Kineret®
(anakinra)

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. Each prefilled glass syringe contains: 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP.

CLINICAL PHARMACOLOGY

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

IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammatory and immunological responses. 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 rheumatoid arthritis (RA) patients are not sufficient to compete with the elevated amount of locally produced IL-1.[3,4,5]

Pharmacokinetics

The absolute bioavailability of Kineret® after a 70 mg SC bolus injection in healthy subjects (n = 11) is 95%. In subjects with RA, maximum plasma concentrations of Kineret® occurred 3 to 7 hours after SC 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 SC 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 SC 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/min[6]), 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**).

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

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® SC 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: Infections**).

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 (ACR_{20}, ACR_{50}, ACR_{70}). In these studies, patients treated with Kineret® were more likely to achieve an ACR_{20} or higher magnitude of response (ACR_{50} and ACR_{70}) than patients treated with placebo (Table 1). 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 2.

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

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

	Study 1 (Patients on MTX)		Study 3 (No DMARDs)		
		Kineret®		Kineret®	
Response	Placebo (n = 251)	100 mg/day (n = 250)	Placebo (n = 119)	75 mg/day (n = 115)	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 2: Median ACR Component Scores in Study 1

	Placebo/MTX (n = 251)		Kineret®/MTX 100 mg/day (n = 250)	
Parameter (median)	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 ACR_{50} 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**).

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 6 months and at 12 months (Table 3).

Table 3: 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).

INDICATIONS AND USAGE

Kineret® is indicated for the 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). Kineret® can be used alone or in combination with DMARDs other than Tumor Necrosis Factor (TNF) blocking agents (see **WARNINGS**).

CONTRAINDICATIONS

Kineret® is contraindicated in patients with known hypersensitivity to *E coli*-derived proteins, Kineret®, or any components of the product.

WARNINGS

KINERET® HAS BEEN ASSOCIATED WITH AN INCREASED INCIDENCE OF SERIOUS INFECTIONS (2%) VS. PLACEBO (< 1%). 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.

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). CONCURRENT THERAPY WITH KINERET® AND ETANERCEPT IS NOT RECOMMENDED.

PRECAUTIONS

General

Hypersensitivity reactions associated with Kineret® administration are rare. If a severe hypersensitivity reaction occurs, administration of Kineret® should be discontinued and appropriate therapy initiated.

Immunosuppression

The impact of treatment with Kineret® on active and/or chronic infections and the development of malignancies is not known (see **WARNINGS** and **ADVERSE REACTIONS: Infections and Malignancies**).

Immunizations

No data are available on the effects of vaccination in patients receiving Kineret®. Live vaccines should not be given concurrently with Kineret®. No data are available on the secondary transmission of infection by live vaccines in patients receiving Kineret® (see **PRECAUTIONS: Immunosuppression**). Since Kineret® interferes with normal immune response mechanisms to new antigens such as vaccines, vaccination may not be effective in patients receiving Kineret®.

Information for Patients

If a physician has determined that a patient can safely and effectively receive Kineret® at home, patients and their caregivers should be instructed on the proper dosage and administration of Kineret®. All patients should be provided 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.

Patients should be informed of the signs and symptoms of allergic and other adverse drug reactions and advised of appropriate actions. Patients and their caregivers should be thoroughly instructed in 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.

Laboratory Tests

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 1 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 10^9/L). This is discussed in more detail in the **ADVERSE REACTIONS: 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.

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. In a study in which patients with active RA were treated for up to 24 weeks with concurrent Kineret® and etanercept therapy, a 7% rate of serious infections was observed, which was higher than that observed with etanercept alone (0%) (see also **WARNINGS**). Two percent of patients treated concurrently with Kineret® and etanercept developed neutropenia (ANC < 1 x 10^9/L).

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.

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.

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.

Pediatric Use

The safety and efficacy of Kineret® in patients with juvenile rheumatoid arthritis (JRA) have not been established.

Geriatric Use

A total of 752 patients ≥ 65 years of age, including 163 patients ≥ 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.

ADVERSE REACTIONS

The most serious adverse reactions were:

- Serious Infections - see **WARNINGS**
- 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). The majority of ISRs were reported as mild. These typically lasted for 14 to 28 days and were characterized by 1 or more of the following: erythema, ecchymosis, inflammation, and pain. In studies 1 and 4, 71% of patients developed an ISR, which was typically reported within the first 4 weeks of therapy. The development of ISRs in patients who had not previously experienced ISRs was uncommon after the first month of therapy.

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, rather than unusual, opportunistic, fungal, or viral infections. Patients with asthma appeared to be at higher risk of developing serious infections; Kineret® 4% vs. placebo 0%. Most patients continued on study drug after the infection resolved.

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, rare 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®, treatment was associated with small reductions in the mean values for total white blood count, platelets, and absolute neutrophil count (ANC), and a small increase in the mean eosinophil differential percentage.

In all placebo-controlled studies, 8% of patients receiving Kineret® had decreases in ANC of at least 1 WHO toxicity grade, compared with 2% of placebo patients. Nine Kineret®-treated patients (0.4%) developed neutropenia (ANC $< 1 \times 10^9$/L). Two percent of patients treated concurrently with Kineret® and etanercept developed neutropenia (ANC $< 1 \times 10^9$/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

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 4 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 4: 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%
URI	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%

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.

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. Higher doses did not result in a higher response. The dose should be administered at approximately the same time every day.

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

CLINICAL PHARMACOLOGY, Pharmacokinetics: Patients with Renal Impairment.

Kineret® is provided in single-use prefilled glass syringes. The needle cover contains dry natural rubber (latex), which should not be handled by persons sensitive to this substance. 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. If particulates or discoloration are observed, the prefilled syringe should not be used.

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

HOW SUPPLIED

Kineret® is supplied in single-use preservative free, prefilled glass syringes with 27 gauge needles. Each prefilled glass syringe contains 0.67 mL (100 mg) of anakinra. Kineret® is dispensed in a 4 x 7 syringe dispensing pack containing 28 syringes (NDC 55513-177-28).

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

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