Anakinra (All Populations Monograph)

Indications/Dosage

Labeled

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

Off-Label, Recommended

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

† Off-label indication

For reducing the signs and symptoms and slowing the progression of structural damage of moderately to severely active rheumatoid arthritis in patients who have failed 1 or more disease modifying antirheumatic drugs (DMARDs)

NOTE: Anakinra may be given alone or in combination with other DMARDs except for other tumor necrosis factor inhibitors.

Subcutaneous dosage

- Adults

  100 mg (0.67 mL) subcutaneously once daily, every 24 hours, at approximately the same time each day. Higher doses do not result in increased response.

- Children and Adolescents

  Safety and efficacy have not been established.
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. 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. 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 cryopyrin-associated periodic syndromes (CAPS), specifically Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

**Subcutaneous dosage**

- **Adults**

  Initially, 1—2 mg/kg subcutaneously once daily. If needed, increase by 0.5—1 mg/kg increments to maximum of 8 mg/kg/day. The daily dose may be split into twice daily administrations for better control of disease activity. In a clinical trial of 43 patients (ages 0.7 to 46 years), the average maintenance dose needed to control signs and symptoms of NOMID was 3—4 mg/kg/day. [27940]

- **Infants, Children, and Adolescents**

  Initially, 1—2 mg/kg subcutaneously once daily. If needed, increase by 0.5—1 mg/kg increments to a maximum of 8 mg/kg/day. Splitting the daily dose into twice daily
administrations may result in better symptom control for some patients. In a clinical trial of patients with NOMID, an average maintenance dose of 3—4 mg/kg/day was adequate to maintain clinical response in pediatric patients irrespective of age; however, a higher dose was occasionally required in severely affected patients. This 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—20 years) required dosages of 1—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. Anakinra was initiated at 1 mg/kg/day in all patients. The dosage was increased after a minimum of 6 months of treatment in the older group if desired response was not achieved. All of the 8 oldest patients experienced a rapid clinical response to anakinra with remission of rash, fever, arthralgia, and myalgia within 24 hours. The 2 youngest patients experienced improvement after anakinra administration, but the rash reappeared 6—8 hours after injections, which prompted more rapid dosage increases compared to the older patients. One of the youngest patients experienced disease stabilization on 6 mg/kg/day, and the other continued to develop episodic rashes during viral infections even on 10 mg/kg/day. In these young infants, baseline irritability improved rapidly; CSF parameters improved within 3 months and complete normalization was evident after 12 months. One infant developed mild retardation.[56308]

Maximum Dosage Limits

- Adults
  100 mg/day SC for RA and 8 mg/kg/day SC for NOMID.

- Geriatric
  100 mg/day SC for RA.

- Adolescents
  8 mg/kg/day SC for NOMID.

- Children
  8 mg/kg/day SC for NOMID.

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

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/min: 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

Revision Date: 04/10/2020 10:44:59 AM

References


How Supplied

<table>
<thead>
<tr>
<th>Product</th>
<th>Approval Numbers</th>
<th>Manufacturer</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kineret 100mg/0.67ml Solution for Injection</td>
<td>55513-0177</td>
<td>Amgen Inc</td>
<td>(off market)</td>
</tr>
<tr>
<td>Kineret 100mg/0.67ml Solution for Injection</td>
<td>66658-0234</td>
<td>SOBI ab</td>
<td></td>
</tr>
</tbody>
</table>
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. During clinical trials, rheumatoid arthritis patients treated with anakinra experienced clinical responses, including improvement in swollen and painful joints, within 4 to 13 weeks. After 6 months of therapy, 38% of patients treated with anakinra, alone or in combination with methotrexate, achieved a 20% improvement in the American College of Rheumatology criteria. In addition, 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).[33464] [33465] [33468] [33469] 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 worsened usually within 5 days of anakinra withdrawal and promptly responded to anakinra re-initiation.[27940] The FDA approved anakinra for the treatment of rheumatoid arthritis in November 2001 and for the treatment of NOMID in December 2012.

Updates for coronavirus disease 2019 (COVID-19):

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
References


Administration Information

General Administration Information

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

Route-Specific Administration

Injectable Administration

• For subcutaneous use only. Do not inject intravenously or intramuscularly.
• Visually inspect parenteral product 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 care provider. Patients or care providers should not administer anakinra until they have demonstrated a thorough understanding of the procedures and ability to inject the medication. The U.S. Kineret Customer Call Center at 1-866-KINERET or (866)-546-3738 can answer questions or can provide a travel cooler.
- Administer subcutaneously at approximately the same time each day.
- Take the syringe out of the refrigerator and allow the solution to warm to room temperature for 30 minutes before the injection.
- Wash hands before administration.
- Injection sites include 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.
- Rotate injection sites with each injection.
- Clean the injection site with the alcohol swab and let dry.
- 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.
- You may notice a small air bubble in the prefilled syringe. You do not have to remove the air bubble before injecting.
- Remove the needle cover immediately before needle insertion.
- 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.
- Dispose of used syringes and needles properly, including any unused opened medicine; anakinra contains no preservatives.[27940]

Clinical Pharmaceutics Information

From Trissel's 2™ Clinical Pharmaceutics Database

Anakinra

1. pH Range

   pH 6.5

References

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**


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).

---

Revision Date: 06/13/2018 05:27:25 PM

Copyright 2004-2015 by Lawrence A. Trissel. All Rights Reserved.

**References**


**Adverse Reactions**

- abdominal pain
- anaphylactoid reactions
- angioedema
- antibody formation
- arthralgia
- diarrhea
- ecchymosis
- edema
- elevated hepatic enzymes
- erythema
The most common adverse reaction of anakinra 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, 71% of 1565 patients developed an injection site reaction. In an open-label trial of 43 patients with NOMID, 16.3% experienced an injection site reaction. During the 60-month study period for NOMID, 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—28 days and are characterized by 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.

Anakinra has been associated with an increased risk of serious infections during clinical trials. Anakinra should be discontinued in patients with rheumatoid arthritis (RA) who develop serious infection, and treatment should not be initiated in patients with active 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 of blinded treatment in anakinra-treated patients was 39% and 37% in placebo-treated patients. Reported infections included upper respiratory tract infections (14%), sinusitis (7%), and influenza-like symptoms (6%). Serious infections occurred in 2% of anakinra-treated patients compared with < 1% of placebo-treated patients. These 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. 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 patients < 12 years of age. Of pediatric patients, 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, and nasopharyngitis (11.6%). There were no deaths or permanent treatment discontinuation due to infection. Anakinra may increase the risk of tuberculosis (TB) or other atypical opportunistic infections because drugs that block tumor necrosis factor (TNF) have been associated with an increased risk of reactivation of latent TB. During post-marketing observation and in clinical studies, opportunistic infections consisting of fungal, mycobacterial, and bacterial pathogens have occurred. CDC guidelines should be used to evaluate for and to treat possible latent TB infections before initiating therapy with anakinra. Patients with asthma had a higher incidence of serious infections during treatment with anakinra versus placebo-treated asthma patients (4.5% vs 0%). In patients receiving anakinra plus etanercept, the incidence of serious infection (e.g., bacterial pneumonia and cellulitis) was 7%. One patient with pneumonitis and pulmonary fibrosis died due to respiratory failure. Most patients (73%) continued anakinra therapy once the infection resolved.
Anakinra treatment has been associated with reductions in white blood cell counts and platelets and small increases in eosinophils. 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 1000/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 of at least 1 WHO toxicity grade. WHO toxicity grade 1 decreases in platelets occurred in 2% of patients. Thrombocytopenia, including severe thrombocytopenia (i.e., platelet counts less than 10 x 10$^9$/L), has been reported with the post-market use of anakinra. Monitoring of ANC is recommended prior to and during the first year of treatment with anakinra (monitor at baseline, each month for 3 months, then quarterly).[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 5300 patients with rheumatoid arthritis treated with anakinra was 0.12/100 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]

As with all therapeutic proteins, the use of anakinra carries the risk for immunogenicity. Antibody formation to anakinra detected by 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 of the 1615 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]

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

Headache and arthralgia are 2 of the most common adverse reactions to anakinra treatment. Headache occurred in 12—14% of patients during 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]

Hypersensitivity reactions including anaphylactoid reactions, angioedema, urticaria, rash (unspecified), and pruritus have been reported with anakinra. The needle cover of the prefilled syringe contains dry natural rubber (a latex derivative), which may cause allergic reactions in patients with a latex allergy. If a severe hypersensitivity reaction occurs, discontinue anakinra and initiate appropriate therapy.[27940]

Post-marketing, elevated hepatic enzymes and non-infectious hepatitis have been reported with anakinra.[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]

Hypercholesterolemia has been reported in some patients receiving anakinra therapy (incidence unknown).[27940]

Revision Date: 03/14/2018 11:22:06 AM

References


Contraindications/Precautions

Absolute contraindications are italicized.

- E. coli protein hypersensitivity
- latex hypersensitivity
- asthma
- bone marrow suppression
- breast-feeding
- geriatric
- immunosuppression
- infants
- infection
- intramuscular administration
- intravenous administration
- neonates
- neoplastic disease
- pregnancy
- renal disease
- 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. The Kineret needle cover contains latex and may cause reactions in patients with latex hypersensitivity. The only recommended route of anakinra administration is subcutaneously; anakinra should not be given by intravenous administration or intramuscular administration.

Do not initiate anakinra in patients with an active infection, and the safety and efficacy of anakinra in patients with immunosuppression such as bone marrow suppression or in patients with chronic infections have not been evaluated. The impact of anakinra on active or chronic infections and on the development of neoplastic disease is not known. Also, anakinra may increase the risk of tuberculosis or other atypical or opportunistic infections. Follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before anakinra initiation. Determine neutrophil counts before anakinra initiation, monthly for 3 months, and quarterly thereafter for the first year. Cautious use of anakinra is warranted in patients with asthma, as they appear 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]
No data are available on the effects of vaccination in patients receiving anakinra; live virus vaccines should not be given to patients receiving anakinra. Since anakinra interferes with normal immune response mechanisms to new antigens, vaccination may not be effective.

Data from retrospective studies and case reports on anakinra use during pregnancy are insufficient to identify a drug associated risk of major birth defects, miscarriage, or maternal and fetal adverse events. 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 cryopyrin-associated periodic syndromes (CAPS) included 9 live births, 1 miscarriage, and 1 fetal death in a twin pregnancy (the surviving twin was healthy). These data cannot establish or exclude any anakinra-associated risks during pregnancy. Reproductive studies in animal revealed no evidence of fetal harm at doses up to 25 times the maximum recommended human dose. [27940] Guidelines suggest that until further data are available, anakinra use should be avoided during pregnancy.[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 on breast-fed 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 on the breast-fed infant from anakinra or from the underlying maternal condition. [27940] Guidelines suggest that until further data are available, anakinra use should be approached with caution and avoided if possible during breast-feeding.[62180]

Because the kidney substantially excretes anakinra, patients with renal impairment or renal failure (creatinine clearance < 30 mL/min) may be at increased risk for adverse reactions. Consider administration of the prescribed anakinra dose every other day for patients who have severe renal insufficiency or end stage renal disease defined as creatinine clearance < 30 mL/min.[27940]

Very limited data are available describing the use of anakinra in infants; neonates and young infants were not included in the trial that resulted in FDA-approval in pediatric patients for the treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID). In addition, the FDA-approved product labeling states that the prefilled syringes are unable to deliver a dosage < 20 mg. Although anakinra has been studied in pediatric patients with juvenile rheumatoid arthritis (JRA)/juvenile idiopathic arthritis (JIA), efficacy has not been established.[27940]

Revision Date: 06/13/2018 05:21:57 PM

References


Mechanism of Action
Anakinra acts similarly to the native interleukin-1 receptor antagonist (IL-1Ra). IL-1Ra blocks 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. Preliminary research indicates that IL-1 plays a dominant role in cartilage damage and bone resorption in rheumatoid arthritis, while TNF-alpha is more responsible for inflammation. 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.

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] Enhanced IL-1 beta production in CINCA syndrome and Muckle-Wells syndrome led to the efficacy testing of anakinra. Anakinra receipt to several patients with different CAPS phenotypes led to the reduction of many CAPS clinical manifestations.

IL-1beta inhibits the apoptosis of polymorphonuclear cells. Interleukin-1 blockade may interfere with immune response to infections.

References


Pharmacokinetics

Anakinra is given subcutaneously. The terminal half-life of anakinra ranges from 4—6 hours among patients with rheumatoid arthritis. Among patients with Neonatal Onset Multisystem Inflammatory Disease, the median half life was 5.7 hours (range, 3.1—28.2 hours). Anakinra is eliminated renally.[27940]

Route-Specific Pharmacokinetics

• Subcutaneous Route

The absolute bioavailability of anakinra after subcutaneous injection in healthy subjects is 95%. After administration to subjects with rheumatoid arthritis, the maximum plasma concentration occurs within 3—7 hours.

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

Among patients with severe or end-stage renal disease (creatinine clearance < 30 mL/min), the mean plasma clearance of anakinra decreased 70—75%. The mean plasma clearance of anakinra decreased by 50% in patients with a CrCl of 30—49 mL/minute and by 16% in patients with a CrCl of 50—80 mL/minute. Less than 2.5% of an administered dose is removed by either hemodialysis or continuous ambulatory peritoneal dialysis.[27940]

Revision Date: 06/23/2015 11:42:44 AM

References


Pregnancy/Breast-feeding
Pregnancy

Data from retrospective studies and case reports on anakinra use during pregnancy are insufficient to identify a drug associated risk of major birth defects, miscarriage, or maternal and fetal adverse events. 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 cryopyrin-associated periodic syndromes (CAPS) included 9 live births, 1 miscarriage, and 1 fetal death in a twin pregnancy (the surviving twin was healthy). These data cannot establish or exclude any anakinra-associated risks during pregnancy. Reproductive studies in animal revealed no evidence of fetal harm at doses up to 25 times the maximum recommended human dose. [27940] Guidelines suggest that until further data are available, anakinra use should be avoided during pregnancy.[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 on breast-fed 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 on the breast-fed infant from anakinra or from the underlying maternal condition. [27940] Guidelines suggest that until further data are available, anakinra use should be approached with caution and avoided if possible during breast-feeding.[62180]

References


Interactions

Level 1 (Severe)

- Adalimumab
- Bacillus Calmette-Guerin Vaccine, BCG
- 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
- Rotavirus Vaccine
- Rubella Virus Vaccine Live
- Smallpox and Monkeypox Vaccine, Live, Nonreplicating
- Smallpox Vaccine, Vaccinia Vaccine
- Tumor Necrosis Factor modifiers
- Typhoid Vaccine
- Varicella-Zoster Virus Vaccine, Live
- Yellow Fever Vaccine, Live

Level 2 (Major)

- Abatacept
- Baricitinib
- Canakinumab
- Rilonacept
- Rituximab
- Rituximab; Hyaluronidase
- Sarilumab
- Tocilizumab
- Tofacitinib
- Upadacitinib

Level 3 (Moderate)

- Tuberculin Purified Protein Derivative, PPD

**Abatacept**: (Major) Based on the potential for serious infection and additive immunologic effects, concurrent use is not recommended. There is insufficient experience to assess the safety and efficacy of abatacept administered concurrently with anakinra. [27940] [31761]

**Adalimumab**: (Severe) Anakinra should not be used in combination with tumor necrosis factor (TNF) inhibitors because of the increased risk of infection or other adverse events with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and etanercept are used in combination (7%) compared with anakinra given alone (3%) or etanercept alone (0%). Neutropenia (neutrophil count (1000/mm3 or less) was observed in 2% of patients. In addition, the use of anakinra and etanercept in combination did not yield any additional clinical benefit as compared to the use of etanercept alone. In a 24-week trial of anakinra plus etanercept, the ACR(50) response rate in patients receiving anakinra plus etanercept was 31% as compared to 41% in patients receiving etanercept alone. These data are likely applicable to other TNF inhibitors. [27939] [27940] [27994] [28060] [33930] [35501]

**Bacillus Calmette-Guerin Vaccine, BCG**: (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [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) The concomitant administration of canakinumab with other drugs that also block interleukin (IL)-1, such as anakinra, has not been studied; however, based on the duplicate pharmacology and upon the potential for serious infection associated with the use of both drugs, concomitant administration of anakinra with canakinumab is not recommended. [27940] [41378]

Certolizumab pegol: (Severe) Anakinra should not be used in combination with tumor necrosis factor (TNF) inhibitors because of the increased risk of infection or other adverse events with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and etanercept are used in combination (7%) compared with anakinra given alone (3%) or etanercept alone (0%). Neutropenia (neutrophil count (1000/mm³ or less) was observed in 2% of patients. In addition, the use of anakinra and etanercept in combination did not yield any additional clinical benefit as compared to the use of etanercept alone. In a 24-week trial of anakinra plus etanercept, the ACR(50) response rate in patients receiving anakinra plus etanercept was 31% as compared to 41% in patients receiving etanercept alone. These data are likely applicable to other TNF inhibitors. [27939] [27940] [27994] [28060] [33930] [35501]

Etanercept: (Severe) Anakinra should not be used in combination with tumor necrosis factor (TNF) inhibitors because of the increased risk of infection or other adverse events with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and etanercept are used in combination (7%) compared with anakinra given alone (3%) or etanercept alone (0%). Neutropenia (neutrophil count (1000/mm³ or less) was observed in 2% of patients. In addition, the use of anakinra and etanercept in combination did not yield any additional clinical benefit as compared to the use of etanercept alone. In a 24-week trial of anakinra plus etanercept, the ACR(50) response rate in patients receiving anakinra plus etanercept was 31% as compared to 41% in patients receiving etanercept alone. These data are likely applicable to other TNF inhibitors. [27939] [27940] [27994] [28060] [33930] [35501]

Golimumab: (Severe) Anakinra should not be used in combination with tumor necrosis factor (TNF) inhibitors because of the increased risk of infection or other adverse events with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and etanercept are used in combination (7%) compared with anakinra given alone (3%) or etanercept alone (0%). Neutropenia (neutrophil count (1000/mm³ or less) was observed in 2% of patients. In addition, the use of anakinra and etanercept in combination did not yield any additional clinical benefit as compared to the use of etanercept alone. In a 24-week trial of anakinra plus etanercept, the ACR(50) response rate in patients receiving anakinra plus etanercept was 31% as compared to 41% in patients receiving etanercept alone. These data are likely applicable to other TNF inhibitors. [27939] [27940] [27994] [28060] [33930] [35501]

Infliximab: (Severe) Anakinra should not be used in combination with tumor necrosis factor (TNF) inhibitors because of the increased risk of infection or other adverse events with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and etanercept are used in combination (7%) compared with anakinra given alone (3%) or etanercept alone (0%). Neutropenia (neutrophil count (1000/mm³ or less) was observed in 2% of patients. In addition, the use of anakinra and etanercept in combination did not yield any additional clinical benefit as compared to the use of etanercept alone. In a 24-week trial of anakinra plus etanercept, the ACR(50) response rate in patients receiving anakinra plus etanercept was 31% as compared to 41% in patients receiving etanercept alone. These data are likely applicable to other TNF inhibitors. [27939] [27940] [27994] [28060] [33930] [35501]

Influenza Virus Vaccine: (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally
contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

**Intranasal Influenza Vaccine:** (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

**Live Vaccines:** (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

**Measles Virus; Mumps Virus; Rubella Virus; Varicella Virus Vaccine, Live:** (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

**Measles/Mumps/Rubella Vaccines, MMR:** (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]
Rilonacept: (Major) The concomitant administration of rilonacept with other drugs that also block interleukin (IL)-1, such as anakinra, has not been studied; however, based on the duplicate pharmacology and upon the potential for serious infection associated with the use of both drugs, concomitant administration of anakinra with rilonacept is not recommended. [27940] [33837]

Rituximab: (Major) The concomitant use of rituximab with other biologic agents, such as anakinra, 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) The concomitant use of rituximab with other biologic agents, such as anakinra, 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: (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

Rubella Virus Vaccine Live: (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [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: (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines
regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

Smallpox Vaccine, Vaccinia Vaccine: (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [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) Concomitant use of tofacitinib with biologic DMARDs, such as anakinra, is not recommended because of the possibility of increased immunosuppression and increased infection risk. Tofacitinib may be used as monotherapy or concomitantly with methotrexate or other nonbiologic DMARDs. [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: (Severe) Anakinra should not be used in combination with tumor necrosis factor (TNF) inhibitors because of the increased risk of infection or other adverse events with no additional clinical benefit. Data suggest a higher rate of serious infections when anakinra and etanercept are used in combination (7%) compared with anakinra given alone (3%) or etanercept alone (0%). Neutropenia (neutrophil count (1000/mm[^3] or less) was observed in 2% of patients. In addition, the use of anakinra and etanercept in combination did not yield any additional clinical benefit as compared to the use of etanercept alone. In a 24-week trial of anakinra plus etanercept, the ACR(50) response rate in patients receiving anakinra plus etanercept was 31% as compared to 41% in patients receiving etanercept alone. These data are likely applicable to other TNF inhibitors. [27939] [27940] [27994] [28060] [33930] [35501]

Typhoid Vaccine: (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

Upadacitinib: (Major) Concomitant use of upadacitinib with biologic DMARDs, such as anakinra, 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:** (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

**Yellow Fever Vaccine, Live:** (Severe) Live vaccines should not be given concurrently with anakinra. No data are available on the effects of vaccination with live virus vaccines in patients receiving anakinra. Live virus vaccines should generally not be administered to an immunosuppressed patient. Live virus vaccines may induce the illness they are intended to prevent and are generally contraindicated for use during immunosuppressive treatment. 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. Practitioners should refer to the most recent CDC guidelines regarding vaccination of patients who are receiving drugs that adversely affect the immune system. [27940] [43236]

Revision Date: 04/11/2020 02:36:00 AM

**References**


Monitoring Parameters

- CBC with differential
- tuberculin skin test

IV Compatibility of Anakinra with:

Legend

- 
  = Compatible
- 
  = Incompatible
- 
  = Results uncertain, variable or dependent on conditions
- ND = No Data Available

From Trissel's 2™ Clinical Pharmaceutics Database

<table>
<thead>
<tr>
<th></th>
<th>Admixture</th>
<th>Syringe</th>
<th>Y-Site Administration</th>
<th>For Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Cefazolin sodium</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>Admixture</td>
<td>Syringe</td>
<td>Y-Site Administration</td>
<td>For Dilution</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------</td>
<td>---------</td>
<td>-----------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Ceftriaxone sodium</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Cimetidine hydrochloride</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
<tr>
<td>Clindamycin phosphate</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
<tr>
<td>Famotidine</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
<tr>
<td>Ondansetron hydrochloride</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
<tr>
<td>Piperacillin sodium</td>
<td>ND</td>
<td>ND</td>
<td>△</td>
<td>ND</td>
</tr>
<tr>
<td>Ranitidine hydrochloride</td>
<td>ND</td>
<td>ND</td>
<td>♕</td>
<td>ND</td>
</tr>
</tbody>
</table>

Copyright 2004-2015 by Lawrence A. Trissel. All Rights Reserved.

**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)