

PRODUCT MONOGRAPH

Pr Kineret®

anakinra

150 mg/mL Solution for Injection in a Prefilled Syringe, 100 mg per syringe

Subcutaneous Injection

Pharmaceutical Standard: Professed

Immunomodulatory Agent

Manufactured by:  
Amgen Manufacturing, Limited, a subsidiary of Amgen Inc.  
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Distributed by:  
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# KINERET<sup>®</sup>

anakinra

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Subcutaneous Injection (SC)	Sterile solution for injection in a prefilled syringe/ 0.67 mL of 150 mg/mL solution (100 mg per syringe)	Not Applicable  <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

### DESCRIPTION

KINERET<sup>®</sup> (anakinra) is a recombinant, non-glycosylated version of the human interleukin-1 receptor antagonist (IL-1Ra) and is identical to the natural non-glycosylated form of human IL-1Ra, except for the addition of a single methionine residue at the N-terminus. The recombinant protein consists of 153 amino acids with a molecular weight of 17.3 kilodaltons. KINERET<sup>®</sup> is produced using an *Escherichia coli* (*E. coli*) bacterial expression system.

### INDICATIONS AND CLINICAL USE

KINERET<sup>®</sup> (anakinra) is indicated for:

- reducing the signs and symptoms of active rheumatoid arthritis in patients 18 years of age or older.
- inhibiting the progression of structural damage by reducing erosions and cartilage degradation in patients with active rheumatoid arthritis despite treatment with stable doses of methotrexate (MTX).

KINERET<sup>®</sup> can be used alone or in combination with other disease-modifying antirheumatic drugs (DMARDs), particularly MTX.

#### **Geriatrics (>65 years of age):**

In the pivotal controlled trials, 752 patients 65 years of age or older were enrolled. No differences in safety or efficacy were observed between these patients and younger patients.

#### **Pediatrics (< 18 years of age):**

The safety and efficacy of KINERET<sup>®</sup> in these patients have not been established.

## **CONTRAINDICATIONS**

KINERET<sup>®</sup> (anakinra) is contraindicated in patients with known hypersensitivity to *E.coli*-derived proteins, KINERET<sup>®</sup>, or any components of the product. For a complete listing of components, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

## **WARNINGS AND PRECAUTIONS**

### **Serious Infections**

KINERET<sup>®</sup> (ANAKINRA) HAS BEEN ASSOCIATED WITH AN INCREASED INCIDENCE OF SERIOUS INFECTIONS (1.7%) vs. PLACEBO (1.0%). ADMINISTRATION OF KINERET<sup>®</sup> SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION. TREATMENT WITH KINERET<sup>®</sup> SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS. THE SAFETY AND EFFICACY OF KINERET<sup>®</sup> IN IMMUNOSUPPRESSED PATIENTS OR IN PATIENTS WITH CHRONIC INFECTIONS HAVE NOT BEEN EVALUATED.

### **Use with other TNF Blocking Agents**

CONCURRENT INTRODUCTION OF KINERET<sup>®</sup> AND ETANERCEPT THERAPIES HAS NOT BEEN ASSOCIATED WITH INCREASED CLINICAL BENEFIT TO PATIENTS AND HAS RESULTED IN AN INCREASED RATE OF SERIOUS INFECTIONS. IN TWO STUDIES WHERE PATIENTS RECEIVED CONCURRENT ETANERCEPT AND KINERET<sup>®</sup> THERAPY FOR UP TO 24 WEEKS, A 7% RATE OF SERIOUS INFECTIONS WAS OBSERVED. SIMILAR EFFECTS HAVE BEEN OBSERVED WITH A SECOND INVESTIGATIONAL TNF BLOCKING AGENT. BASED ON THESE DATA, USE OF KINERET<sup>®</sup> IN COMBINATION WITH TNF BLOCKING AGENTS IS NOT RECOMMENDED.

### **General**

Allergic reactions associated with administration of KINERET<sup>®</sup> during clinical trials have been reported infrequently. If a severe allergic reaction occurs, administration of KINERET<sup>®</sup> 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.

Efficacy studies with DMARDs, other than methotrexate, have not been conducted.

## **Carcinogenesis, Mutagenesis and Impairment of Fertility**

The carcinogenic potential of KINERET<sup>®</sup> has not been fully evaluated. KINERET<sup>®</sup> failed to induce bacterial or mammalian cell gene mutations in a standard battery of tests. Similarly, KINERET<sup>®</sup> did not increase the incidence of chromosomal abnormalities or micronuclei in bone marrow or peripheral blood erythrocytes in mice. KINERET<sup>®</sup> had no observed effect on the fertility, early development, embryo-fetal development, or peri- and postnatal development in the rat at doses up to 100 times the human dose. No effects on embryo-fetal development in the rabbit were observed at doses 100 times the human dose.

## **Immune**

### **Immunosuppression:**

The impact of treatment with KINERET<sup>®</sup> on active and/or chronic infections and the development of malignancies are not known. (See WARNINGS AND PRECAUTIONS/ Serious Infections, and ADVERSE REACTIONS, Infections and Malignancies)

### **Immunizations:**

No data are available on the effects of vaccination in patients receiving KINERET<sup>®</sup>. Live vaccines should not be given concurrently with KINERET<sup>®</sup>. No data are available on the secondary transmission of infection by live vaccines.

## **Special Populations**

### **Pregnant Women:**

There are no adequate and well-controlled studies in pregnant women. KINERET<sup>®</sup> should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive studies have been conducted with KINERET<sup>®</sup> in rats and rabbits at doses up to 100 times the human dose and have revealed no evidence of harm to the fetus. Because animal reproduction studies are not always predictive of human response, KINERET<sup>®</sup> should be used during pregnancy only if medically necessary.

### **Nursing Women:**

It is not known whether KINERET<sup>®</sup> is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised if KINERET<sup>®</sup> is administered to a nursing woman.

### **Pediatrics (<18 years of age):**

Pediatric use of KINERET<sup>®</sup> is not recommended. The safety and efficacy have not been established in the limited data available in patients with juvenile rheumatoid arthritis. The prefilled syringes do not permit accurate dosing lower than 100 mg.

**Geriatrics (>65 years of age):**

In the pivotal controlled trials, 752 patients 65 years of age or older were enrolled. No differences in safety or efficacy were observed between these patients and younger patients.

Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

**Renally Impaired Patients:**

KINERET<sup>®</sup> is known to be substantially excreted by the kidney. The mean plasma clearance of KINERET<sup>®</sup> decreased 70-75% in subjects with severe or end stage renal disease (defined as creatine clearance less than 30 mL/minute). Patients with renal impairment should be carefully evaluated before initiating therapy. A dose schedule change may be considered for subjects with severe renal insufficiency or end stage renal disease (see DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions).

**Hepatically Impaired Patients:**

No formal studies have been conducted examining the pharmacokinetics of KINERET<sup>®</sup> administered subcutaneously in RA patients with hepatic impairment.

**Asthmatic Patients:**

In cumulative experience across clinical trials with anakinra, the incidence of serious infections in a small subset of RA patients with asthma was higher (4.5%) in patients treated with anakinra than those treated with placebo (0.0%).

**Monitoring and Laboratory Tests**

Patients receiving KINERET<sup>®</sup> may experience a decrease in neutrophils counts. In placebo-controlled studies, 9 KINERET<sup>®</sup>-treated patients (0.4%) experienced neutropenia [absolute neutrophil count (ANC) <1 x 10<sup>9</sup>/L]. None of these patients had serious infections associated with the neutropenia. KINERET<sup>®</sup> treatment should not be initiated in patients with neutropenia (ANC <1 x 10<sup>9</sup>/L). Neutrophil counts should be assessed prior to initiating KINERET<sup>®</sup> treatment, and quarterly while receiving KINERET<sup>®</sup> for a period up to 1 year.

**ADVERSE REACTIONS****Adverse Drug Reaction Overview**

KINERET<sup>®</sup> (anakinra) has been used in studies enrolling over 3000 patients with RA and in studies enrolling over 1400 patients with other diseases. The data described herein reflect exposure to KINERET<sup>®</sup> in 2805 patients including 1958 exposed for at least 6 months and 884 exposed for at least 1 year. The most common and consistently reported treatment related adverse events were injection site reactions (ISRs). With the exception of ISRs, there appears to be no difference in the

proportion of patients who discontinued treatment because of adverse events in the KINERET<sup>®</sup> groups and the placebo group.

### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Adverse events reported in at least 5% of patients treated with KINERET<sup>®</sup> in the pivotal clinical trials that used the 100 mg/day dose over a 6-month period are shown in Table 1.

**Table 1: Summary of Adverse Events Reported in  $\geq 5\%$  of KINERET<sup>®</sup>-treated Patients in Pivotal Placebo-controlled Clinical Trials Conducted at the 100 mg/day Dose**

	Placebo-treated Patients (%) N = 733	KINERET <sup>®</sup> -treated Patients (%) N = 1565
Injection Site Reactions	28.5	70.8
Exacerbation of RA	28.9	19.3
Upper Respiratory Infection	16.6	13.8
Headache	9.0	11.6
Nausea	6.7	8.4
Diarrhea	5.2	6.9
Sinusitis	6.7	6.9
Influenza-like Symptoms	5.5	5.9
Arthralgia	6.4	5.9
Abdominal Pain	4.8	5.2

### **Injection-Site Reactions**

Injection-site reactions (ISRs) were the most common adverse events associated with KINERET<sup>®</sup> therapy. ISRs were typically described as mild to moderate with the most frequently reported symptoms of ISRs being erythema, pruritus, rash, and pain. In the pivotal studies, the incidence of ISRs among the higher anakinra dose groups was approximately 60% to 80%.

ISRs were typically reported within the first 4 weeks after initiation of therapy and lasted for 14 to 28 days (first ISR encountered to last ISR resolved). The development of ISRs in patients who had not previously experienced ISRs were uncommon after the first month of therapy. The overall withdrawal rate due to ISRs across the pivotal studies was 6%.

The occurrence of severe ISRs was infrequent. ISRs were typically treated with topical corticosteroids or antihistamines, or less frequently with oral corticosteroids.

### **Infections**

An increased susceptibility to infection is a potential safety issue with chronic administration of agents that alter cytokine responses. Upper respiratory infections, sinusitis, influenza-like symptoms, urinary tract infections, and bronchitis were the most frequently reported infections and occurred at similar rates in patients receiving KINERET<sup>®</sup> or placebo.

The incidence of serious infections in the pivotal studies combined was 1.7% in KINERET<sup>®</sup>-treated patients and 1.0% in placebo-treated patients. The infections consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections. There were no reports of unusual opportunistic, fungal or viral infections. In cumulative experience across clinical trials with anakinra, the incidence of serious infections in a small subset of RA patients with asthma was higher (4.5%) in patients treated with anakinra than those treated with placebo (0.0%). Most patients continued on study drug after the infections resolved. There were no on-study deaths due to serious infectious episodes. Of note, previous studies in subjects with sepsis demonstrated no worsening of patient outcomes with KINERET<sup>®</sup> as compared with placebo.

In open-label extension studies the overall rate of serious infections was stable over time and comparable to that observed in controlled studies. In clinical studies and post marketing experience, rare cases of opportunistic infections have been observed and included fungal, mycobacterial, bacterial and viral pathogens. Infections have been noted in all organ systems and have been reported in patients receiving KINERET<sup>®</sup> alone or in combination with immunosuppressive agents.

### **Malignancies**

RA patients may be at higher risk (up to several fold) for the development of lymphoma. An increased rate of up to several fold has been reported in the RA population, and may be further increased in patients with more severe disease activity. In clinical trials, RA patients treated with KINERET<sup>®</sup> had an incidence of lymphoma that was higher than the rate expected in the general population based on the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database.<sup>1</sup> 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.

Malignancies of various types were observed at a rate similar to the rate expected for the general population.

It is unknown if chronic exposure to KINERET<sup>®</sup> can increase the incidence of malignancies. The overall incidence of malignancies has not increased with extended exposure to KINERET<sup>®</sup>.

### **Laboratory Tests**

In pivotal placebo-controlled studies of KINERET<sup>®</sup>, treatment was associated with small reductions in the mean values for total white blood cell count, absolute neutrophil count, alkaline phosphatase, and a small increase in the mean eosinophil differential percentage. There was no dose-response relationship for any of these changes. These findings were not associated with adverse clinical consequences.

In all placebo-controlled studies 8% of patients receiving KINERET<sup>®</sup> had decreases in ANC of at least 1 World Health Organization toxicity grade, compared with 2% of placebo patients. Nine KINERET<sup>®</sup>-treated patients (0.4%) developed neutropenia (ANC <1 x 10<sup>9</sup>/L). None of these patients had serious infections associated with the neutropenia.

### **Antibodies**

In the large pivotal studies conducted using the 100 mg/day dose, serum samples were obtained for antibody testing. In studies from which data is available for up to 36 months, between 50 and 60% of patients tested positively at one or more timepoints for anti-anakinra antibodies-in a highly sensitive, anakinra-binding biosensor assay. Up to 3% of patients tested seropositive at least once during the study for antibodies capable of neutralizing the biologic effects of anakinra. The occurrence of antibodies was typically transient and not associated with clinical adverse reactions or diminished efficacy.

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 samples handling, concomitant medications, and underlying disease. For these reasons comparison of the incidence of antibodies to KINERET<sup>®</sup> with the incidence of antibodies to other products may be misleading.

## **DRUG INTERACTIONS**

No formal studies have been done in humans to evaluate possible drug interactions.

A formal toxicologic and toxicokinetic interaction study in rats revealed no evidence that KINERET<sup>®</sup> alters the toxicologic or pharmacokinetic profile of methotrexate (MTX). There is no evidence that KINERET<sup>®</sup> or MTX adverse events were any different between patients taking KINERET<sup>®</sup> in combination with MTX and patients taking placebo in combination with MTX.

### **TNF Blocking Agents**

Concurrent administration of KINERET<sup>®</sup> and etanercept has resulted in an increased rate of serious infections. 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 (see WARNINGS and PRECAUTIONS/

Use with other TNF Blocking Agents). Two percent (3/139) of patients treated concurrently with KINERET<sup>®</sup> and etanercept developed neutropenia (ANC < 1 x 10<sup>9</sup>/L). One neutropenic patient developed cellulitis which resolved with antibiotic therapy.

In clinical trials, drug interactions between KINERET<sup>®</sup> and other drugs (including nonsteroidal anti-inflammatory drugs, corticosteroids, and other DMARDs such as methotrexate, hydroxychloroquine, sulfasalazine, leflunomide and azathioprine) have not been observed.

## **DOSAGE AND ADMINISTRATION**

### **Recommended Dose and Dosage Adjustment**

The recommended dose of KINERET<sup>®</sup> (anakinra) for the treatment of active RA is 100 mg/day administered daily by SC injection. The dose should be administered at approximately the same time of day every day. For patient convenience, KINERET<sup>®</sup> will be provided in single-use prefilled syringes.

Physicians may consider an alternate dose of 100 mg of KINERET<sup>®</sup> every other day for patients with severely reduced renal function such as End Stage Renal Disease (ESRD).<sup>2</sup> (see WARNINGS and PRECAUTIONS: Special Populations and ACTION AND CLINICAL PHARMACOLOGY: Special Populations and Conditions).

### **Missed Dose**

Patients who miss a dose by more than a few hours should be instructed to take the missed dose as soon as possible and contact your doctor or nurse. The dose the next day should not be doubled.

### **Administration**

Instructions on appropriate use should be given by the health care professional to the patient or care provider. See the “Consumer Information” for detailed instructions on the handling and injection of KINERET<sup>®</sup>. Administer only one dose (the entire contents of one prefilled glass syringe) per day. Discard any unused portions. After administration of KINERET<sup>®</sup>, it is essential to follow the proper procedure for disposal of syringes and needles (see CONSUMER INFORMATION for instructions).

Do not use KINERET<sup>®</sup> beyond the expiration date shown on the carton and prefilled syringe. Visually inspect the solution for particulate matter and discoloration before administration. There may be small translucent-to-white particles of protein in the solution. This is not unusual for proteinaceous solutions. The prefilled syringe should not be used if the solution is discoloured or cloudy, or if foreign particulate matter is present.

The needle cover contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to this substance.

## **OVERDOSE**

There have been no reported cases of overdose with KINERET<sup>®</sup> (anakinra). In clinical trials with KINERET<sup>®</sup> carried out for sepsis, subjects received the drug over a 72-hour period for a dose of KINERET<sup>®</sup> that was up to 34.7 times higher than the recommended daily dose for RA patients (100 mg). In these trials there were no serious acute toxicities attributable to KINERET<sup>®</sup>.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

KINERET<sup>®</sup> (anakinra) neutralizes the biological activity of interleukin-1 (IL-1) by competitively inhibiting IL-1 binding to the interleukin-1 type 1 receptor (IL-1R1), which is expressed in a wide variety of tissues and organs.<sup>3</sup> KINERET<sup>®</sup> binds to IL-1R1 but does not associate with IL-1 receptor accessory protein (IL-1 R-AcP) and as such, is incapable of initiating signaling events and thus has no agonist activity.<sup>4</sup>

IL-1 is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation and subsequently joint destruction in rheumatoid arthritis (RA).<sup>5</sup> IL-1 is found in the plasma and synovial fluid of patients with RA and a correlation has been reported between IL-1 concentrations in the plasma and the activity of the disease.<sup>6</sup> IL-1 has a broad range of activities including increased production of cytokines [i.e. tumour necrosis factor-alpha (TNF- $\alpha$ )] and chemokines by T cells, macrophages, and several mesenchymal cells<sup>5</sup>; increased production of nitric oxide, prostaglandin and collagenase by fibroblasts and chondrocytes; cartilage degradation by its induction of the rapid loss of proteoglycans, as well as stimulation of bone resorption<sup>7</sup>; increased production of adhesion molecules (ICAM-1) by vascular endothelium; and release of histamine and thromboxane.<sup>8</sup>

### **Pharmacodynamics**

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder of unknown etiology, although it is thought to be mediated by antigen-driven T-cells and macrophages that produce proinflammatory cytokines such as IL-1 and TNF- $\alpha$ .<sup>3,9</sup>

IL-1 is a potent stimulator of synoviocytes, chondrocytes, and osteoblasts. Upon exposure to IL-1, fibroblast-like synoviocytes proliferate and produce prostaglandins as well as metalloproteinases such as collagenases and stromelysin.<sup>7</sup> Thus, IL-1 activates effector molecules responsible for joint destruction in addition to its proinflammatory effects. IL-1 inhibits proteoglycan synthesis and stimulates collagen

breakdown by chondrocytes.<sup>10, 11</sup> Increased RANK (receptor activator of NF-B) ligand production from IL-1-stimulated osteoblasts leads to osteoclast activation and proliferation, resulting in enhanced bone resorption.

In addition to IL-1, IL-1Ra also has been identified in the synovial fluid and synovial lining of RA and osteoarthritis (OA) patients.<sup>12</sup> The levels of the naturally occurring IL-1Ra in these patients are not sufficient to compete with the elevated amount of locally produced IL-1.

## **Pharmacokinetics**

### **Absorption:**

KINERET<sup>®</sup> is well absorbed after SC bolus injection in healthy subjects (n = 11) with an absolute bioavailability of 95% at a dose of 70 mg. The absorption process is the rate-limiting factor for the disappearance of KINERET<sup>®</sup> from the plasma after SC injection. Maximum plasma concentrations of KINERET<sup>®</sup> occurred at approximately 3 to 7 hours after SC injection of KINERET<sup>®</sup> at clinical relevant doses (1 to 2 mg/kg) to patients with RA (n = 18). The terminal half-life ranged from 4 to 6 hours. There was no unexpected accumulation in plasma concentrations of KINERET<sup>®</sup>, after daily SC doses, for up to 24 weeks.

### **Distribution:**

KINERET<sup>®</sup> initially distributes into a volume corresponding to the plasma volume, followed by distribution into a steady-state volume, similar in magnitude to the extracellular water volume.<sup>13</sup>

### **Metabolism and Excretion:**

After single intravenous (IV) administration of KINERET<sup>®</sup> at doses ranging from 1 to 2 mg/kg in healthy subjects (n = 2), the KINERET<sup>®</sup> plasma clearance values were independent of dose and ranged from 132 to 171 mL/min, which were moderately higher than the estimate of the glomerular filtration rate (creatinine clearance range = 99 to 149 mL/min).

Animal data demonstrate that the kidney is the major organ responsible for elimination of KINERET<sup>®</sup> (80% in rats). Since very little KINERET<sup>®</sup> appears in the urine (<10%), it is postulated that KINERET<sup>®</sup>, like other therapeutic proteins of similar size, is filtered at the glomeruli and reabsorbed in the proximal tubules wherein it is metabolized.<sup>14</sup> The mechanism for non-renal clearance has not been identified.

## **Special Populations and Conditions**

### **Age/Gender:**

The influence of demographic covariates on the pharmacokinetics of KINERET<sup>®</sup> was studied using population pharmacokinetic analysis with sparse data (1-5 samples per subject) obtained from 341 patients with active RA. Patients received daily SC injection of KINERET<sup>®</sup> at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated KINERET<sup>®</sup> clearance increased with increasing creatinine clearance and body weight.

Population pharmacokinetic analysis demonstrated that the mean plasma clearance value after SC bolus administration was approximately 14% higher in men (n = 79) than in women (n = 262) and approximately 10% higher in subjects < 65 years (n = 262) than in subjects ≥65 years (n = 79). However after adjusting for creatinine clearance and body weight, sex and age were not significant factors for mean plasma clearance.

### **Hepatic Insufficiency:**

After IV administration of 1 mg/kg KINERET<sup>®</sup> in normal patients with hepatic dysfunction (Child classification B, n = 12), plasma clearance was reduced by 30% compared with that in healthy volunteers (95.1 vs. 141 mL/min). The decrease in plasma clearance correlated with a slight decrease in estimates of creatinine clearance in this population. No formal studies have been conducted to examine the pharmacokinetics of KINERET<sup>®</sup> administered subcutaneously in patients with rheumatoid arthritis who have hepatic dysfunction.

### **Renal Insufficiency:**

The mean plasma clearance of KINERET<sup>®</sup> in subjects with severe renal insufficiency and end stage renal disease (creatinine clearance <30 mL/min<sup>8</sup>), has been observed to decline by 70% and 75% respectively and the mean terminal half life increases approximately two-fold of that in healthy individuals. Less than 2.5% of the administered dose of KINERET<sup>®</sup> was removed by hemodialysis or continuous ambulatory peritoneal dialysis.<sup>2</sup> Based on these observations, a dose schedule change may be considered for subjects with severe renal insufficiency or end stage renal disease (see DOSAGE AND ADMINISTRATION). There were no formal studies conducted to examine the pharmacokinetics of KINERET<sup>®</sup> administered subcutaneously in patients with rheumatoid arthritis who have renal impairment.

## **STORAGE AND STABILITY**

Do not use KINERET<sup>®</sup> beyond the expiry date shown on the carton. Store at 2° to 8°C (36° to 46°F). Do not freeze or shake. Protect from light.

## SPECIAL HANDLING INSTRUCTIONS

### **Information for Patients**

In those situations in which the physician determines that a patient can safely and effectively self-administer KINERET<sup>®</sup> (anakinra), the patient and family member or caregiver should be instructed as to the proper administration technique. Patients should be referred to the “Consumer Information” section of the monograph. This is intended as a guide for patients; however, it is not a disclosure of all possible side effects. Patients should be informed of the signs and symptoms of allergic 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.

If home use is prescribed for a patient, the patient should be thoroughly instructed in the importance of proper disposal of syringes and cautioned against the re-use of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according to the directions provided by the physician, pharmacist or nurse.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

KINERET<sup>®</sup> (anakinra) is available as single-use, preservative-free prefilled syringes with 27-gauge needles containing 100 mg (150 mg/mL) in dispensing packs of 7 or 28 syringes.

The composition of KINERET<sup>®</sup> 100 mg prefilled syringes (150 mg/mL) is shown in Table 2 below.

**Table 2: Composition**

100 mg anakinra
1.29 mg sodium citrate
4.62 mg sodium chloride
0.12 mg disodium EDTA
0.70 mg polysorbate 80
Water for Injection to 0.67 mL

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name:	anakinra
Chemical name:	Not applicable. Anakinra is not a chemical. Anakinra is a recombinant methionyl Human Interleukin-1 Receptor Antagonist
Molecular formula and molecular mass:	Anakinra consists of 153 amino acids with a molecular weight of 17.3 kilodaltons.
Physicochemical properties:	KINERET <sup>®</sup> is supplied in single use prefilled glass syringes with 27 gauge needles as a sterile, clear, colourless-to-white, preservative-free solution for daily subcutaneous (SC) administration. The solution may contain some small translucent-to-white proteinaceous particles. 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 (4.62 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in Water for Injection, USP.

#### Product Characteristics

KINERET<sup>®</sup> (anakinra) is a recombinant, non-glycosylated version of the human interleukin-1 receptor antagonist (IL-1Ra) and is identical to the natural non-glycosylated form of human IL-1Ra, except for the addition of a single methionine residue at the N-terminus. The recombinant protein consists of 153 amino acids with a molecular weight of 17.3 kilodaltons. KINERET<sup>®</sup> is produced using an *Escherichia coli* (*E. coli*) bacterial expression system.

### CLINICAL TRIALS

#### Study demographics and trial design

The safety and efficacy of KINERET<sup>®</sup> have been demonstrated in 4 large, randomised, well-controlled trials (studies 0560, 960180, 990145 and 990757). Data from these trials represent the experience of 3189 patients (2261 treated with KINERET<sup>®</sup>). A description and the design of these pivotal trials are provided in Table 3.

**Table 3: Summary of patient demographics for pivotal clinical trials with KINERET®**

Study#	Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Endpoints
0560 monotherapy	Double-blind, randomized, placebo-controlled  Active RA; DMARD-naïve DMARD failures	Fixed dosing 30, 75, or 150 mg/day 24 weeks <sup>a</sup> SC	N=472	Primary: ACR <sub>20</sub> at 24 weeks Secondary: Sustained ACR <sub>20</sub> , ACR <sub>50</sub> , ACR <sub>70</sub> , X-ray scoring of Radiographic Progression (Larsen and Genant modified Sharp)
960180 MTX combination	Double-blind. Randomized, placebo-controlled  Active RA; On MTX	Weight-based dosing 0.04, 0.1, 0.4, 1.0 or 2.0 mg/kg/day 24 weeks SC	N=419	Primary: ACR <sub>20</sub> at 12 weeks Secondary: ACR <sub>20</sub> at 24 weeks, Sustained ACR <sub>20</sub> , ACR <sub>50</sub> , ACR <sub>70</sub>
990145 Confirmatory Efficacy Study MTX combination	Double-blind, randomized, placebo-controlled  Active RA; On MTX	Fixed dosing 100 mg/day 52 weeks <sup>c</sup> SC	N=899 <sup>b</sup>	Primary: X-ray scoring at 52 weeks Secondary: ACR <sub>20</sub> at 24 weeks, Sustained ACR <sub>20</sub> , ACR <sub>50</sub> , ACR <sub>70</sub>
990757 Safety Study Concurrent DMARDs	Double-blind, Randomized, placebo-controlled  Active RA; DMARD-naïve DMARD failures Concurrent DMARDs	Fixed dosing 100 mg/day 24 weeks <sup>d</sup> SC	N=1399	Primary: Safety assessment

N = Number of subjects treated; SC = Subcutaneous; MTX = methotrexate

<sup>a</sup>A 24-week follow-up study was conducted. Efficacy evaluations were performed out to 48 weeks.

<sup>b</sup>501 of these patients were evaluated for the effect on signs and symptoms of active RA.

<sup>c</sup>First 52 weeks is double-blind, placebo-controlled. After 52 weeks, trial becomes open-label for an additional 2 years.

<sup>d</sup>First 24 weeks is double blind, placebo-controlled. After 24 weeks, trial becomes open-label for additional 2.5 years.

## Study Results

### Study 0560

In study 0560, KINERET<sup>®</sup>-treated patients were more likely to achieve an ACR<sub>20</sub> response at week 24 than were placebo patients.<sup>15</sup> The onset of response to KINERET<sup>®</sup> was evident by week 1 and statistically significant differences versus placebo were evident by week 2 for all 3 KINERET<sup>®</sup> dose groups. Subjects receiving anakinra were more than twice as likely to maintain a sustained ACR<sub>20</sub> response over the 24 week period as compared with placebo subjects. In addition, the magnitude of clinical response (ACR<sub>50</sub> and ACR<sub>70</sub>) increased across the doses explored. The ACR results from this study are presented in Table 4. In an open label extension study the effects of KINERET<sup>®</sup> were maintained over an additional 24 weeks.<sup>16</sup>

Study 0560 provided promising evidence that KINERET<sup>®</sup> decreases the rate of radiographic progression of disease. Subjects treated with KINERET<sup>®</sup> showed a significant slowing of radiographic progression of disease as early as 24 weeks, which further increased by week 48.<sup>16,17</sup>

### Study 960180

The therapeutic benefit of KINERET<sup>®</sup> in combination with MTX was examined in study 960180. A significant KINERET<sup>®</sup> treatment effect with regard to the ACR<sub>20</sub> response was seen in the 1.0 and 2.0 mg/kg dose groups.<sup>18</sup> Results, presented in Table 4, indicate that KINERET<sup>®</sup> achieves a rapid response that is maintained throughout the treatment period. Examination of the effects of anakinra across the entire 24-week treatment period demonstrates that the ACR<sub>20</sub> responses were sustained.

### Study 990145

#### *Signs and Symptoms of RA*

In study 990145, subjects treated with 100 mg/day of KINERET<sup>®</sup> plus background MTX were more likely to achieve an ACR<sub>20</sub> response at week 24, than subjects treated with placebo and background MTX (Table 4). In addition, as in the previous studies, KINERET<sup>®</sup> subjects were more likely than placebo subjects to achieve a sustained ACR<sub>20</sub> response during the 24-week period than placebo patients. The effects of KINERET<sup>®</sup> was rapid and was usually observed within the first 4 weeks of therapy (Figure 1). Additionally, KINERET<sup>®</sup>-treated subjects were twice as likely to achieve an ACR<sub>50</sub>, and almost three times as likely to achieve an ACR<sub>70</sub> than placebo subjects receiving MTX alone.

KINERET<sup>®</sup> therapy was associated with significant improvements over placebo in patient centered outcomes which are components of the ACR composite score. The results of pain, Health Assessment Questionnaire (HAQ), and Patients Global assessment for study 990145 are shown in Table 5.

**Table 4: Proportion of ACR Responses in Studies 990145, 960180, and 0560 (Percent of Patients)**

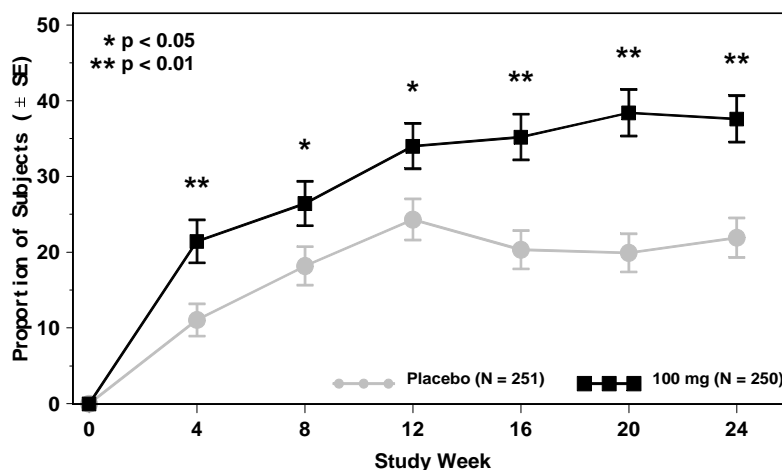
Response	990145 (Patients on MTX)		960180 (Patients on MTX)			0560 (No DMARDS)		
	Placebo (n=251)	Kineret® 100 mg/day (n=250)	Placebo (n=74)	Kineret® 1.0 mg/kg/day (n=59)	Kineret® 2.0 mg/kg/day (n=72)	Placebo (n=119)	Kineret® 75 mg/day (n=115)	Kineret® 150 mg/day (n=115)
ACR 20								
Month 3	24%	34% <sup>a</sup>	19%	46% <sup>c</sup>	38% <sup>c</sup>	23%	33%	33%
Month 6	22%	38% <sup>c</sup>	23%	42% <sup>a</sup>	35%	27%	34%	43% <sup>a</sup>
ACR 50								
Month 3	6%	13% <sup>b</sup>	4%	19% <sup>c</sup>	24% <sup>c</sup>	5%	10%	8%
Month 6	8%	17% <sup>b</sup>	4%	24% <sup>c</sup>	17% <sup>a</sup>	8%	11%	19% <sup>a</sup>
ACR 70								
Month 3	0%	3% <sup>a</sup>	0%	5% <sup>a</sup>	11% <sup>c</sup>	0%	0%	0%
Month 6	2%	6% <sup>a</sup>	0%	10% <sup>a</sup>	7% <sup>a</sup>	1%	1%	1%

<sup>a</sup>p<0.05 Kineret® versus placebo

<sup>b</sup>p<0.01 Kineret® versus placebo

<sup>c</sup>p<0.001 Kineret® versus placebo

**Figure 1: Proportion of Patients Achieving an ACR 20 Response by Visit 990145 Nonresponder Imputation**



**Table 5: Summary of Patient Centered Outcomes of ACR Composite Score Study 990145**

	Mean Change From Baseline at Week 24		Percentage Improvement
	Placebo plus MTX	KINERET® (100 mg/day) plus MTX	
Subject's assessment of disease activity	-8.92	-17.73**	99%
Subject's assessment of pain activity	-11.71	-19.00**	62%
Health assessment questionnaire	-0.18	-0.29*	59%

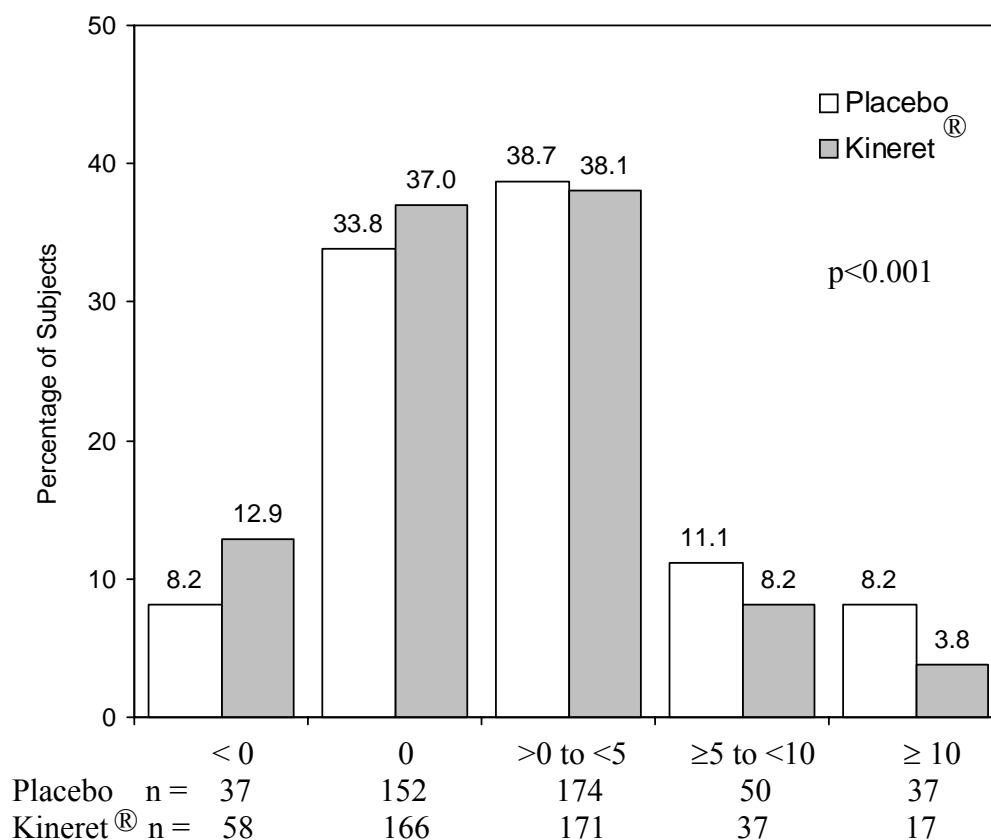
\*p-value <0.05

\*\*p-value <0.01

### **Radiographic Response**

In study 990145, the ability of KINERET® to inhibit structural damage was assessed by measuring the change from baseline at week 52 in the Total Modified Sharp Score (TMSS) and its subcomponents, the joint space narrowing score (JS) and erosion score (ES).<sup>18</sup> KINERET® treatment was associated with a highly significant ( $p < 0.001$ ) reduction in radiographically measured disease progression (Figure 2). The mean change from baseline in TMSS was 36% lower in the KINERET® group compared with placebo. KINERET® had an early onset of action, as reflected by a statistically significant difference between treatments at week 24 ( $p = 0.012$ ).<sup>7</sup>

**Figure 2: Distribution of Changes From Baseline Over 1 Year in TMSS**



Change From Baseline at Week 52

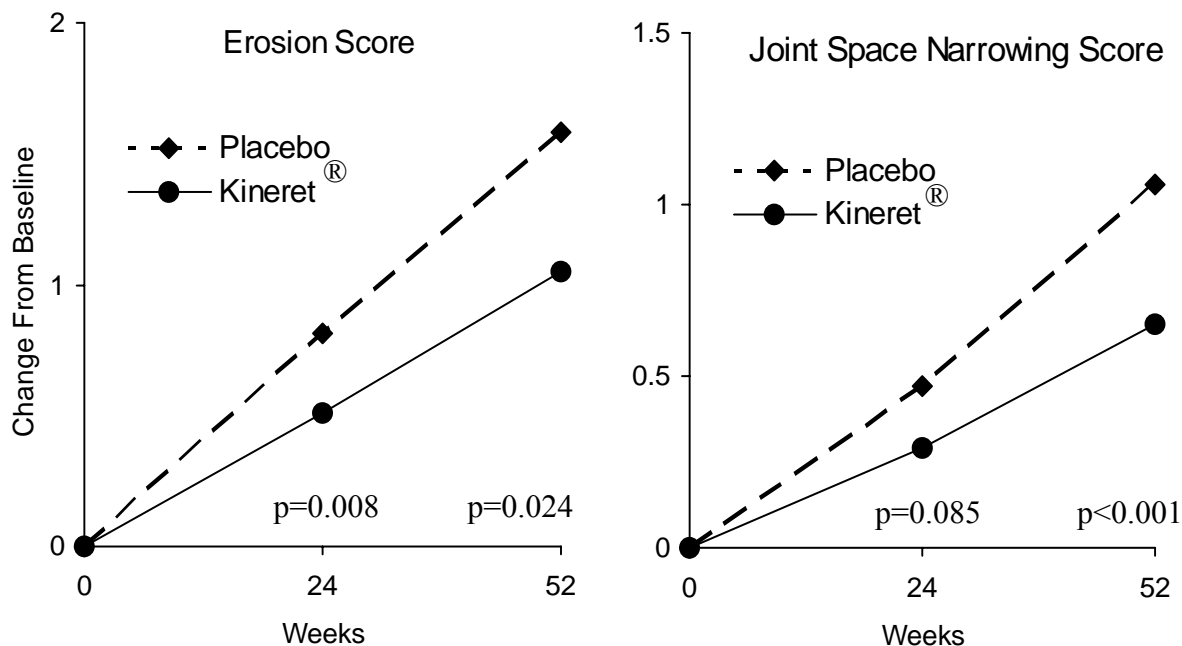
n = Number of subjects who were randomized and received at least 1 dose of study drug.

p-value by Wilcoxon rank-sum test

Results for the ES (Figure 3) were similar to those for the TMSS with significant reduction in disease progression in the KINERET® group at both week 24 (p = 0.008) and week 52 (p = 0.024) compared with placebo. The mean change from baseline in ES was reduced by 37% and 34% in the KINERET® group compared with placebo at weeks 24 and 52, respectively.

Similarly, the mean change from baseline in JS (Figure 3) was reduced by 39% in the KINERET® group compared with placebo at week 52 (p < 0.001). The mean change from baseline in the KINERET® group was 38% lower than that of the placebo group at week 24 (p = 0.085).

**Figure 3: Change From Baseline in Erosion and Joint Space Narrowing Scores**  
**p-value by Wilcoxon rank-sum test**



### Physical Function

At 52 weeks, patients who received KINERET<sup>®</sup> showed improvement of physical function compared to placebo at 52 weeks. The mean HAQ scores improved by 0.26, which was significantly different ( $p = 0.007$ ) from placebo (0.15). Consistent with improvements seen in HAQ, mean change in the Short Form 35 Physical Component score was statistically significantly superior for patients receiving KINERET<sup>®</sup> compared to those on placebo ( $p = 0.001$ ), and by week 8 improved by more than 2 points.

### DETAILED PHARMACOLOGY

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder of unknown etiology, although it is thought to be mediated by antigen-driven T-cells and macrophages that produce proinflammatory cytokines such as IL-1 and tumor necrosis factor-alpha (TNF $\alpha$ ).<sup>3,9</sup> The evidence linking IL-1 to RA is compelling. In animals, direct injection of IL-1 into joints is arthritogenic and causes transient synovitis.<sup>19</sup> Moreover, continuous infusion of IL-1 $\alpha$  into knee joints of rabbits resulted in an arthritis with signs of both acute (serous and fibrinous exudation, polymorphonuclear cell infiltration) as well as chronic (synovial cell proliferation and fibrosis, pannus formation, cartilage and bone erosion) inflammation.<sup>19</sup> Similarly, constitutive intra-articular expression of human IL-1 $\beta$  following gene transfer to rabbit synovium

produces all major pathologies of RA.<sup>20</sup> Systemic administration of IL-1 enhances the incidence and severity of arthritis in several animal models of inflammatory arthritis. For example, IL-1 can serve as an adjuvant in murine arthritis models by greatly enhancing the synovial inflammatory response.<sup>21</sup> Furthermore, intra-articular injection of IL-1 during the chronic phase of murine antigen-induced arthritis results in exacerbation of the disease.<sup>10</sup> In addition, IL-1 is found in the plasma and synovial fluid of RA patients, and a correlation has been reported between IL-1 concentrations in the plasma and the activity of the disease.<sup>6</sup> The appearance of IL-1 in synovial fluid from RA patients seems to correspond with acute inflammation of the joints, whether due to exacerbated symptoms or joint traumatization. Production of IL-1 *in vitro* by explanted synovial tissues from RA patients has been correlated with arthroscopic results indicating the extent of inflammation.<sup>22</sup>

IL-1 is a potent stimulator of synoviocytes, chondrocytes, and osteoblasts. Upon exposure to IL-1, fibroblast-like synoviocytes proliferate and produce prostaglandins as well as metalloproteinases such as collagenases and stromelysin.<sup>5</sup> Thus, IL-1 activates effector molecules responsible for joint destruction in addition to its proinflammatory effects. IL-1 inhibits proteoglycan synthesis and stimulates collagen breakdown by chondrocytes.<sup>10,11</sup> Increased RANK (receptor activator of NFκB) ligand production from IL-1-stimulated osteoblasts leads to osteoclast activation and proliferation, resulting in enhanced bone resorption.

In addition to IL-1, IL-1Ra also has been identified in the synovial fluid and synovial sublining of RA and osteoarthritis (OA) patients.<sup>12</sup> The levels of the naturally occurring IL-1Ra in these patients are not sufficient to compete with the elevated amount of locally produced IL-1.

## TOXICOLOGY

KINERET<sup>®</sup> (anakinra) has been well characterized in *in vitro* and *in vivo* nonclinical studies and is a selective antagonist of IL-1. Inhibition of inflammation, bone destruction, and cartilage degeneration has been observed in several animal models of arthritis following treatment with anakinra.

Anakinra is similar, but not identical, to the analogous receptor antagonist proteins of other species, and has been shown to be biologically active in a wide variety of species, including those used in the toxicity studies. Subchronic and chronic toxicity studies were conducted in rats and subchronic studies were conducted in nonhuman primates. Because the principal biological action of anakinra is to antagonize the effects of IL-1 and because anakinra does not possess intrinsic agonist activity, no exaggerated pharmacologic effects from high doses of anakinra were expected, nor were any seen. Anakinra is a foreign protein in the species used for preclinical safety assessment; as such, anti-anakinra antibodies were an anticipated finding. Non-neutralizing anti-anakinra antibodies were detectable in both rats and monkeys.

The following is a brief summary of completed studies.

### **Acute and Multiple Dose Toxicity**

In non-human primates, the no observed effect level (NOEL) based on systemic toxicity effects is considered to be 100 mg/kg/day; based on local injection site effects the NOEL is less than 10 mg/kg/day.

Twice-daily SC administration of anakinra (BID) for 6 months to rats at total doses of 2, 20, and 200 mg/kg/day produced local injection site inflammation at all dosages, the incidence and severity of which increased with dose. Systemic toxicity at 200 mg/kg/day was limited to the kidney with increased kidney weights, proteinuria, and chronic progressive nephropathy being the principal findings after 6 months of dosing. Chronic progressive nephropathy is a background disease in aging rats, with higher incidence in males, and is known to be influenced by protein levels. Kidney toxicity was not evident at the 1-month interim necropsy or after the 1-month recovery period.

### **Reproductive Toxicity**

No adverse effects of anakinra were noted in any reproductive toxicity or teratology studies in rats and rabbits, conducted at dosages up to 200 mg/kg/day.

### **Mutagenicity**

No evidence of genotoxicity was found in mutagenicity assays.

Neither pre-neoplastic lesions nor tumors related to anakinra treatment were observed in a 6-month study of anakinra in rats at doses up to 200 mg/kg/day. Thus, there is no evidence of anakinra being involved in direct tumor production.

### **Immunogenicity**

In preclinical toxicology studies in rats and monkeys, no evidence of immunosuppression was seen. Additionally, anakinra had no effect on specific immune function tests, such as antibody formation to keyhole limpet hemocyanin or sheep red blood cells, cytolytic T lymphocyte response in mice or NK cell activity in rats and monkeys.

### **Host Resistance Assays**

Published studies, including studies on IL-1 knockout and IL-1Ra over-expressing mice do not reveal a clear or consistent picture on the role of IL-1 inhibition in compromising host resistance to bacterial infection. For example, IL-1 $\beta$  or IL-1R knock-out mice showed no increased susceptibility to infectious challenges, while IL-1Ra over-expressing mice were more susceptible.

In acute host resistance rat models infected with *E. coli*, *S. aureus*, and *L. monocytogenes*, anakinra did not increase mortality following these infections and its

effect on host resistance (based on CFU in blood, liver, or spleen) was slight to non-existent. Therefore, in animal models, anakinra does not appear to greatly impair host resistance mechanisms.

### **Safety Pharmacology**

The effects of combined administration of anakinra with MTX or with cytokine inhibitors were investigated.

Coadministration of anakinra and MTX (in rats) or PEG sTNF-RI (in rats and monkeys), did not identify any toxicity or pharmacokinetic interactions between the two agents.

There was no evidence in monkeys and rats of detrimental anakinra interaction with the cytokine inhibitors, etanercept and PEG sTNF-RI in blood cell counts, body and lymphoid organ (spleen, thymus) weights, lymphoid organ cellularity, lymphoid organ viability, NK cell function, immune cell phenotype, and antibody response to keyhole limpet hemocyanin or the anti-sheep red blood antibody-forming cell (AFC) assay.

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**PART III: CONSUMER INFORMATION****KINERET<sup>®</sup>**  
anakinra

This leaflet is part III of a three-part “Product Monograph” published when KINERET<sup>®</sup> (anakinra) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about KINERET<sup>®</sup>. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**What the medication is used for:

KINERET<sup>®</sup> is used to help reduce the signs and symptoms of rheumatoid arthritis and slow damage to bone and joints. KINERET<sup>®</sup> inhibits the progression of structural damage by reducing erosions and cartilage degradation in patients with active rheumatoid arthritis despite treatment with stable doses of methotrexate (MTX). Rheumatoid arthritis causes swelling in the lining of joints (e.g. hand, knee, and wrist joints) and, in some cases, may affect internal organs. Rheumatoid arthritis can last many years, and can ultimately cause damage to cartilage, bone, tendons, and ligaments in joints throughout the body.

What it does:

KINERET<sup>®</sup> is a laboratory copy of a natural protein (cytokine inhibitor) produced in our bodies. This natural protein is called interleukin-1 (in-ter-lew-kin) receptor antagonist or IL-1ra. Cytokines are a type of protein made in the human body. They coordinate the communication between different cells and help control cell activity. In rheumatoid arthritis, a cytokine called interleukin-1 (IL-1) contributes to the swelling and tissue destruction in joints. The interleukin-1 receptor antagonist (IL-1ra) blocks these effects of IL-1. KINERET<sup>®</sup> is a laboratory-made copy of IL-1ra, which helps to reduce the pain and swelling of rheumatoid arthritis.

When it should not be used:

You should not use KINERET<sup>®</sup> if you have an allergy to proteins made from bacterial cells (*E. coli*) or any ingredients in KINERET<sup>®</sup>.

What the medicinal ingredient is:

anakinra

What the important nonmedicinal ingredients are:

Sodium citrate, sodium chloride, disodium EDTA, polysorbate 80 and water for injection.

What dosage forms it comes in:

KINERET<sup>®</sup> is available as single-use, preservative-free prefilled syringes containing 100 mg (150 mg/mL) in dispensing packs of 7 or 28 syringes.

**WARNINGS AND PRECAUTIONS**

All medicines have side effects. Medicines, like KINERET<sup>®</sup>, that affect your immune system can cause serious side effects. The possible serious side effects include:

- **Serious Infections.** Patients taking KINERET<sup>®</sup> have a greater chance of developing a serious infection. If you have an infection or suffer from asthma, tell your healthcare provider **before** you start taking KINERET<sup>®</sup>. If you get an infection that does not go away while taking KINERET<sup>®</sup>, tell your healthcare provider right away. If you are using ENBREL<sup>®</sup> (etanercept), Humira (adalimumab), or Remicade (infliximab) you could also be at greater risk for getting a serious infection.
- **Malignancies.** The risk of developing cancer for patients taking KINERET<sup>®</sup> appears to be the same as that for patients not taking KINERET<sup>®</sup>. RA patients, particularly those with highly active RA, may be at higher risk for lymphoma (a type of cancer). In clinical trials, patients treated with KINERET<sup>®</sup> had an incidence of lymphoma higher than that expected in the general population. The role of KINERET<sup>®</sup> in the development of cancer is not known.
- **Blood Problems.** KINERET<sup>®</sup> may cause certain white blood cells called neutrophils to decrease in number (neutropenia). It is recommended that you have a blood test before starting treatment with KINERET<sup>®</sup>, and that you have your blood checked every three months for up to one year from the start of KINERET<sup>®</sup> therapy.
- **Allergic reactions.** Allergic reactions rarely occur in patients taking KINERET<sup>®</sup>. If you get a rash over your whole body, shortness of breath, wheezing, low blood pressure, racing pulse, extreme sweating, hives, or swelling of mouth or eyes after your KINERET<sup>®</sup> injection, contact your doctor or the nearest hospital immediately. These symptoms may mean that you are allergic to KINERET<sup>®</sup>. Severe cases of this type of allergy may be dangerous and should be closely monitored by a doctor or emergency medical personnel.

BEFORE you use KINERET<sup>®</sup> talk to your doctor or pharmacist if you:

- think you have an infection or are being treated for infection
- get a lot of infections or have infections that keep coming back
- 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<sup>®</sup>
- take other medicines that affect your immune system
- have an allergy to rubber or latex. The needle cover on the prefilled syringe contains latex (dry natural rubber).
- have kidney problems
- are scheduled to receive any vaccines. Patients taking KINERET<sup>®</sup> should not receive live vaccines.

What are the common side effects?

KINERET<sup>®</sup> is generally well tolerated, the most common side effect was:

- Reactions at the site where KINERET<sup>®</sup> was injected. These reactions include redness, swelling, bruising, or itching and/or stinging. Most injection site reactions are mild and last about 2 to 4 weeks. If you are having problems with your injection sites, call your healthcare provider.

What are other possible side effects with KINERET<sup>®</sup>?

The KINERET<sup>®</sup> needle cover contains dry natural rubber (a derivative of latex). If you know you are allergic to latex, talk to your healthcare provider before using KINERET<sup>®</sup>.

When can I expect to see results from taking KINERET<sup>®</sup>?

Only you and your doctor can determine if KINERET<sup>®</sup> 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<sup>®</sup>.

Can I use KINERET<sup>®</sup> if I am pregnant or breastfeeding?

There have not been any studies on the use of KINERET<sup>®</sup> by pregnant women. KINERET<sup>®</sup> should only be used during pregnancy if medically necessary. If you are planning to become pregnant, are pregnant or nursing a baby, talk to your doctor before using KINERET<sup>®</sup>.

**INTERACTIONS WITH THIS MEDICATION**

It is important that you tell your doctor about any other medicines (for example, high blood pressure medicine) you are taking for other conditions before you start taking KINERET<sup>®</sup>. You should also tell your doctor about any over-the-counter drugs, herbal medicines and vitamin and mineral supplements you are taking.

Taking KINERET<sup>®</sup> with Enbrel<sup>®</sup> or other tumour necrosis blocking agents (ie. Humira or Remicade) is not recommended because this may increase your risk of getting a serious infection.

**PROPER USE OF THIS MEDICATION**

KINERET<sup>®</sup> is given as an injection under your skin (subcutaneous). Your doctor will tell you how much you should take, and how often you need to take it. Whether you are giving yourself the daily injections or having someone else give them to you, you must take KINERET<sup>®</sup> exactly as your doctor tells you in order to get the most benefit from your medication.

KINERET<sup>®</sup> is packaged in prefilled syringes (small disposable tubes attached to needles). The prefilled syringe is already filled with the correct amount of KINERET<sup>®</sup> you need to take each day. The syringes are for single use only. Any unused portion of a prefilled syringe must be discarded. Make sure the solution in the prefilled syringe is clear and colourless. You may notice small white particles in the solution. These particles are formed from

KINERET<sup>®</sup> and this is acceptable. However, do not inject the solution if it is cloudy or discoloured, or contains large or coloured particles.

Do not shake the KINERET<sup>®</sup> prefilled syringe. If the prefilled syringe has been shaken vigorously the solution may be frothy or have bubbles at the top. The effectiveness of KINERET<sup>®</sup> will not be altered by shaking, but you may not be able to deliver the total amount of medication from the syringe. If the solution is frothy, let the prefilled syringe sit undisturbed for a few minutes to decrease the amount of froth or bubbles.

The expiry date for each KINERET<sup>®</sup> product is stamped on the pack and on the syringe label. Do not use KINERET<sup>®</sup> after the last day of the month and the year shown.

What do I need to know if I am giving myself KINERET<sup>®</sup> injections?

**IMPORTANT: TO HELP AVOID CONTAMINATION AND POSSIBLE INFECTION DUE TO INJECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.**

This section contains information on how to give yourself an injection under the skin (subcutaneous). Together you and your doctor will decide if you are able to give yourself the injections without special training from your doctor or nurse. It is also very important to put the used prefilled syringe and needle in a puncture-proof container (see **Disposal** section). If you are unsure about giving yourself the injections, or have any questions, talk to your doctor or nurse.

**Instructions for preparing and giving an injection of KINERET<sup>®</sup>**

Setting Up For Injection with KINERET<sup>®</sup> Prefilled Syringes

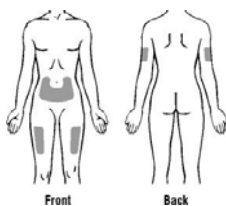
You should find a comfortable, well-lit working place and inject KINERET<sup>®</sup> at the same time each day. Remove a prefilled syringe of KINERET<sup>®</sup> from the refrigerator. **DO NOT SHAKE THE PREFILLED SYRINGE.** Allow 30 minutes for the medication to reach room temperature (Note: KINERET<sup>®</sup> can be left out at room temperature for up to 24 hours). Check the expiration date on the KINERET<sup>®</sup> prefilled syringe to be sure that the drug has not expired. Make sure the solution in the prefilled syringe is clear and colourless. You may notice small white particles in the solution. These particles are formed from KINERET<sup>®</sup> and this is acceptable. However, do not inject the solution if it is cloudy or discoloured, or contains large or coloured particles.

STEP I: Preparing for the injection

1. Find a comfortable, well-lit, clean, working place or surface.
2. Assemble the supplies you will need for your injection:

For KINERET<sup>®</sup> prefilled syringes you will need: prefilled syringe of KINERET<sup>®</sup>, alcohol swabs, and puncture-proof disposal container. Note: Do not remove the needle cover from the prefilled syringe until you or your caregiver is ready to give the injection.

3. Wash your hands thoroughly with soap and water before preparing to inject the medication.
4. Determine the site for injection. Alternate the injection site each time you inject KINERET<sup>®</sup>, as directed by your doctor, to avoid soreness at any one site.
  - a. Back of the upper arms (if someone is giving you the injection)
  - b. Abdomen, except for the navel and waist (belt line)
  - c. Upper thighs



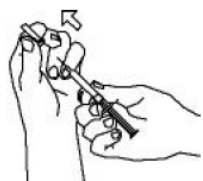
Occasionally, a local reaction may develop at the injection site. If you notice a lump, swelling, redness, bruising, or itching that doesn't go away, contact your doctor.

5. Clean the injection site with an alcohol swab. Use circular motions from the inside to the outside in a spiral motion. Let the area dry.



**STEP II: Preparing the dose from prefilled syringes**

1. Holding the syringe with the needle pointing upward, carefully pull the needle cover straight off. A slight twisting motion might help in the removal. Take care not to touch the needle. Put the needle cover into the disposal container.



2. Holding the syringe with the needle pointing up, check the syringe for air bubbles. Air bubbles are harmless but can reduce the dose you should be receiving. To remove the air bubbles, continue to hold the syringe with the needle pointing upward and

pull back on the plunger slightly to remove any medication that may be inside the needle. Gently tap the syringe with your finger until the bubbles rise to the top of the syringe barrel, and then slowly push the plunger to force air out of the syringe. Double check for air bubbles. If necessary, repeat this procedure.

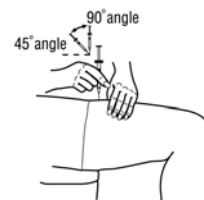
3. Hold the syringe in the hand that you will use to inject yourself. Do not lay the syringe down or allow the needle to touch anything. You can now use the prefilled syringe (see STEP III).

**STEP III: Injecting the medication**

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



2. Hold the syringe the way you would hold a pencil and insert the needle either straight up and down (at a 90-degree angle) or at a slight angle (45 degrees) to the skin.



3. After the needle is in, let go of the skin. Pull the plunger back slightly. If blood comes into the syringe, do not inject KINERET<sup>®</sup>, because the needle has entered a blood vessel. Withdraw the syringe and reinsert at a different place which has been cleaned with the alcohol swab. Repeat this procedure checking for blood.



4. If no blood appears, slowly push the plunger all the way down until all the medication is gone from the syringe.

5. As you pull the needle out of the skin, place the alcohol swab over the injection site, then press for several seconds.



6. Dispose of the syringe as instructed (see **Disposal** section).  
Note: use the syringe only once to ensure sterility of the syringe and needle, and to ensure accuracy of the dose.

7. You may want to apply a bandage to prevent any drops of blood from getting on your clothing.

Disposal

Dispose of syringes and needles as directed by your doctor, or by following these simple steps:

1. Place all used needles, needle covers, and syringes in a hard plastic container, or a metal container with a plastic lid. Do not attempt to disassemble the syringe or replace the needle cover. Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store. Always store the container out of the reach of children, and properly label the container to indicate its contents.

a. If a metal container (such as a coffee can with a plastic lid) is used, cut a small hole in the plastic lid and tape the lid onto the metal container.

b. If a hard plastic container with a screw-on cap is used, always screw the cap on tightly after each use.

2. When the container is full, tape around the cap or lid and dispose of the container according to your doctor's or healthcare provider's instructions.

3. Check with your doctor, nurse, or pharmacist for other suggestions for disposal. There may be special provincial and local laws that they will discuss with you.

Important Notes

If your doctor allows you to self-administer KINERET® at home, please note the following:

1. Always follow your doctor's instructions concerning the dosage and administration of KINERET®. Do not change the dose or administration of KINERET® without consulting with your doctor.

2. Your doctor will tell you what to do if you miss a dose of KINERET®.

3. If you develop a fever or symptoms of infection, contact your doctor.

4. Consult your doctor if you notice anything unusual about your condition or your use of KINERET®.

5. For further information about injecting KINERET®, please contact your doctor or nurse.

Overdose:

Call your doctor if you accidentally inject KINERET® more frequently than instructed.

Missed Dose:

If you miss your dose by more than a few hours, take the missed dose as soon as possible and contact your doctor or nurse. Do not take double the dose the next day.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Upper Respiratory Infection		X	
Common	Serious Infection		X	X

*This is not a complete list of side effects. For any unexpected effects while taking KINERET®, contact your doctor or pharmacist.*

**HOW TO STORE IT**

KINERET® should be kept in the refrigerator (between 2° to 8°). KINERET® can be left out at room temperature for up to 24 hours. If you think that KINERET® has been frozen or left in direct sunlight, contact your doctor, nurse, or pharmacist before you use it. When travelling, keep KINERET® in a cool area out of the sun and avoid extreme temperature changes. Return medication to refrigeration conditions as soon as possible.

As with all medications, keep KINERET® out of sight and reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Online: [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)  
Toll-free phone: 1-866-234-2345  
Toll-free fax: 1-866-678-6789

Postage Paid Mail: Canada Vigilance Program  
Health Canada  
AL 0701C  
Ottawa, Ontario K1A 0K9

*Note: Should you require information related to the management of the side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.*

#### **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting:  
Kineret Hands on Program at: 1-866-204-3546

This leaflet was prepared by Amgen Canada Inc.

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