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

SERIOUS INFECTIONS

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.

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). USE OF KINERET® IN COMBINATION WITH TNF BLOCKING AGENTS 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. 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.

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

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® (see **PRECAUTIONS: Immunosuppression**). Therefore, live vaccines should not be given concurrently with 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. The patient should be informed 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. 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.

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 also **WARNINGS: Use with TNF Blocking Agents**). Two percent of patients treated concurrently with Kineret® and etanercept developed neutropenia (ANC < 1 x 10^9/L). Use of Kineret® in combination with TNF blocking agents is not recommended.

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

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. Pediatric use of Kineret® is 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.

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 when treated with Kineret® (8 of 177 patients, 4.5%) compared to placebo (0 of 50 patients, 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**.

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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Patient Information
Kineret® (KIN-eh-ret)
(anakinra)

Read the patient information that comes with Kineret® before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Kineret®?

Kineret® is a medicine that affects your immune system. Kineret® can lower the ability of your immune system to fight infections. Serious infections have happened in patients taking Kineret®. Taking Kineret® may give you a higher chance for getting an infection or make any infection you have worse.

Before starting Kineret®, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of infection such as fever, chills, or have any open sores on your body
- have asthma. Patients with asthma may have a higher chance of getting an infection if they take Kineret®.
- get a lot of infections or have infections that keep coming back
- take other medicines that affect your immune system

If you take other medicines that affect the immune system, such as ENBREL® (etanercept), Humira® (adalimumab), or Remicade® (infliximab) while you are taking Kineret®, you could also have an increased risk for getting a serious infection. It is recommended that you do not take these medications (Tumor Necrosis Factor or TNF blocking agents) while taking Kineret®.

What is Kineret®?

Kineret® is an interleukin-1 receptor antagonist (IL-1ra). Kineret® is used to reduce the signs and symptoms, and slow down damage that happens in patients with moderate to severe active Rhematoid Arthritis (RA), but it can also lead to serious side effects because of the affects on your immune system. See *"What is the most important information I should know about* Kineret®*?"* and *"What are the possible side effects with* Kineret®*?"*

Kineret® is only for adults who have taken other medicines for their RA that have not worked. Kineret® can be taken alone or along with other RA medicines except for TNF blocking agents.

Who should not take Kineret®?

Do not take Kineret® if you have an allergy to:

- proteins made from bacterial cells (*E coli*). Ask your healthcare provider if you are not sure.
- any of the ingredients in Kineret®. See the end of this leaflet for a complete list of ingredients in Kineret®.

What should I tell my healthcare provider before taking Kineret®?

Kineret® may not be right for you. Tell your healthcare provider about all of your medical conditions, including if you:

- **have an infection, a history of infections that keep coming back or other conditions that can increase your risk of infections.** See "What is the most important information I should know about Kineret®?"
- **have an allergy to rubber or latex. The needle cover on the prefilled syringe contains latex. Do not handle the needle cover if you are allergic to latex.**
- **have kidney problems**
- **are scheduled to receive any vaccines.** Patients taking Kineret®should not receive live vaccines.

Tell your healthcare provider if you are pregnant, plan to become pregnant, or breastfeeding. Kineret® has not been studied in pregnant or nursing women. Kineret® should be used during a pregnancy only if needed. It is not known if Kineret® will pass into your breast milk. Discuss treatment options with your doctor if you plan on breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Tell your healthcare provider if you take other medicines that affect your immune system.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new prescription.

How should I take Kineret®?

- Kineret® is taken by injection under the skin. Your healthcare provider should instruct you on how to inject, how often to inject Kineret®, and the correct way to dispose of used syringes.
- Take Kineret® exactly as your healthcare provider tells you to
- If you have a kidney problem your healthcare provider may need to change how often you take your Kineret® injections
- Inject Kineret® at about the same time each day, on a schedule that works best for you
- If you miss a dose of Kineret®, contact your healthcare provider to find out when to take your next injection
- Only you and your healthcare provider can determine how well Kineret® is working for you. The time it takes to see improvement in symptoms varies from person to person. In clinical studies, most patients saw their arthritis symptoms improve within 12 weeks of starting Kineret®.

What are the possible side effects of Kineret®?

Kineret® may cause serious side effects, including:

- **Serious Infections.** See "What is the most important information I should know about Kineret®."

  During treatment with Kineret®, call your healthcare provider right away if you get an infection, any sign of an infection including a fever, chills, or have any open sores on your body.

- **Blood problems.** Kineret® may cause certain white blood cells called neutrophils to decrease in number (neutropenia). Neutrophils are important in fighting infections. You will need to have blood tests before starting treatment with Kineret®, then monthly for three months. After the first three months you will be asked to have your blood tested every three months for up to one year.

The most common side effect with Kineret® is injection site reaction. These reactions may include redness, swelling, bruising, itching and stinging. Most injection site reactions are mild and last about 2 to 4 weeks.

Side effects that are rare include:

- **Malignancies.** Patients with rheumatoid arthritis (RA) may be at higher risk for lymphoma (a type of cancer).
- **Allergic reactions**. Allergic reactions rarely occur in patients taking Kineret®. If you develop a severe rash, swollen face or difficulty breathing while taking Kineret®, call your doctor right away or seek emergency care immediately. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of Kineret®. For more information, ask your healthcare provider or pharmacist.

How should I store Kineret®?

- Store Kineret® in its original carton in the refrigerator at 36°F to 46°F (2°C to 8°C)
- **DO NOT FREEZE OR SHAKE Kineret®**
- Keep Kineret® away from light
- When traveling, make sure you store Kineret® at the correct temperature
- Safely dispose of Kineret® that is out of date or no longer needed

Keep Kineret® and all medicines out of the reach of children.

General Information about Kineret®

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use Kineret® for a condition for which it was not prescribed. Do not give Kineret® to other people, even if they have the same symptoms that you have. It may harm them.

This patient information leaflet summarizes the most important information about Kineret®. If you would like more information about Kineret® talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about

Kineret® that is written for health professionals. For more information go to www.kineretrx.com or call **1-866-546-3738**.

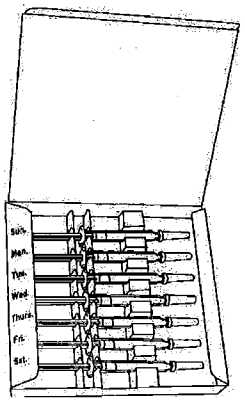
What are the ingredients in Kineret®?

Active ingredients: anakinra

Inactive ingredients: sodium citrate, sodium chloride, disodium EDTA, and polysorbate 80 in Water for Injection, USP

What do I need to know to prepare and give an injection of Kineret®?

Each Kineret® dose comes in a prefilled glass syringe. There are 7 syringes in each box, one for each day of the week. Use a new syringe each day. Use the Kineret® prefilled syringe that matches the day of the week until all 7 are used.



Use each Kineret® prefilled syringe only once. Be sure to inject all of the solution in the syringe. If you notice some solution remaining in the syringe, do not re-inject. You should discard the syringe with any remaining solution in the puncture-resistant container. (See "Disposal of Syringes and Supplies").

If you drop a syringe, **do not use the syringe**. This is for your safety in case the glass syringe is broken, or the needle is bent or dirty. Dispose of the syringe and replace it with a new one. Take the new syringe from what would be the last day of the week in your current box. For example, if you start on Wednesday, the last day of the week in your series is Tuesday. After using all the remaining syringes in your current box, start your next box.

Setting up for an Injection

1. Find a clean, flat work surface, such as a table.
2. Assemble the supplies needed for an injection:
   - One alcohol swab
   - A dry gauze or cotton-ball
   - Kineret® prefilled syringe
   - A puncture-resistant container

3. Take the carton containing the prefilled syringes of Kineret® out of the refrigerator. Remove the prefilled syringe from the box that matches the day of the week. Return the carton containing the remaining prefilled syringes back into the refrigerator.

4. Check the expiration date on the syringe label. If the expiration date has passed, do not use the syringe. Contact your pharmacist or call 1-866-Kineret (1-866-546-3738) for assistance.

5. Let the Kineret® solution warm to room temperature for 60 to 90 minutes prior to injection. **Do not remove the needle cover during this process.**

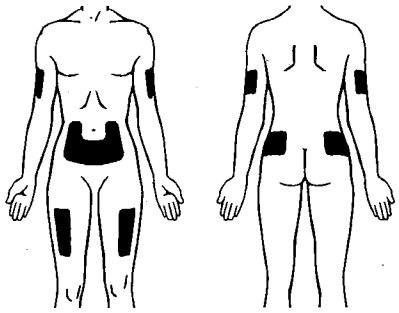
6. Do not shake the prefilled syringe. If the solution is foamy, allow the prefilled syringe to sit for a few minutes until it clears.

7. Do not use a prefilled syringe if the contents appear discolored or cloudy, or if there are any particles in the syringe. Call your healthcare provider or pharmacist if you have any questions about the way the solution looks.

8. Wash your hands with soap and warm water.

Selecting and preparing the injection site

1. Choose an injection site. Recommended injection sites include:
   - The outer area of the upper arms
   - The abdomen (except the two-inch area around the navel)
   - The front of the middle thighs
   - The upper outer areas of the buttocks

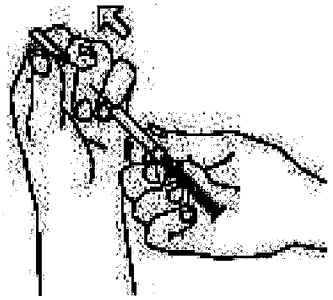


Choose a new site each time you use Kineret®. Choosing a new site can help avoid soreness at any one site. Do not inject Kineret® into an area that is tender, red, bruised, or hard. Avoid areas with scars or stretch marks. Do not inject close to a vein that you can see under the surface of your skin.

2. Clean the injection site with an alcohol swab. Let the area dry completely. Injecting through a site that is still moist from an alcohol swab may cause stinging.

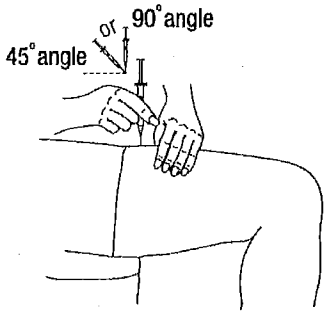
Administering the subcutaneous injection

1. Pick up the prefilled syringe from your flat work surface. Hold the syringe in the hand you will use to inject Kineret®. Remove the needle cover. Twisting the needle cover while pulling will help in the removal. Do not touch the needle or allow it to touch any surface. You may notice a small air bubble in the prefilled syringe. You do not have to remove the air bubble. Injecting the solution with the air bubble is harmless.



2. With your free hand, gently pinch a fold of skin at the cleaned injection site.

3. 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.



4. After the needle is inserted, gently let go of the skin. Pull the plunger back slightly. If no blood appears in the syringe, slowly push the plunger all the way down to inject Kineret®.

   If blood comes into the syringe, do not inject Kineret®, because the needle has entered a blood vessel. Withdraw the needle. Dispose of the used prefilled syringe in a puncture-resistant container. Prepare a new injection site and use a new prefilled syringe.

5. When the syringe is empty, pull the needle out of the skin, being careful to keep it at the same angle as inserted.

6. Place a cotton ball or gauze over the injection site and press for several seconds. Do not use an alcohol swab as it may cause stinging. If there is a little bleeding, you may cover the injection site with a small bandage.

Disposal of the syringe and supplies

- The syringes should **NEVER** be reused. **NEVER** recap a needle.

- Place the used syringe in a puncture-resistant container. A coffee can with a plastic lid or a hard plastic container with a screw-on top may be used. Puncture-resistant containers can also be purchased at your local pharmacy.

- Talk to your healthcare provider or pharmacist about how to properly dispose of your used syringes. There may be special local and state laws for disposing of used needles and syringes. **Do not throw the disposal container in the household trash. Do not recycle.**

- The needle cover, alcohol swabs, and other used supplies can be placed in the trash.

- Always keep all syringes, injection supplies, and disposal containers out of the reach of children.

AMGEN®

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