CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

APPLICATION NUMBER:

103950/0

APPROVED LABELING

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 1 mL prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless-to-white, preservative-free solution for daily subcutaneous (SC) administration. Each 1 mL 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 anakinra 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™ decreased 70-75% in normal subjects with severe or end stage renal disease (defined as creatinine clearance less than 30 mL/minute, as estimated from serum creatinine levels[6]). No formal studies have been conducted examining the pharmacokinetics of Kineret™ administered subcutaneously in rheumatoid arthritis patients with renal impairment.

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 1392 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) (studies 1 and 2) or as a monotherapy (study 3).

Study 1 evaluated 501 patients with active RA who had been on a stable dose of methotrexate (MTX) (10 to 25 mg/week) for at least 8 weeks. In addition, they 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.

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, hydrochloroquine, 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 all three 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)		
Response	Placebo (n=251)	Kineret™ 100 mg/day (n=250)	Placebo (n=119)	Kineret™ 75 mg/day (n=115)	Kineret™ 150mg/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

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[a] $p<0.05$, Kineret™ versus placebo
[b] $p<0.01$, Kineret™ versus placebo
[c] $p<0.001$, Kineret™ versus placebo

Table 2. Effect of Kineret on Median ACR Component Scores in Study 1

Parameter (median)	Placebo/MTX (N = 251) Baseline	Placebo/MTX (N = 251) Month 6	Kineret™/MTX 100 mg/day (N = 250) Baseline	Kineret™/MTX 100 mg/day (N = 250) 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

INDICATIONS AND USAGE

Kineret™ is indicated for the reduction in signs and symptoms of 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. THE SAFETY OF KINERET™ USED IN COMBINATION WITH TNF BLOCKING AGENTS HAS NOT BEEN ESTABLISHED. PRELIMINARY DATA SUGGEST A HIGHER RATE OF SERIOUS INFECTIONS (7%, 4/58) WHEN KINERET™ AND ETANERCEPT ARE USED IN COMBINATION COMPARED WITH WHEN KINERET™ IS USED ALONE. IN THIS COMBINATION STUDY NEUTROPENIA (NEUTROPHIL COUNT $\leq$ 1000/mm^3) WAS OBSERVED IN 3% OF PATIENTS (2/58). USE OF KINERET™ WITH TNF BLOCKING AGENTS SHOULD ONLY BE DONE WITH EXTREME CAUTION AND WHEN NO SATISFACTORY ALTERNATIVES EXIST.

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, 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 and Caregivers" insert. While this "Information for Patients and Caregivers" 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 professional.

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. Six Kineret™-treated patients (0.3%) experienced neutropenia (ANC $\leq 1 \times 10^9$/L). This is discussed in more detail in the Adverse Events-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.

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 653 patients ≥ 65 years of age, including 135 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 – see **WARNINGS**

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 2606 patients, including 1812 exposed for at least 6 months and 570 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 40% in the Kineret™ -treated patients and 35% in placebo-treated patients. The incidence of serious infections in studies 1 and 4 was 1.8% in Kineret™-treated patients and 0.6% in placebo-treated patients over 6 months. 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™ 5% versus placebo <1%. Most patients continued on study drug after the infection resolved. There were no on-study deaths due to serious infectious episodes in either study.

In a study in which patients were receiving both etanercept and Kineret™ for up to 24 weeks, the incidence of serious infections was 7%. These infections consisted of bacterial pneumonia (2 cases) and cellulitis (2 cases), which recovered with antibiotic treatment.

Malignancies

Twenty-one malignancies of various types were observed in 2531 RA patients treated in clinical trials with Kineret™ for up to 50 months. The observed rates and incidences were similar to those expected for the population studied.

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 blood 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. Six Kineret™-treated patients (0.3%) developed neutropenia (ANC $\leq 1 \times 10^9$/L). Additional patients treated with Kineret™ plus etanercept (2/58, 3%) developed ANC $\leq 1 \times 10^9$/L. While neutropenic, one patient developed cellulitis and the other patient developed pneumonia. Both patients recovered with antibiotic therapy.

Immunogenicity

In Study 4, 28% of patients tested positively for anti-Kineret™ antibodies at month 6 in a highly sensitive, Kineret™-binding biosensor assay. Of the 1274 subjects with available data, <1% (n = 9) were seropositive in a cell-based bioassay for antibodies capable of neutralizing the biologic effects of Kineret™. None of these 9 subjects were positive for neutralizing antibodies at more than 1 time point, and all of these subjects were negative for neutralizing antibodies by 9 months. No correlation between antibody development and clinical response or adverse events was observed. The long-term immunogenicity of Kineret™ is unknown.

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 3 reflects adverse events in Studies 1 and 4, that occurred with a frequency of ≥ 5% and a higher frequency in Kineret™-treated patients.

Table 3. Percent of RA Patients Reporting Adverse Events (Studies 1 and 4)

Preferred Term	Placebo (N = 534)	Kineret™ 100 mg/day (N = 1366)
Injection Site Reaction	28 %	71 %
Infection	35 %	40 %
URI	13 %	13 %
Sinusitis	4 %	6 %
Influenza-Like Symptoms	4 %	5 %
Other	23 %	26 %
Headache	9 %	12 %
Nausea	6 %	8 %
Diarrhea	5 %	7 %
Sinusitis	6 %	7 %
Influenza-Like Symptoms	5 %	6 %
Pain Abdominal	4 %	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. Kineret™ is provided in single-use 1 mL prefilled glass syringes. Instructions on appropriate use should be given by the health care professional to the patient or care provider. Patients or care providers should not be allowed to administer Kineret™ until he/she 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 and Caregivers" leaflet for detailed instructions on the handling and injection of Kineret™.

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 1 dose (the entire contents of 1 prefilled glass syringe) per day. Discard any unused portions; Kineret™ contains no preservative. Do not save unused drug for later administration.

HOW SUPPLIED

Kineret™ is supplied in single-use preservative free, 1 mL prefilled glass syringes with 27 gauge needles. Each prefilled glass syringe contains 0.67 mL (100 mg) of anakinra. Kineret™ is dispensed in packs containing 7 syringes. It is also available in a 4x7 syringe dispensing pack (28 syringes). The NDC number for Kineret™ is 55513-177-07.

Storage

Do not use Kineret™ beyond the expiration date shown on the carton. Kineret™ should be stored in the refrigerator at 2° to 8°C (36° to 46°F). **DO NOT FREEZE OR SHAKE.** Protect from light.

References

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7. 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.

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Issue Date: XX/XX/XXXX

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Information for Patients and Caregivers

This patient package insert contains information and directions for patients and their caregivers on self-injection of Kineret™. This insert does not include all information about Kineret™. You should discuss any questions about treatment with Kineret™ with your doctor.

What is Kineret™?

Kineret™ is a medicine that is used to reduce the pain and swelling associated with moderate to severe active rheumatoid arthritis.

How does Kineret™ work?

Kineret™ is a man-made protein that is similar to a naturally occurring protein called interleukin-1 receptor antagonist (IL-1ra) found in the body. In people with rheumatoid arthritis (RA), the body produces too much of certain proteins that lead to joint damage. One of these proteins is called Interleukin-1 (IL-1). Too much IL-1 contributes to the pain, swelling, and stiffness associated with RA. Kineret can block the action of IL-1.

Only you and your doctor 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, some patients saw their arthritis symptoms improve in about 4 weeks after starting Kineret treatment.

Who should not use Kineret™?

You should not use Kineret if you have an infection that requires treatment with prescription antibiotics or an infection that is serious enough for you to be admitted to the hospital.

You should not use Kineret if you have an allergy to proteins made from bacteria cells (*E. coli*), or any of the ingredients in Kineret™.

You should not use Kineret if you are taking Enbrel (etanercept) or Remicade (infliximab) unless your doctor has told you to. When Kineret is used with Enbrel or Remicade you may increase your risk of getting a serious infection.

What important information do I need to know about taking Kineret™ ?

Patients taking Kineret have a greater chance of developing a serious infection. If you have an infection, tell your doctor **before** you start taking Kineret. If you get an infection that does not go away while taking Kineret, tell your doctor right away.

If you have asthma you could be at increased risk for getting a serious infection.

If you are using Enbrel (etanercept) or Remicade (infliximab) under your doctor's orders, you could also be at greater risk for getting a serious infection.

Kineret may cause the number of one type of white blood cell to decrease. 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 checked every three months for up to one year.

What are other possible side effects of Kineret™ ?

Most people have a reaction at the site where Kineret is injected. These reactions include redness, swelling, bruising, itching and/or stinging. Most of the time the reactions are mild and last about 2-4 weeks (see section titled "**Helpful hints**" for how to manage some of these effects)

The Kineret™ needle cover contains latex. If you know you are allergic to latex, talk to your doctor before using Kineret™.

If you experience any side effects that concern you, or if you develop an infection call your doctor.

Can I use Kineret™ if I am pregnant or breast-feeding?

Kineret™ has not been studied in pregnant women or nursing mothers. If you are pregnant or breast feeding, talk to your doctor before using Kineret™.

How should I store Kineret™ ?

Store Kineret™ in the refrigerator 36° to 46° F (2° to 8° C) until you are ready to prepare your injection. Do not freeze. Do not use a syringe that has been left at room temperature for longer than 24 hours.

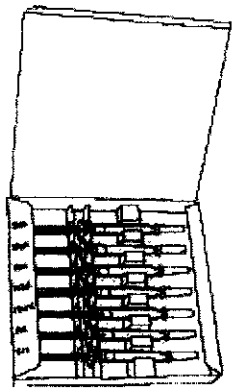
If you are traveling, make sure you store Kineret™ at the correct temperature. For a complimentary travel cooler, call toll free: 1-866-Kineret. If you have questions, consult with your doctor or pharmacist.

How do I use Kineret™ ?

Your doctor should have instructed you on how to inject Kineret™, how often it should be injected, and the proper disposal method for used Kineret™ syringes.

Kineret™ should be administered once every 24 hours. Try to inject Kineret™ at the same time each day on a schedule that works best for you.

Each Kineret™ dose comes in a 1 mL prefilled glass syringe. There are 7 syringes in each box, one for each of the 7 days 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, and 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 proof container.

Dispose of the syringe as instructed under the **Disposal of syringe and supplies** section.

If you drop a syringe, **do not use the syringe.** This is for your safety in case the 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.

What do I need to know to prepare and give a Kineret™ injection?

Preparing for injection

1. Assemble the supplies needed for injection:
   - alcohol wipe,
   - dry gauze or cotton-ball,
   - small adhesive bandage, (Tip: open adhesive bandage prior to injection).
   - Kineret™ syringe, and
   - a puncture-resistant container for disposing your used syringes.

2. Remove the prefilled syringe from the box that matches the day of the week. Place all of the remaining syringes back in the refrigerator.

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

4. Check the expiration date printed on the syringe label. If the syringe has expired, call your pharmacist for instructions.

5. Do not use Kineret™ if the contents of the prefilled syringe appear discolored or cloudy, or if there is anything floating in it. Call your doctor or pharmacist if you have any questions about the way the solution looks.

Selecting and preparing the injection site

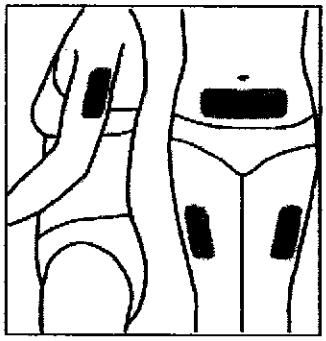
6. Wash your hands thoroughly with soap and warm water.

7. Choose an area of the body for the injection. Recommended injection sites include the following:

- Outer thighs
- Stomach

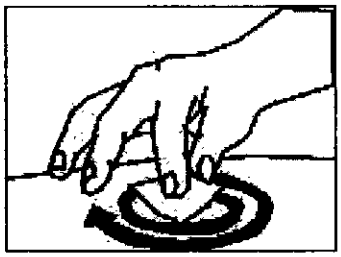
If someone is giving you an injection you can also use:

- Back of arms
- Buttocks



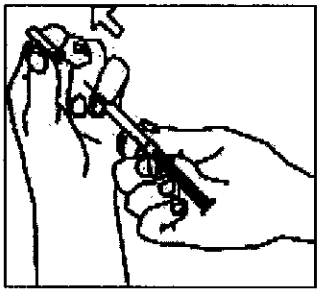
It is important to change the injection site each time you use Kineret™ to reduce the possibility of soreness or redness. While you do not have to change the area of the body for the injection each day, the new injection should be given at least 1 inch from the previous day's injection site. Do not to inject yourself close to a vein that you can see under the surface of your skin.

8. Clean the injection site with an alcohol wipe using a circular motion, starting from the middle and going out. Let the area dry completely.

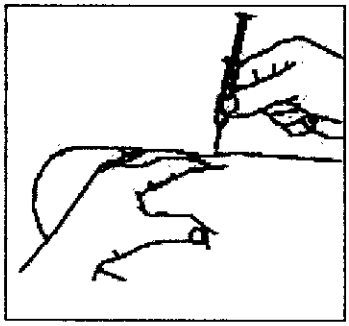


Administering the subcutaneous injection

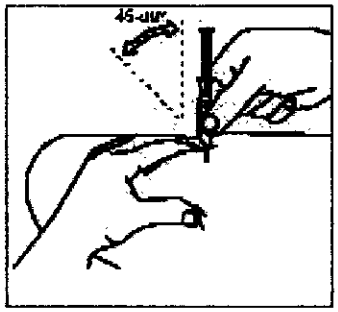
9. Hold the syringe and pull the needle cover off. Twisting the needle cover while pulling will help in the removal. Do not touch the needle. You may notice a small air bubble in the prefilled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.



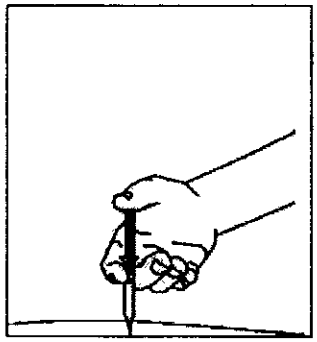
10. Hold the syringe in the hand you use to inject yourself. If possible, use your other hand to pinch a fold of skin at the clean injection site. Do not lay the syringe down or allow the needle to touch anything.



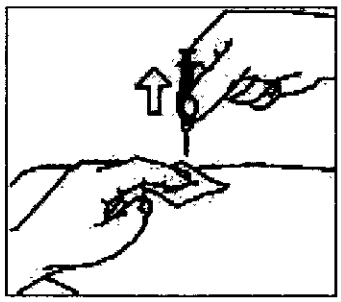
11. Hold the syringe firmly between your thumb and fingers so that you have steady control. Insert the needle into the skin with a quick, short motion at a 45 to 90 degree angle. The needle should be inserted at least half way.



12. After the needle is inserted, you can gently let go of the skin. Be sure the needle remains in your skin. Slowly push the plunger down into the syringe until it stops.



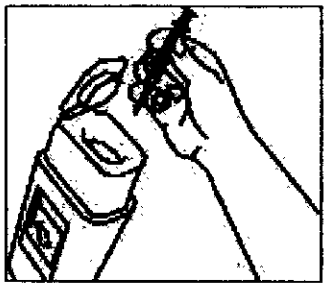
13. Remove the needle and do not re-cap it. Press dry gauze over the injection site. (Do not use an alcohol wipe).



14. You may want to apply a small adhesive bandage over the injection site.

Disposal of the syringe and supplies

15. Place the entire used syringe in a puncture-resistant container. A coffee can with a plastic lid, a hard plastic container with a screw-on top may be used, or puncture resistant containers, like a Home Sharps Container, can be purchased at your local pharmacy.



Talk to your doctor, nurse, or pharmacist, about how to properly dispose a filled container of your used syringes. There may be special local and state laws for disposing used needles and syringes. **Do not throw the filled container in the household trash and do not recycle.**

The needle cover, alcohol wipes, and other used supplies can be thrown out with your regular trash.

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

Helpful hints

Problem	Solution
Swelling or bruising at injection site	Apply cold pack on injection site immediately after injection.
Itching at injection site	Talk to your doctor.
Pain during and/or after injection	Try different injection locations. The stomach might be the best site due to the low number of nerve cells. Let the Kineret™ solution warm to room temperature prior to injection. This usually takes about 60-90 minutes at room temperature. Apply a cold pack on the injection site a few minutes prior to your injection. Allow the injection site to dry before injecting Kineret™; injecting through a site that is still moist from an alcohol wipe may cause stinging. Wiping the injection site with an alcohol wipe after you inject Kineret™ is not necessary and may cause stinging.
Remembering to take medication	Try to inject Kineret™ at the same time each day. Schedule your Kineret™ injections with another task you do each day, such as getting dressed in the morning.
Difficulty with self-injection	Medical devices are available that are designed to help you with self-injections. Ask your doctor or nurse for more information about them, or call toll-free: 1-866-Kineret.

To build a good understanding about your therapy with Kineret™, call the Kineret Customer Call Center weekdays from 8:00 a.m. to 11:00 p. m. EST. On weekends, you can leave a message and someone will call you back shortly.

You can:

- Talk to a nurse about Kineret™ or issues related to self-injection
- Speak with a reimbursement counselor about your insurance coverage

Kineret Customer Call Center: Call toll-free at 1-866-Kineret (1-866-546-3738)

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