics

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References

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

33464 – Hawkins PN, Lachmann HJ, Aganna E, et al. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum 2004;50:607-12.

33465 – Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. N Engl J Med 2003;348:2583-4.

33468 – Frenkel J, Wulffraat NM, Kuis W. Anakinra in mutation-negative NOMID/CINCA syndrome. Arthritis Rheum 2004;50:3738-9.

33469 – Goldbach-Mansky R, Dailey NJ, Canna SW, et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1beta inhibition. N Engl J Med 2006;355:581-92.

56233 – Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. Arthritis Care & Research 2012;64(5):625-639.

65194 – University Hospital Ghent. Treatment of COVID-19 patients With anti-interleukin drugs (COV-AID). Retrieved April 2, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04330638?cond=Coronavirus&intr=Tocilizumab&draw=2&rank=4.

65215 – Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1-26.

65233 – Swedish Orphan Biovitrum. Efficacy and safety of emapalumab and anakinra in reducing hyperinflammation and respiratory distress in patients with COVID-19 infection. Retrieved April 9, 2020. Available on the World Wide Web: https://clinicaltrials.gov/ct2/show/NCT04324021

65234 – Hellenic Institute for the study of sepsis. Personalized immunotherapy for SARS-CoV-2 (COVID-19) associated with organ dysfunction (ESCAPE). Retrieved April 9, 2020. Available on

the World Wide Web: https://clinicaltrials.gov/ct2/show/NCT04339712?term=anakinra&cond=covid&draw=2&rank=2

65314 – COVID-19 treatment guidelines panel. COVID-19 treatment guidelines. National Institutes of Health Web site. Accessed April 22, 2020. Available at: https://covid19treatmentguidelines.nih.gov/.

Administration Information

General Administration Information

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

Route-Specific Administration

Injectable Administration

- Prefilled syringes are for subcutaneous administration.
- Visually inspect parenteral products for particulate matter and discoloration prior to administration whenever solution and container permit.
- Do not use the prefilled syringe if the solution is discolored or cloudy or if foreign particulate matter is present. Trace amounts of small, translucent-to-white, amorphous particles of protein may be in the solution. However, do not use the syringe if the number of translucent-to-white, amorphous particles appears excessive.[27940]

Subcutaneous Administration

- Instructions for appropriate use should be given to the patient and/or patient's caregiver. Patients or patient's caregiver should not administer anakinra until they have demonstrated a thorough understanding of the procedures and the ability to inject the medication.
- Inject the subcutaneous dose at about the same time(s) each day.[27940]

Prefilled Syringe:

- Remove the prefilled syringe from the refrigerator and allow it to sit at room temperature outside of the carton for 30 minutes before the injection. Do not warm anakinra in any other way.
- Wash hands before administration.
- The prefilled syringe does not allow doses lower than 20 mg to be administered. For a dose that is less than 100 mg, follow the manufacturer directions for preparing the dose needed. Small air bubbles may be present in the solution and do not need to be removed prior to administration.
- Pick an injection site such as the front of the middle thigh, the abdomen outside the 2 inches around the navel, the upper outer buttocks, or the outer area of the upper arm. Do not administer where skin is tender, bruised, red, or hard. Do not administer into scars or stretch marks. Do not inject near a vein that is visible under the skin surface.

- Rotate injection sites with each injection.
- Clean the injection site with the alcohol swab and let dry.
- Gently pinch a fold of skin at the cleaned injection site. With your other hand, hold the syringe like a pencil at a 45 to 90-degree angle to the skin. With a quick, dart-like motion insert the needle into the skin.
- Slowly push the plunger down to inject the dose. When the syringe is empty, remove the needle from the skin at the same angle it was inserted. Do not recap the needle.
- Dispose of used needles and syringes in an FDA-cleared sharps disposal container right away after use. The prefilled syringes do not contain preservatives and are for single-use only. If a syringe contains medicine after administration, it should be disposed of properly and not reused.[27940]

Clinical Pharmaceutics Information

From Trissel's 2™ Clinical Pharmaceutics Database

Anakinra

1. **pH Range**

   pH 6.5

   # References

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

2. **Osmolality/Osmolarity**

   Based on the formulation, anakinra injection should be near isotonicity.

   # References

   Anon. Manufacturer's information and labeling. (Package insert).

3. **Stability**

   Intact syringes of anakinra are stable until their labeled expiration date but should not be used past that time point. Anakinra syringes are for single use and contain no preservative. Any unused portions remaining in the syringes should be discarded. Do not shake syringes.

References

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

4. **Sorption Leaching**

Polysorbate 80, a surfactant known to leach diethylhexyl phthalate plasticizer from polyvinyl chloride (PVC) infusion solution bags and sets, is a component of the formulation of anakinra. However, the surfactant is present in small quantity and substantial leaching of plasticizer is not likely to occur.

References

Anon. Manufacturer's information and labeling. (Package insert).

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References

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

Adverse Reactions

- abdominal pain
- anaphylactoid reactions
- angioedema
- antibody formation
- arthralgia
- diarrhea
- ecchymosis
- elevated hepatic enzymes
- eosinophilia
- fever
- headache
- hepatitis
- hypercholesterolemia
- infection
- injection site reaction
- nausea
- neutropenia
- new primary malignancy
- pharyngitis
- pruritus
- rash
- sinusitis
- thrombocytopenia
- urticaria
- vomiting

Hypersensitivity reactions including anaphylactoid reactions, angioedema, urticaria, rash (unspecified), and pruritus have been reported with the use of anakinra. If a severe hypersensitivity reaction occurs, discontinue anakinra and initiate appropriate therapy.[27940]

The most common adverse reaction of anakinra subcutaneous administration is injection site reaction, which usually occurs during the first 4 weeks of treatment and is more common in

patients with rheumatoid arthritis (RA) than in patients with Neonate-Onset Multisystem Inflammatory Disease (NOMID). In clinical trials of patients with RA (n= 1,565), 71% of patients developed an injection site reaction; 72.6% were characterized as mild, 24.1% as moderate, and 3.2% as severe. In an open-label trial of NOMID patients (n = 43), 16.3% experienced an injection site reaction; during the 60-month study period, 65% of the injection site reactions occurred during the first month and 76% were reported during the first 6 months; 76% were characterized as mild and 24% as moderate. These reactions typically last for 14 to 28 days and are characterized by localized erythema, ecchymosis, edema, inflammation, itching, and/or pain. To decrease pain, swelling, and bruising at the injection site, apply a cold compress before and/or after the injection and allow the solution warm to room temperature prior to injection.[27940]

Anakinra has been associated with an increased risk of serious infections during clinical trials. Anakinra may increase the risk of tuberculosis (TB) or other atypical opportunistic infections. During postmarketing observation and in clinical studies, opportunistic infections consisting of fungal, mycobacterial, and bacterial pathogens have occurred. Infections have been noted in all organ systems and have been reported in patients receiving anakinra alone or in combination with immunosuppressive agents. Anakinra should be discontinued in patients with rheumatoid arthritis (RA) who develop a serious infection. In anakinra-treated patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), the risk of a NOMID flare when discontinuing anakinra should be weighed against the potential risk of continued treatment. During RA clinical trials, the incidence of infection during the first 6 months in anakinra-treated patients was 39% vs. 37% in placebo-treated patients. Reported infections in RA patients included upper respiratory tract infections (14%), sinusitis (7%), and influenza-like symptoms (6%). Serious infections occurred in 2% of anakinra-treated RA patients over 6 months of therapy and 3% of treated patients after over 1 year of therapy. The serious infections were primarily bacterial infections such as cellulitis, pneumonia, and bone and joint infections. In open-label extension studies, the overall rate of serious infections was comparable to that observed during controlled trials. The use of TNF blockers with anakinra should be avoided. In RA patients who received both anakinra and a TNF blocker (etanercept) for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure. RA patients with asthma had a higher incidence of serious infections during treatment with anakinra versus placebo-treated patients (4.5% vs 0%). In an open-label study of 43 patients with NOMID, infections were the most common type of serious adverse event; reporting frequency was highest in pediatric patients less than 12 years of age and those younger than 2 years had the highest incidence of infection and related symptoms. The most common infections were upper respiratory tract infection, sinusitis, ear infections (otitis media), and naso-pharyngitis (11.6%). The most common serious infections in NOMID patients were pneumonia and gastroenteritis. There were no deaths or permanent treatment discontinuation due to infection. Most NOMID patients (73%) have continued anakinra therapy once the infection resolved.[27940]

Anakinra treatment has been associated with hematologic side effects, including neutropenia. Monitoring of the absolute neutrophil count (ANC) is recommended prior to and during the first year of treatment with anakinra (monitor at baseline, each month for 3 months, then quarterly). In clinical trials, 8% of patients with rheumatoid arthritis (RA) receiving anakinra had decreases in neutrophil counts of at least one World Health Organization (WHO) toxicity grade compared with 2% in the control group. Neutropenia (ANC 1,000/mm^3 or less) was reported in 9 anakinra-treated patients (0.4%) and in 2% of patients treated with anakinra plus etanercept. Two of 43 (4.7%) patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID) experienced neutropenia after starting anakinra in a clinical trial; both cases resolved during continued anakinra treatment. In RA trials, a total of 9% of anakinra recipients experienced increases in eosinophil differential percentage (eosinophilia) of at least 1 WHO toxicity grade compared to 3% of placebo-treated patients. WHO toxicity grade 1 decreases in platelet countss occurred in 2% of

anakinra treated-patients and 0% of placebo-treated patients. Thrombocytopenia, including severe thrombocytopenia (i.e., platelet count less than 10,000/mm^3), has been reported with the postmarket use of anakinra.[27940]

Adverse gastrointestinal (GI) events reported in 5% or more of patients treated with anakinra during rheumatoid arthritis clinical trials include nausea (8%), diarrhea (7%), and abdominal pain (5%). In an open-label study in 43 NOMID patients, vomiting (14%) was the most common GI adverse event.[27940]

Headache and arthralgia are two of the most common adverse reactions to anakinra treatment. Headache occurred in 12% to 14% of patients during all clinical trials. Arthralgia occurred in 6% of anakinra-treated patients during rheumatoid arthritis (RA) clinical trials over a 6 month period and in 11.6% of 43 patients in a study of anakinra for Neonatal-Onset Multisystem Inflammatory Disease (NOMID). In the RA trials, a total of 19% of anakinra recipients experienced worsening of rheumatoid arthritis, compared to 29% of placebo recipients.[27940]

In an open-label study in 43 patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID), treatment-emergent pyrexia (fever) was reported in 11.6% of patients. Fever was not reported as an adverse event in clinical trials of patients with rheumatoid arthritis.[27940]

Cholesterol elevations were observed in some patients treated with anakinra therapy (hypercholesterolemia incidence not reported).[27940]

Elevated hepatic enzymes and non-infectious hepatitis have been reported postmarketing with the use of anakinra.[27940]

As with all therapeutic proteins, the use of anakinra carries the risk for immunogenicity. Antibody formation to anakinra detected by the use of a highly sensitive anakinra-binding biosensor assay was present at least once over 36 months in 49% of patients with rheumatoid arthritis in 2 clinical trials. After at least 12 weeks of anakinra, 30 (2%) of the 1,615 patients with available data were seropositive in a cell-based assay for neutralizing antibodies against anakinra. Thirteen of the 30 patients had follow-up data; 5 remained positive for neutralizing antibodies at week 24. No correlation between antibody development and adverse events was noted. Immunogenicity was not evaluated in trials of patients with Neonatal-Onset Multisystem Inflammatory Disease (NOMID).[27940]

The role of interleukin-1 blockers such as anakinra in the development of new primary malignancy is unknown. In clinical trials, the number of lymphoma cases among 5,300 patients with rheumatoid arthritis treated with anakinra was 0.12 per 100 patient-years. The rate is 3.6-fold higher than the expected rate for the general population, based upon the National Cancer Institute's Surveillance Epidemiology and End Results database. In addition to lymphoma, 37 other cancers were observed including breast, melanoma, respiratory system, and digestive system.[27940]

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References

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

Contraindications/Precautions

Absolute contraindications are italicized.

- *E. coli protein hypersensitivity*
- asthma
- bone marrow suppression
- breast-feeding
- fungal infection
- geriatric
- immunosuppression
- infants
- infection
- mycobacterial infection
- neonates
- neoplastic disease
- neutropenia
- new primary malignancy
- pregnancy
- renal failure
- renal impairment
- tuberculosis
- vaccination

Anakinra is contraindicated in patients with *E. coli protein hypersensitivity* or *hypersensitivity to anakinra* or any components of the product. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported with the use of anakinra. If a severe hypersensitivity reaction occurs, administration of anakinra should be discontinued and appropriate therapy initiated.[27940]

Patients who receive anakinra are at increased risk for developing serious infections. Anakinra should not be initiated in patients with an active infection. Administration of anakinra should be discontinued if a patient with rheumatoid arthritis (RA) develops a serious infection. In NOMID patients, the risk of a NOMID flare upon discontinuation of anakinra should be weighed against the potential risk of continued treatment. The safety and efficacy of anakinra in patients with chronic infections or immunosuppression, such as bone marrow suppression, have not been evaluated. The impact of anakinra therapy on active or chronic infections is not known. Similar to other drugs that affect the immune system, anakinra may increase the risk of tuberculosis or other atypical or opportunistic infections. In clinical studies and postmarketing experience, cases of opportunistic infections have been observed and included fungal infection, mycobacterial infection, and infection with bacterial pathogens. Infections have been noted in all organ systems and have been reported in patients receiving anakinra alone or in combination with immunosuppressive agents. Follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before anakinra initiation. In RA trials, patients with asthma appeared to be at a higher risk of developing serious infections during anakinra treatment. Also, anakinra should be used cautiously in geriatric patients, as there is, in general, a higher incidence of infections in the elderly.[27940]

Decreases in neutrophil count and neutropenia have been reported with anakinra therapy. Neutrophil counts should be checked before anakinra receipt, every month for 3 months, and quarterly after that for a period up to 1 year.[27940]

Anakinra is substantially excreted by the kidney; thus, patients with severe renal impairment or renal failure with a creatinine clearance (CrCL) less than 30 mL/minute may be at increased risk for adverse reactions. Consider administration of the prescribed anakinra dose every other day for these patients.[27940]

Anakinra is an immunosuppressant and treatment with immunosuppressants may result in an increased risk of cancer. The impact of anakinra on the development of a new primary malignancy is unknown, but malignancies were observed in clinical studies. Consider the risks and benefits of

anakinra before initiation in patients with a history of neoplastic disease. Also, consider the risk and benefits of anakinra continuation in patients who develop a malignancy.[27940]

Avoid use of live vaccines concurrently with anakinra. No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving anakinra. No data are available on the effectiveness of vaccination with inactivated antigens, other than tetanus/diphtheria toxoids vaccine, in patients receiving anakinra. In one clinical trial, no difference in the anti-tetanus antibody response to tetanus/diphtheria toxoids vaccine was noted between patients receiving anakinra and placebo. Since anakinra interferes with normal immune response mechanisms to new antigens, vaccination may not be effective. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.[27940]

Available data from retrospective studies and case reports on anakinra use during human pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or maternal and fetal adverse events. The available data have not identified an increased frequency or pattern of birth defects, miscarriage, or adverse maternal or fetal outcomes. Published data do suggest an increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis (RA) or cryopyrin-associated periodic syndromes (CAPS) who have increased disease activity. An international retrospective study of pregnancy outcomes with interleukin-1 inhibitors reported on 23 anakinra-exposed pregnancies. There were 21 live births of healthy infants, 1 miscarriage, and 1 infant with left renal agenesis. The estimated background rate of detected renal malformations is 0.2% to 2% of all newborns. Data for another retrospective study of 10 anakinra-exposed pregnancies in women with CAPS included 9 live births, 1 miscarriage, and 1 fetal death in a twin pregnancy (the surviving twin was healthy). Overall, these data cannot definitively establish or exclude any anakinra-associated risks during pregnancy. Methodological limitations of these data include small sample size and the inability to control for confounders such as the timing of drug exposure, underlying maternal disease, and concomitant medication use. Reproductive studies in animals (rats, rabbits) revealed no evidence of fetal harm at doses up to 25 times the maximum recommended human dose (MRHD) on an mg/kg basis.[27940] Guidelines suggest that until further data are available, anakinra use should be avoided during pregnancy if possible in patients with RA.[62180]

There are no data on the presence of anakinra in either human or animal milk or the effects on milk production. Limited data from a small retrospective study and postmarketing case reports do not establish an association between maternal anakinra use during lactation and adverse effects in breastfed infants. These limited data during lactation preclude a clear determination of the risk of anakinra to an infant during lactation. The developmental and health benefits of breast-feeding should be considered along with the clinical need for anakinra in the mother and any potential adverse effects to the nursing infant from anakinra or from the underlying maternal condition.[27940] Guidelines suggest that until further data are available, anakinra use in patients with RA should be approached with caution and avoided if possible during breast-feeding.[62180]

Very limited data are available describing the use of anakinra in infants; use with caution in young infants. Neonates and infants less than 1 month of age were not included in the trial for the treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID). Anakinra prefilled syringes are unable to deliver an anakinra dosage less than 20 mg. Although anakinra has been studied in pediatric patients 2 to 17 years of age with juvenile rheumatoid arthritis (JRA)/juvenile idiopathic arthritis (JIA), the study data were insufficient to demonstrate efficacy.[27940]

References

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

62180 – Gotestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75:795-810.

Mechanism of Action

Anakinra acts similarly to the native interleukin-1 receptor antagonist (IL-1Ra). IL-1Ra blocks the effects of IL-1 by competitively inhibiting the binding of IL-1, specifically IL-1alpha and IL-1beta, to the interleukin-1 type 1 receptor (IL-1R1), which is expressed in a wide variety of tissues. IL-1Ra is part of the feedback loop that is designed to balance the effects of inflammatory cytokines. IL-1 is one of the primary pro-inflammatory cytokines associated with rheumatoid arthritis, acting synergistically with tumor necrosis factor-alpha (TNF-alpha). Both IL-1 and TNF-alpha are expressed in the synovium of rheumatoid arthritis patients, although, IL-1, specifically IL-1beta, is secreted to a greater extent than TNF-alpha. IL-1 causes cartilage degradation by inducing the rapid loss of proteoglycans and stimulating the production of neutral proteinases in chondrocytes. Since IL-1 stimulates osteoclasts, bone resorption occurs. Rheumatoid arthritis patients who have bone erosions also have higher synovial fluid levels of IL-1 than rheumatoid arthritis patients with no bone erosions. These higher levels of IL-1 cannot be overcome by endogenous IL-1Ra. By administering exogenous IL-1Ra (i.e., anakinra), the erosive bone effects and bone resorption associated with IL-1 may be inhibited.[27940][65258]

The efficacy of anakinra for the treatment of familial cold autoinflammatory syndrome appears to be related to inhibition of IL-1beta, IL-6, and IL-8 in affected skin and to inhibition of increased IL-6 serum concentrations after cold exposure.[33471] In excess, IL-1 has been shown to be a key driver of inflammation in cryopyrin-associated periodic syndromes (CAPS), which is caused by a range of mutations in the gene CIAS1 that encodes the protein cryopyrin. Cryopyrin binds with an intrinsic inhibitor and controls the activation of caspase-1. Caspase-1 cleaves pro-interleukin-1beta and IL-18 into the biologically active forms. Patients with CAPS have increased caspase activity and thus, increased biologically active IL-1 beta. Enhanced caspase-1 activity with subsequent enhanced IL-1 beta and IL-18 release has been demonstrated in a patient with chronic infantile neurologic, cutaneous, articular (CINCA) syndrome.[33840] Anakinra receipt to several patients with different CAPS phenotypes led to the reduction of many CAPS clinical manifestations.[27940]

Revision Date: 04/15/2020 10:38:25 AM

References

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

33471 – Hoffman HM, Rosengren S, Boyle DL, et al. Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. Lancet 2004;364:1779-85.

33840 – Janssen R, Verhard E, Lankester A, et al. Enhanced interleukin-1beta and interleukin-18 release in a patient with chronic infantile neurologic, cutaneous, articular syndrome. Arthritis Rheum 2004;50:3329-33.

65258 – Furst DE. Review of recombinant human interleukin-1 receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther 2004;26:1960-1975.

Pharmacokinetics

Anakinra is given subcutaneously. In patients with rheumatoid arthritis (RA), no unexpected accumulation of anakinra was observed after daily subcutaneous doses for up to 24 weeks. The terminal half-life of anakinra ranges from 4 to 6 hours among patients with RA. Among patients with Neonatal Onset Multisystem Inflammatory Disease (NOMID), the median half-life was 5.7 hours (range, 3.1 to 28.2 hours). Anakinra is renally eliminated; the mean clearance of the drug increases with increasing creatinine clearance and body weight.[27940]

Route-Specific Pharmacokinetics

- **Subcutaneous Route**

  The absolute bioavailability of anakinra after subcutaneous injection in healthy subjects is 95%. After administration to subjects with RA, the maximum plasma concentration occurs within 3 to 7 hours. In NOMID patients (n = 16) receiving a median dose of 3 mg/kg once daily subcutaneously and a median treatment time of 3.5 years, the steady-state median (range) maximal concentration (Cmax) was 3,628 (655 to 8,511) ng/mL and the median (range) 24-hour concentration was 203 (53 to 1,979) ng/mL.[27940]

Special Populations

- **Hepatic Impairment**

  No formal studies have been performed to examine the pharmacokinetic parameters of anakinra administered subcutaneously in patients with hepatic impairment.[27940]

- **Renal Impairment**

  The estimated anakinra clearance increased with increasing creatinine clearance and body weight in a pharmacokinetic study using daily subcutaneous doses of anakinra. Among patients with severe or end-stage renal disease, defined as creatinine clearance

(CrCl) less than 30 mL/minute, the mean plasma clearance of anakinra decreased by 70% and 75%, respectively. The mean plasma clearance of anakinra decreased by 50% in patients with a CrCl of 30 to 49 mL/minute and by 16% in patients with a CrCl of 50 to 80 mL/minute. Less than 2.5% of an administered dose is removed by either hemodialysis or continuous ambulatory peritoneal dialysis. Based on these observations, a dose schedule change should be considered for subjects with severe renal insufficiency or end-stage renal disease.[27940]

- **Geriatric**

  After adjusting for creatinine clearance and body weight, age was not a significant factor for the mean plasma clearance of anakinra during a pharmacokinetic study. [27940]

- **Gender Differences**

  After adjusting for creatinine clearance and body weight, gender was not a significant factor for the mean plasma clearance of anakinra in a pharmacokinetic study. In a study of NOMID patients, there was no obvious gender influence on anakinra pharmacokinetics.[27940]

- **Obesity**

  The estimated anakinra clearance increased with increasing creatinine clearance and body weight in a pharmacokinetic study.[27940]

Revision Date: 04/15/2020 12:10:15 PM

References

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

Pregnancy/Breast-feeding

Pregnancy

Available data from retrospective studies and case reports on anakinra use during human pregnancy are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or maternal and fetal adverse events. The available data have not identified an increased frequency or pattern of birth defects, miscarriage, or adverse maternal or fetal outcomes. Published data do suggest an increased risk of adverse pregnancy outcomes in women with rheumatoid arthritis (RA) or cryopyrin-associated periodic syndromes (CAPS) who have increased disease activity. An international retrospective study of pregnancy outcomes with interleukin-1 inhibitors reported on 23 anakinra-exposed pregnancies. There were 21 live births of healthy infants, 1 miscarriage, and 1 infant with left renal agenesis. The estimated background rate of detected renal malformations is 0.2% to 2% of all newborns. Data for another retrospective study of 10 anakinra-exposed pregnancies in women with CAPS included 9 live births, 1 miscarriage, and 1 fetal death in a twin pregnancy (the surviving twin was healthy). Overall, these data cannot definitively establish or exclude any anakinra-associated risks during pregnancy. Methodological limitations of these data

include small sample size and the inability to control for confounders such as the timing of drug exposure, underlying maternal disease, and concomitant medication use. Reproductive studies in animals (rats, rabbits) revealed no evidence of fetal harm at doses up to 25 times the maximum recommended human dose (MRHD) on an mg/kg basis.[27940] Guidelines suggest that until further data are available, anakinra use should be avoided during pregnancy if possible in patients with RA.[62180]

Breast-Feeding

There are no data on the presence of anakinra in either human or animal milk or the effects on milk production. Limited data from a small retrospective study and postmarketing case reports do not establish an association between maternal anakinra use during lactation and adverse effects in breastfed infants. These limited data during lactation preclude a clear determination of the risk of anakinra to an infant during lactation. The developmental and health benefits of breast-feeding should be considered along with the clinical need for anakinra in the mother and any potential adverse effects to the nursing infant from anakinra or from the underlying maternal condition. [27940] Guidelines suggest that until further data are available, anakinra use in patients with RA should be approached with caution and avoided if possible during breast-feeding.[62180]

Revision Date: 04/15/2020 10:57:59 AM

References

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

62180 – Gotestam Skorpen C, Hoeltzenbein M, Tincani A, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75:795-810.

Interactions

Level 2 (Major)

- Abatacept
- Adalimumab
- Bacillus Calmette-Guerin Vaccine, BCG
- Baricitinib
- Canakinumab
- Certolizumab pegol
- Etanercept
- Golimumab
- Infliximab
- Influenza Virus Vaccine
- Intranasal Influenza Vaccine
- Live Vaccines
- Measles Virus; Mumps Virus; Rubella Virus; Varicella Virus Vaccine, Live
- Measles/Mumps/Rubella Vaccines, MMR
- Rilonacept
- Rituximab
- Rituximab; Hyaluronidase
- Rotavirus Vaccine
- Rubella Virus Vaccine Live
- Sarilumab
- Smallpox and Monkeypox Vaccine, Live, Nonreplicating
- Smallpox Vaccine, Vaccinia Vaccine
- Tocilizumab
- Tofacitinib
- Tumor Necrosis Factor modifiers

- Typhoid Vaccine
- Upadacitinib
- Varicella-Zoster Virus Vaccine, Live
- Yellow Fever Vaccine, Live

Level 3 (Moderate)

- Tuberculin Purified Protein Derivative, PPD

Abatacept: (Major) Concomitant use of abatacept with biological DMARDs, such as anakinra, is not recommended because of the possibility of additive immunosuppression and increased risk of infection. There is insufficient experience to assess the safety and efficacy of abatacept administered concurrently with anakinra. [27940] [31761]

Adalimumab: (Major) Avoid the concomitant use of anakinra with biological DMARDs, such as tumor necrosis factor (TNF) modifiers; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and a TNF inhibitor is used in combination with anakinra compared with either drug given alone. Neutropenia (1,000/mcL or less) was observed in 2% of patients receiving the combination. The use of anakinra with a TNF inhibitor in combination did not yield any additional clinical benefit as compared to the use of the TNF inhibitor alone. [27939] [27940] [27994] [28060] [33930] [35501]

Bacillus Calmette-Guerin Vaccine, BCG: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Baricitinib: (Major) Concomitant use of baricitinib with biologic DMARDs, such as anakinra, is not recommended because of the possibility of increased immunosuppression and increased infection risk. Baricitinib may be used as monotherapy or concomitantly with methotrexate or other nonbiologic DMARDs. [63229]

Canakinumab: (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]

Certolizumab pegol: (Major) Avoid the concomitant use of anakinra with biological DMARDs, such as tumor necrosis factor (TNF) modifiers; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and a TNF inhibitor is used in combination with anakinra compared with either drug given alone. Neutropenia (1,000/mcL or less) was observed in 2% of patients receiving the combination. The use of anakinra with a TNF inhibitor in combination did not yield any additional clinical benefit as compared to the use of the TNF inhibitor alone. [27939] [27940] [27994] [28060] [33930] [35501]

Etanercept: (Major) Avoid the concomitant use of anakinra with biological DMARDs, such as tumor necrosis factor (TNF) modifiers; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and a TNF inhibitor is used in combination with anakinra compared with either drug given alone. Neutropenia (1,000/mcL or less) was observed in 2% of patients receiving the combination. The use of anakinra with a TNF inhibitor in combination did not yield any additional clinical benefit as compared to the use of the TNF inhibitor alone. [27939] [27940] [27994] [28060] [33930] [35501]

Golimumab: (Major) Avoid the concomitant use of anakinra with biological DMARDs, such as tumor necrosis factor (TNF) modifiers; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and a TNF inhibitor is used in combination with anakinra compared with either drug given alone. Neutropenia (1,000/mcL or less) was observed in 2% of patients receiving the combination. The use of anakinra with a TNF inhibitor in combination did not yield any additional clinical benefit as compared to the use of the TNF inhibitor alone. [27939] [27940] [27994] [28060] [33930] [35501]

Infliximab: (Major) Avoid the concomitant use of anakinra with biological DMARDs, such as tumor necrosis factor (TNF) modifiers; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and a TNF inhibitor is used in combination with anakinra compared with either drug given alone. Neutropenia (1,000/mcL or less) was observed in 2% of patients receiving the combination. The use of anakinra with a TNF inhibitor in combination did not yield any additional clinical benefit as compared to the use of the TNF inhibitor alone. [27939] [27940] [27994] [28060] [33930] [35501]

Influenza Virus Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Intranasal Influenza Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Live Vaccines: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra

treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Measles Virus; Mumps Virus; Rubella Virus; Varicella Virus Vaccine, Live: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Measles/Mumps/Rubella Vaccines, MMR: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Rilonacept: (Major) Concomitant use of anakinra with other drugs that also block interleukin (IL)-1, such as rilonacept, is not recommended; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [27940] [33837]

Rituximab: (Major) Utilize caution with concomitant use of rituximab with other biologic agents, such as anakinra; coadministration may result in additive immunosuppression and an increased risk of infection. Limited data are available on the safety of the use of biologic agents in rheumatoid arthritis patients exhibiting peripheral B-cell depletion following treatment with rituximab. Monitor patients closely for signs or symptoms of infection. [27940] [49773]

Rituximab; Hyaluronidase: (Major) Utilize caution with concomitant use of rituximab with other biologic agents, such as anakinra; coadministration may result in additive immunosuppression and an increased risk of infection. Limited data are available on the safety of the use of biologic agents in rheumatoid arthritis patients exhibiting peripheral B-cell depletion following treatment with rituximab. Monitor patients closely for signs or symptoms of infection. [27940] [49773]

Rotavirus Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an

immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Rubella Virus Vaccine Live: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

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

Smallpox and Monkeypox Vaccine, Live, Nonreplicating: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Smallpox Vaccine, Vaccinia Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Tocilizumab: (Major) Avoid the concomitant use of tocilizumab with biological DMARDs, including interleukin-1 receptor antagonists such as anakinra; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [27940] [38283]

Tofacitinib: (Major) Avoid concomitant use of tofacitinib with biologic DMARDs, such as anakinra; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [52315]

Tuberculin Purified Protein Derivative, PPD: (Moderate) Since anakinra interferes with normal immune response mechanisms to new antigens such as tuberculin purified protein derivative, PPD, reactivity to the test may be decreased. Consider deferring the skin test until completion of anakinra therapy. [43298] [43299] [4656]

Tumor Necrosis Factor modifiers: (Major) Avoid the concomitant use of anakinra with biological DMARDs, such as tumor necrosis factor (TNF) modifiers; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and a TNF inhibitor is used in combination with anakinra compared with either drug given alone. Neutropenia (1,000/mcL or less) was observed in 2% of patients receiving the combination. The use of anakinra with a TNF inhibitor in combination did not yield any additional clinical benefit as compared to the use of the TNF inhibitor alone. [27939] [27940] [27994] [28060] [33930] [35501]

Typhoid Vaccine: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Upadacitinib: (Major) Avoid the concomitant use of upadacitinib with biologic DMARDs, such as anakinra; coadministration has not been studied and may result in additive immunosuppression and increased risk of infection. [64572]

Varicella-Zoster Virus Vaccine, Live: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Yellow Fever Vaccine, Live: (Major) Avoid concurrent use of live vaccines during treatment with anakinra due to potentially increased risk of infections; clinical safety of live vaccines during anakinra treatment has not been established. Live virus vaccines should generally not be administered to an immunosuppressed patient, as they may induce the illness they are intended to prevent. The immune response of the immunocompromised patient to vaccines may be decreased, even despite alternate vaccination schedules or more frequent booster doses. If immunization is necessary, choose an alternative to live vaccination, or, consider a delay or change in the

immunization schedule. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving anakinra. The interval between live vaccinations and initiation of anakinra therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. [27940] [43236]

Revision Date: 04/22/2020 02:35:00 AM

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

27994 – Remicade (infliximab) package insert. Horsham, PA: Janssen Biotech, Inc.; 2018 Jun.

28060 – Enbrel (etanercept injection) package insert. Thousand Oaks, CA: Amgen; 2020 Mar.

31761 – Orencia (abatacept) package insert. Princeton, NJ: Bristol-Myers Squibb Company; 2019 Mar.

33837 – Arcalyst (rilonacept) package insert. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; 2010 Apr.

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35501 – Simponi (golimumab) injection package insert. Horsham, PA: Janssen Biotech, Inc.; 2019 Sept.

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.

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43298 – Aplisol (tuberculin purified protein derivative, diluted) package insert. Rochester, MI: JHP Pharmaceuticals, LLC; 2008 Nov.

43299 – Tubersol (tuberculin purified protein derivative, mantoux) package insert. Swiftwater, PA: Sanofi Pasteur, Inc.; 2013 Feb.

49773 – Rituxan (rituximab) injection package insert. South San Francisco, CA: Genentech, Inc.; 2018 Apr.

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.

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

Monitoring Parameters

- CBC with differential
- tuberculin skin test

IV Compatibility of Anakinra with:

Legend

C = Compatible
I = Incompatible
⚠ = Results uncertain, variable or dependent on conditions
ND = No Data Available

From Trissel's 2™ Clinical Pharmaceutics Database

	Admixture	Syringe	Y-Site Administration	For Dilution
Aztreonam	ND	ND	⚠	ND
Cefazolin sodium	ND	ND	⚠	ND
Cefotaxime	ND	ND	⚠	ND
Cefoxitin	ND	ND	⚠	ND
Ceftazidime	ND	ND	C	ND
Ceftriaxone sodium	ND	ND	⚠	ND
Cefuroxime	ND	ND	⚠	ND
Cimetidine hydrochloride	ND	ND	C	ND
Ciprofloxacin	ND	ND	C	ND
Clindamycin phosphate	ND	ND	C	ND
Famotidine	ND	ND	C	ND
Fluconazole	ND	ND	⚠	ND
Lorazepam	ND	ND	C	ND
Morphine sulfate	ND	ND	C	ND

	Admixture	Syringe	Y-Site Administration	For Dilution
Ondansetron hydrochloride	ND	ND	C	ND
	Admixture	Syringe	Y-Site Administration	For Dilution
Piperacillin sodium	ND	ND	⚠	ND
Ranitidine hydrochloride	ND	ND	C	ND

US Drug Names

- Kineret

Global Drug names

Australia

- Kineret - (Menarini)

Austria

- Kineret - (Biovitrum)

Belgium

- Kineret - (Swedish Orphan)

Canada

- Kineret - (Amgen)

Czech Republic

- Kineret - (Swedish Orphan)

Denmark

- Kineret - (Swedish Orphan)

Finland

- Kineret - (Swedish Orphan)

France

- Kineret - (Biovitrum)

Germany

- Kineret - (Swedish Orphan)

Greece

- Kineret - (Biovitrum)

Hungary

- Kineret - (Swedish Orphan)

Ireland

- Kineret - (Swedish Orphan)

Israel

- Kineret - (Megapharm)

Italy

- Kineret - (Biovitrum)

Netherlands

- Kineret - (Swedish Orphan)

Norway

- Kineret - (Swedish Orphan)

Poland

- Kineret - (Amgen)

Portugal

- Kineret - (Biovitrum)

Singapore

- Kineret - (Swedish Orphan)

Spain

- Kineret - (Biovitrum)

Sweden

- Kineret - (Biovitrum)

United Kingdom

- Kineret - (Swedish Orphan)
