

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Kineret safely and effectively. See full prescribing information for Kineret.

Kineret® (anakinra)

For injection, for subcutaneous use

Initial U.S. Approval: 2001

RECENT MAJOR CHANGES

INDICATIONS AND USAGE

Kineret is an interleukin-1 receptor antagonist indicated for reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs) (1)

DOSAGE AND ADMINISTRATION

- The recommended dose of Kineret for the treatment of patients with rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. The dose should be administered at approximately the same time every day (2.1)
- Physicians should consider a dose of 100 mg of Kineret administered every other day for RA patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels) (2.2)

See full prescribing information for administration instructions (2.3)

DOSAGE FORMS AND STRENGTHS

100 mg/0.67 mL solution for subcutaneous injection (3)

CONTRAINDICATIONS

- Known hypersensitivity to *E coli*-derived proteins, Kineret, or to any component of the product. (4)

WARNINGS AND PRECAUTIONS

- Discontinue use if serious infection develops and do not initiate therapy in patients with active infections (5.1)
- Use in combination with Tumor Necrosis Factor (TNF) blocking agents is not recommended (5.2)
- Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported (5.3)
- The impact of treatment with Kineret on active and/or chronic infections and the development of malignancies is not known (5.4)
- Live vaccines should not be given concurrently with Kineret (5.5)
- Neutrophil counts should be assessed prior to initiating Kineret treatment, and while receiving Kineret, monthly for 3 months, and thereafter quarterly for a period up to 1 year (5.6)

ADVERSE REACTIONS

Most common adverse reactions (incidence \geq 5%) are injection site reaction, worsening of rheumatoid arthritis, upper respiratory tract infection, headache, nausea, diarrhea, sinusitis, arthralgia, flu like-symptoms, and abdominal pain (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact 1-866-773-5274, FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- A higher rate of serious infections has been observed in patients treated with concurrent Kineret and etanercept therapy than in patients treated with etanercept alone. Use of Kineret in combination with TNF blocking agents is not recommended (7)

USE IN SPECIFIC POPULATIONS

- Pediatric use: Not recommended because the prefilled syringes do not permit accurate dosing lower than 100 mg and efficacy could not be demonstrated due to low trial enrollment (8.4)
- Geriatric use: Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (8.5)
- Renal impairment: This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

1.1 Active Rheumatoid Arthritis

2 DOSAGE AND ADMINISTRATION

2.1 Active Rheumatoid Arthritis

2.2 Renal Impairment

2.3 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

5.2 Use With TNF Blocking Agents

5.3 Hypersensitivity Reactions

5.4 Immunosuppression

5.5 Immunizations

5.6 Neutrophil Count

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Renal Impairment

8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Active Rheumatoid Arthritis

Kineret is indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis (RA), in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs). Kineret can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF) blocking agents [see *Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Active Rheumatoid Arthritis

The recommended dose of Kineret for the treatment of patients with rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. Higher doses did not result in a higher response. The dose should be administered at approximately the same time every day.

2.2 Renal Impairment

Physicians should consider a dose of 100 mg of Kineret administered every other day for RA patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels) [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

2.3 Administration

Instructions on appropriate use should be given by the healthcare provider to the patient or caregiver. Patients or caregivers should not be allowed to administer Kineret until the patient or caregiver has demonstrated a thorough understanding of procedures and an ability to inject the product. After administration of Kineret, it is essential to follow the proper procedure for disposal of syringes and needles. See the "Information for Patients" insert for detailed instructions on the handling and injection of Kineret.

Do not use Kineret beyond the expiration date shown on the carton. Visually inspect the solution for particulate matter and discoloration before administration. There may be trace amounts of small, translucent-to-white amorphous particles of protein in the solution. The prefilled syringe should not be used if the solution is discolored or cloudy, or if foreign particulate matter is present. If the number of translucent-to-white amorphous particles in a given syringe appears excessive, do not use this syringe.

Administer only one dose (the entire contents of one prefilled glass syringe) per day. Discard any unused portions.

3 DOSAGE FORMS AND STRENGTHS

100 mg/0.67 mL solution for subcutaneous injection.

4 CONTRAINDICATIONS

Kineret is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, Kineret, or any components of the product [see section Hypersensitivity Reactions (5.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Kineret has been associated with an increased incidence of serious infections (2%) vs. Placebo (< 1%) in clinical trials. Administration of Kineret should be discontinued if a patient develops a serious infection. Treatment with Kineret should not be initiated in patients with active infections. The safety and efficacy of Kineret in immunosuppressed patients or in patients with chronic infections have not been evaluated.

5.2 Use With TNF Blocking Agents

In a 24-week study of concurrent Kineret and etanercept therapy, the rate of serious infections in the combination arm (7%) was higher than with etanercept alone (0%). The combination of Kineret and etanercept did not result in higher ACR response rates compared to etanercept alone [see *clinical studies (14)*]. Use of Kineret in combination with TNF blocking agents is not recommended.

5.3 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been reported with Kineret. If a severe hypersensitivity reaction occurs, administration of Kineret should be discontinued and appropriate therapy initiated.

The needle cover of the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

5.4 Immunosuppression

The impact of treatment with Kineret on active and/or chronic infections and the development of malignancies is not known [see *Adverse Reactions (6)*].

5.5 Immunizations

In a placebo-controlled clinical trial (n = 126), no difference was detected in anti-tetanus antibody response between the Kineret and placebo treatment groups when the tetanus/diphtheria toxoids vaccine was administered concurrently with Kineret. No data are available on the effects of vaccination with other inactivated antigens in patients receiving Kineret. No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving Kineret. Therefore, live vaccines should not be given concurrently with Kineret.

5.6 Neutrophil Count

Patients receiving Kineret may experience a decrease in neutrophil counts. In the placebo-controlled studies, 8% of patients receiving Kineret had decreases in neutrophil counts of at least one World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Nine Kineret-treated patients (0.4%) experienced neutropenia (ANC < 1 x 10⁹/L). This is discussed in more detail in the *Adverse Reactions (6): Hematologic Events* section. Neutrophil counts should be assessed prior to initiating Kineret treatment, and while receiving Kineret, monthly for 3 months, and thereafter quarterly for a period up to 1 year.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

The most serious adverse reactions were:

- Serious Infections – [see *Warnings and Precautions (5.1)*]
- Neutropenia, particularly when used in combination with TNF blocking agents

The most common adverse reaction with Kineret is injection-site reactions. These reactions were the most common reason for withdrawing from studies.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not predict the rates observed in a broader patient population in clinical practice.

The data described herein reflect exposure to Kineret in 3025 patients, including 2124 exposed for at least 6 months and 884 exposed for at least one year. Studies 1 and 4 used the recommended dose of 100 mg per day. The patients studied were representative of the general population of patients with rheumatoid arthritis.

Injection-site Reactions:

The most common and consistently reported treatment-related adverse event associated with Kineret is injection-site reaction (ISR). In Studies 1 and 4, 71% of patients developed an ISR, which was typically reported within the first 4 weeks of therapy. The majority of ISRs were reported as mild (72.6% mild, 24.1% moderate and 3.2% severe). The ISRs typically lasted for 14 to 28 days and were characterized by 1 or more of the following: erythema, ecchymosis, inflammation, and pain.

Infections:

In Studies 1 and 4 combined, the incidence of infection was 39% in the Kineret-treated patients and 37% in placebo-treated patients during the first 6 months of blinded treatment. The incidence of serious infections in Studies 1 and 4 was 2% in Kineret-treated patients and 1% in patients receiving placebo over 6 months. The incidence of serious infection over 1 year was 3% in Kineret-treated patients and 2% in patients receiving placebo. These infections consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections. Majority of patients (73%) continued on study drug after the infection resolved. No serious opportunistic infections were reported. Patients with asthma appeared to be at higher risk of developing serious infections when treated with Kineret (8 of 177 patients, 4.5%) compared to placebo (0 of 50 patients, 0%).

In open-label extension studies, the overall rate of serious infections was stable over time and comparable to that observed in controlled trials. In clinical studies and postmarketing experience, cases of opportunistic infections have been observed and included fungal, mycobacterial and bacterial pathogens. Infections have been noted in all organ systems and have been reported in patients receiving Kineret alone or in combination with immunosuppressive agents.

In patients who received both Kineret and 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.

Malignancies:

Among 5300 RA patients treated with Kineret in clinical trials for a mean of 15 months (approximately 6400 patient years of treatment), 8 lymphomas were observed for a rate of 0.12 cases/100 patient years. This is 3.6 fold higher than the rate of lymphomas expected in the general population, based on the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database.⁹ An increased rate of lymphoma, up to several fold, has been reported in the RA population, and may be further increased in patients with more severe disease activity. Thirty-seven malignancies other than lymphoma were observed. Of these, the most common were breast, respiratory system, and digestive system. There were 3 melanomas observed in Study 4 and its long-term open-label extension, greater than the 1 expected case. The significance of this finding is not known. While patients with RA, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the role of IL-1 blockers in the development of malignancy is not known.

Hematologic Events:

In placebo-controlled studies with Kineret, 8% of patients receiving Kineret had decreases in total white blood counts of at least one WHO toxicity grade, compared with 2% of placebo patients. Nine Kineret-treated patients (0.4%) developed neutropenia (ANC < 1 x 10⁹/L). 9 % of patients receiving Kineret had increases in eosinophil differential percentage of at least one WHO toxicity grade, compared with 3 % of placebo patients. Of patients treated concurrently with Kineret and etanercept 2% developed neutropenia (ANC < 1 x 10⁹/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy. 2% of patients receiving Kineret had decreases in platelets, all of WHO toxicity grade one, compared to 0% of placebo patients.

Hypersensitivity Reactions:

Hypersensitivity reactions including anaphylactic reactions, angioedema, urticaria, rash, and pruritus have been reported with Kineret.

Immunogenicity:

In Studies 1 and 4, from which data is available for up to 36 months, 49% of patients tested positively at one or more timepoints for anti-anakinra antibodies in a highly sensitive, anakinra-binding biosensor assay. Of the 1615 patients with available data at Week 12 or later, 30 (2%) were seropositive in a cell-based bioassay for antibodies capable of neutralizing the biologic effects of Kineret. Of the 13 patients with available follow-up data, 5 patients remained positive for neutralizing antibodies at the end of the studies. No correlation between antibody development and adverse events was observed.

Antibody assay results are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Kineret with the incidence of antibodies to other products may be misleading.

Other Adverse Events:

Table 1 reflects adverse events in Studies 1 and 4, that occurred with a frequency of ≥ 5% in Kineret-treated patients over a 6-month period.

Table 1: Percent of RA Patients Reporting Adverse Events (Studies 1 and 4)

Preferred term	Placebo (n = 733)	Kineret 100 mg/day (n = 1565)
Injection Site Reaction	29%	71%
Worsening of RA	29%	19%
Upper Respiratory Tract Infections	17%	14%
Headache	9%	12%
Nausea	7%	8%
Diarrhea	5%	7%
Sinusitis	7%	7%
Arthralgia	6%	6%
Flu Like Symptoms	6%	6%
Abdominal Pain	5%	5%

7 DRUG INTERACTIONS

No drug-drug interaction studies in human subjects have been conducted. Toxicologic and toxicokinetic studies in rats did not demonstrate any alterations in the clearance or toxicologic profile of either methotrexate or Kineret when the two agents were administered together.

TNF Blocking Agents: A higher rate of serious infections has been observed in patients treated with concurrent Kineret and etanercept therapy than in patients treated with etanercept alone [see *Warnings and Precautions (5.2)*]. Two percent of patients treated concurrently with Kineret and etanercept developed neutropenia (ANC < 1 x 10⁹/L). Use of Kineret in combination with TNF blocking agents is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B: Reproductive studies have been conducted with Kineret on rats and rabbits at doses up to 100 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Kineret should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether Kineret is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if Kineret is administered to nursing women.

8.4 Pediatric Use

Kineret was studied in a single randomized, blinded multi-center trial in 86 patients with polyarticular course Juvenile Rheumatoid Arthritis (JRA; ages 2-17 years) receiving a dose of 1 mg/kg subcutaneously daily, up to a maximum dose of 100 mg. The 50 patients who achieved a clinical response after a 12-week open-label run-in were randomized to Kineret (25 patients) or placebo (25 patients), administered daily for an additional 16 weeks. A subset of these patients continued open-label treatment with Kineret for up to 1 year in a companion extension study. An adverse event profile similar to that seen in adult RA patients was observed in these studies. These study data are insufficient to demonstrate efficacy and the prefilled syringes do not permit accurate dosing lower than 100 mg. Therefore, Kineret is not recommended for pediatric use.

8.5 Geriatric Use

A total of 752 patients \geq 65 years of age, including 163 patients \geq 75 years of age, were studied in clinical trials. No differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

8.6 Renal Impairment

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function [see *Clinical Pharmacology* (12.3)].

8.7 Hepatic Impairment

No formal studies have been conducted examining the pharmacokinetics of Kineret administered subcutaneously in rheumatoid arthritis patients with hepatic impairment.

10 OVERDOSAGE

There have been no cases of overdose reported with Kineret in clinical trials of RA. In sepsis trials no serious toxicities attributed to Kineret were seen when administered at mean calculated doses of up to 35 times those given patients with RA over a 72-hour treatment period.

11 DESCRIPTION

Kineret (anakinra) is a recombinant, nonglycosylated form of the human interleukin-1 receptor antagonist (IL-1Ra). Kineret differs from native human IL-1Ra in that it has the addition of a single methionine residue at its amino terminus. Kineret consists of 153 amino acids and has a molecular weight of 17.3 kilodaltons. It is produced by recombinant DNA technology using an *E coli* bacterial expression system.

Kineret is supplied in single use prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless-to-white, preservative free solution for daily subcutaneous (SC) administration. The solution may contain trace amounts of small, translucent-to-white amorphous proteinaceous particles. Each prefilled glass syringe contains: 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing disodium EDTA (0.12 mg), sodium chloride (5.48 mg), sodium citrate (1.29 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Kineret blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL 1R1)¹, which is expressed in a wide variety of tissues and organs.¹⁰

IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammatory and immunological responses.¹⁰ IL-1 has a broad range of activities including cartilage degradation by its induction of the rapid loss of proteoglycans, as well as stimulation of bone resorption.² The levels of the naturally occurring IL-1Ra in synovium and synovial fluid from RA patients are not sufficient to compete with the elevated amount of locally produced IL-1.^{3,4,5}

12.3 Pharmacokinetics

The absolute bioavailability of Kineret after a 70 mg subcutaneous bolus injection in healthy subjects (n = 11) is 95%. In subjects with RA, maximum plasma concentrations of Kineret occurred 3 to 7 hours after subcutaneous administration of Kineret at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of Kineret was observed after daily subcutaneous doses for up to 24 weeks.

The influence of demographic covariates on the pharmacokinetics of Kineret was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily subcutaneous injection of Kineret at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated Kineret clearance increased with increasing creatinine clearance and body weight. After adjusting for creatinine clearance and body weight, gender and age were not significant factors for mean plasma clearance.

Patients With Renal Impairment: The mean plasma clearance of Kineret in subjects with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal insufficiency was reduced by 16% and 50%, respectively. In severe renal insufficiency and end stage renal disease (creatinine clearance < 30 mL/min⁶), mean plasma clearance declined by 70% and 75%, respectively. Less than 2.5% of the administered dose of Kineret was removed by 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 [see *Dosage and Administration* (2.2)].

Patients With Hepatic Dysfunction: No formal studies have been conducted examining the pharmacokinetics of Kineret administered subcutaneously in rheumatoid arthritis patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Kineret has not been evaluated for its carcinogenic potential in animals. Using a standard in vivo and in vitro battery of mutagenesis assays, Kineret did not induce gene mutations in either bacteria or mammalian cells. In rats and rabbits, Kineret at doses of up to 100-fold greater than the human dose had no adverse effects on male or female fertility.

14 CLINICAL STUDIES

The safety and efficacy of Kineret have been evaluated in three randomized, double-blind, placebo-controlled trials of 1790 patients ≥ 18 years of age with active rheumatoid arthritis (RA). An additional fourth study was conducted to assess safety. In the efficacy trials, Kineret was studied in combination with other disease-modifying antirheumatic drugs (DMARDs) other than Tumor Necrosis Factor (TNF) blocking agents (Studies 1 and 2) or as a monotherapy (Study 3).

Study 1 involved 899 patients with active RA who had been on a stable dose of methotrexate (MTX) (10 to 25 mg/week) for at least 8 weeks. All patients had at least 6 swollen/painful and 9 tender joints and either a C-reactive protein (CRP) of ≥ 1.5 mg/dL or an erythrocyte sedimentation rate (ESR) of ≥ 28 mm/hr. Patients were randomized to Kineret or placebo in addition to their stable doses of MTX. The first 501 patients were evaluated for signs and symptoms of active RA. The total 899 patients were evaluated for progression of structural damage.

Study 2 evaluated 419 patients with active RA who had received MTX for at least 6 months including a stable dose (15 to 25 mg/week) for at least 3 consecutive months prior to enrollment. Patients were randomized to receive placebo or one of five doses of Kineret subcutaneous daily for 12 to 24 weeks in addition to their stable doses of MTX.

Study 3 evaluated 472 patients with active RA and had similar inclusion criteria to Study 1 except that these patients had received no DMARD for the previous 6 weeks or during the study.⁷ Patients were randomized to receive either Kineret or placebo. Patients were DMARD-naïve or had failed no more than 3 DMARDs.

Study 4 was a placebo-controlled, randomized trial designed to assess the safety of Kineret in 1414 patients receiving a variety of concurrent medications for their RA including some DMARD therapies, as well as patients who were DMARD-free. The TNF blocking agents etanercept and infliximab were specifically excluded. Concurrent DMARDs included MTX, sulfasalazine, hydroxychloroquine, gold, penicillamine, leflunomide, and azathioprine. Unlike Studies 1, 2 and 3, patients predisposed to infection due to a history of underlying disease such as pneumonia, asthma, controlled diabetes, and chronic obstructive pulmonary disease (COPD) were also enrolled [see [Adverse Reactions \(6\)](#)].

In Studies 1, 2 and 3, the improvement in signs and symptoms of RA was assessed using the American College of Rheumatology (ACR) response criteria (ACR₂₀, ACR₅₀, ACR₇₀). In these studies, patients treated with Kineret were more likely to achieve an ACR₂₀ or higher magnitude of response (ACR₅₀ and ACR₇₀) than patients treated with placebo (Table 2). The treatment response rates did not differ based on gender or ethnic group. The results of the ACR component scores in Study 1 are shown in [Table 3](#).

Most clinical responses, both in patients receiving placebo and patients receiving Kineret, occurred within 12 weeks of enrollment.

Table 2: Percent of Patients with ACR Responses in Studies 1 and 3

Response	Study 1 (Patients on MTX)		Study 3 (No DMARDs)		
	Placebo (n = 251)	Kineret 100 mg/day (n = 250)	Placebo (n = 119)	Kineret 75 mg/day (n = 115)	Kineret 150 mg/day (n = 115)
ACR ₂₀					
Month 3	24%	34% ^a	23%	33%	33%
Month 6	22%	38% ^c	27%	34%	43% ^a
ACR ₅₀					
Month 3	6%	13% ^b	5%	10%	8%
Month 6	8%	17% ^b	8%	11%	19% ^a
ACR ₇₀					
Month 3	0%	3% ^a	0%	0%	0%
Month 6	2%	6% ^a	1%	1%	1%

^a p < 0.05, Kineret versus placebo

^b p < 0.01, Kineret versus placebo

^c p < 0.001, Kineret versus placebo

Table 3: Median ACR Component Scores in Study 1

Parameter (median)	Placebo/MTX (n = 251)		Kineret/MTX 100 mg/day (n = 250)	
	Baseline	Month 6	Baseline	Month 6
Patient Reported Outcomes				
Disability index ^a	1.38	1.13	1.38	1.00
Patient global assessment ^b	51.0	41.0	51.0	29.0
Pain ^b	56.0	44.0	63.0	34.0
Objective Measures				
ESR (mm/hr)	35.0	32.0	36.0	19.0
CRP (mg/dL)	2.2	1.6	2.2	0.5
Physician's Assessments				
Tender/painful joints ^c	20.0	11.0	23.0	9.0
Physician global assessment ^b	59.0	31.0	59.0	26.0
Swollen joints ^d	18.0	10.5	17.0	9.0

^a Health Assessment Questionnaire; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

^b Visual analog scale; 0 = best, 100 = worst

^c Scale 0 to 68

^d Scale 0 to 66

A 24-week study was conducted in 242 patients with active RA on background methotrexate who were randomized to receive either etanercept alone or the combination of Kineret and etanercept. The ACR₅₀ response rate was 31% for patients treated with the combination of Kineret and etanercept and 41% for patients treated with etanercept alone, indicating no added clinical benefit of the combination over etanercept alone. Serious infections were increased with the combination compared to etanercept alone [see *Warnings and Precautions (5.1)*].

In Study 1, the effect of Kineret on the progression of structural damage was assessed by measuring the change from baseline at month 12 in the Total Modified Sharp Score (TSS) and its subcomponents, erosion score, and joint space narrowing (JSN) score.⁸ Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months and 12 months and scored by readers who were unaware of treatment group. A difference between placebo and Kineret for change in TSS, erosion score (ES) and JSN score was observed at 12 months (Table 4).

Table 4: Mean Radiographic Changes Over 12 Months in Study 1

	Placebo/MTX (N = 450)		Kineret 100 mg/day /MTX (N = 449)		Placebo/MTX vs. Kineret/MTX	
	Baseline	Change at Month 12	Baseline	Change at Month 12	95% Confidence Interval*	p-value**
TSS	52	2.6	50	1.7	0.9 [0.3, 1.6]	< 0.001
Erosion	28	1.6	25	1.1	0.5 [0.1, 1.0]	0.024
JSN	24	1.1	25	0.7	0.4 [0.1, 0.7]	< 0.001

* Differences and 95% confidence intervals for the differences in change scores between Placebo/MTX and Kineret/MTX

** Based on Wilcoxon rank-sum test

The disability index of the Health Assessment Questionnaire (HAQ) was administered monthly for the first six months and quarterly thereafter during Study 1. Health outcomes were assessed by the Short Form-36 (SF-36) questionnaire. The 1-year data on HAQ in Study 1 showed more improvement with Kineret than placebo. The physical component summary (PCS) score of the SF-36 also showed more improvement with Kineret than placebo but not the mental component summary (MCS).

15 REFERENCES

- Hannum CH, Wilcox CJ, Arend WP, et al. Interleukin-1 receptor antagonist activity of a human interleukin-1 inhibitor. *Nature*. 1990; 343:336-40.
- Van Lent PLEM, Fons AJ, Van De Loo AEM, et al. Major role for interleukin-1 but not for tumor necrosis factor in early cartilage damage in immune complex in mice. *J Rheumatol*. 1995; 22:2250-2258.
- Deleuran BW, Shu CQ, Field M, et al. Localization of interleukin-1 alpha, type 1 interleukin-1 receptor and interleukin-1 receptor antagonist in the synovial membrane and cartilage/pannus junction in rheumatoid arthritis. *Br J Rheumatol*. 1992; 31:801-809.
- Chomarat P, Vannier E, Dechanet J, et al. Balance of IL-1 receptor antagonist/IL-1B in rheumatoid synovium and its regulation by IL-4 and IL-10. *J Immunol*. 1995; 1432-1439.
- Firestein GS, Boyle DL, Yu C, et al. Synovial interleukin-1 receptor antagonist and interleukin-1 balance in rheumatoid arthritis. *Arthritis Rheum*. 1994; 37:644-652.
- Cockcroft DW and Gault HM. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41.
- Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum*. 1998; 41:2196-2204.
- Sharp JT, Young DY, Bluhm GB, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? *Arthritis Rheum*. 1985; 28:1326-1335.
- National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 11 Registries, 1992-1999.
- Dinarello CA. Biologic Basis for Interleukin-1 in Disease. *Blood* 1996; 87:2095-2147.

16 HOW SUPPLIED/STORAGE AND HANDLING

Kineret is supplied in single-use preservative free, prefilled glass syringes with 27 gauge needles. Each prefilled glass syringe contains 100 mg of anakinra per 0.67 mL. Kineret is dispensed in a 4 x 7 syringe dispensing pack containing 28 syringes (NDC 66658-234-28). Kineret is also dispensed in a 1 x 7 syringe dispensing pack containing 7 syringes (NDC 66658-234-07).

Storage

Kineret should be stored in the refrigerator at 2° to 8°C (36° to 46°F). **DO NOT FREEZE OR SHAKE.** Protect from light.

Rx only

17 PATIENT COUNSELING INFORMATION

Instruct patients and their caregivers on the proper dosage and administration of Kineret and provide all patients with the “Information for Patients” insert. While this “Information for Patients” insert provides information about the product and its use, it is not intended to take the place of regular discussions between the patient and healthcare provider.

Inform patients that Kineret may lower the ability of their immune system to fight infections. Advise patients of the importance of contacting their doctor if they develop any symptoms of infection. Inform patients about the signs and symptoms of allergic and other adverse drug reactions and the appropriate actions they should take if they experience any of these signs and symptoms. Inform patients and their caregivers that the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex. Thoroughly instruct patients and their caregivers on the importance of proper disposal and cautioned against the reuse of needles, syringes, and drug product. A puncture-resistant container for the disposal of used syringes should be available to the patient. The full container should be disposed of according to the directions provided by the healthcare provider.



Manufactured by:

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm, Sweden
U.S. License No. 1859

at
Amgen Manufacturing, Limited,
a subsidiary of Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

© Swedish Orphan Biovitrum AB (publ). All rights reserved.

Certain manufacturing operations have been performed by other firms.

The product, its production and/or its use may be covered by one or more US Patents, including US Patent Nos. 6,599,873, 6,858,409 and 5,075,222 as well as other patents or patents pending.

3XXXXXX – v13