## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**Kineret® (anakinra) for injection, for subcutaneous use**
**Initial U.S. Approval: 2001**

### ----------RECENT MAJOR CHANGES----------

- Indications and Usage, CAPS (1.2) 12/2012
- Dosage and Administration, CAPS (2.2) 12/2012
- Warnings and Precautions (5.1; 5.6) 12/2012

### ----------INDICATIONS AND USAGE----------

Kineret is an interleukin-1 receptor antagonist indicated for:

**Rheumatoid Arthritis (RA)**

- Reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs) (1.1)

**Cryopyrin-Associated Periodic Syndromes (CAPS)**

- Treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID) (1.2)

### ----------DOSAGE AND ADMINISTRATION----------

**Rheumatoid Arthritis (RA)**

- The recommended dose of Kineret for the treatment of patients with rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. The dose should be administered at approximately the same time every day (2.1)
- Physicians should consider a dose of 100 mg of Kineret administered every other day for RA patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels) (2.3)

**Cryopyrin-Associated Periodic Syndromes (CAPS)**

- The recommended starting dose of Kineret is 1-2 mg/kg daily for NOMID patients. The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation. (2.2)
- Physicians should consider administration of the prescribed Kineret dose every other day for NOMID patients who have severe renal insufficiency or end stage renal disease (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels) (2.3)

See full prescribing information for administration instructions (2.3)

### ----------DOSAGE FORMS AND STRENGTHS----------

100 mg/0.67 mL solution for subcutaneous injection. Graduated syringe allows for doses between 20 and 100 mg. (3)

### ----------CONTRAINDICATIONS----------

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

### ----------WARNINGS AND PRECAUTIONS----------

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

### ----------ADVERSE REACTIONS----------

**Rheumatoid Arthritis (RA)**

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

**NOMID**

The most common AEs during the first 6 months of treatment (incidence >10%) are injection site reaction, headache, vomiting, arthralgia, pyrexia, and nasopharyngitis (6.2)

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

### ----------DRUG INTERACTIONS----------

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

### ----------USE IN SPECIFIC POPULATIONS----------

- Pediatric use: Kineret is indicated for use in pediatric patients with NOMID (8.4)
- Geriatric use: Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (8.5)
- Renal impairment: This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function (8.6)

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

**Revised: 12/2012**

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**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

### 1.1 Active Rheumatoid Arthritis

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

### 1.2 Cryopyrin-Associated Periodic Syndromes (CAPS)

Kineret is indicated for the treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID).

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Active Rheumatoid Arthritis

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

### 2.2 Cryopyrin-Associated Periodic Syndromes (CAPS)

The recommended starting dose of Kineret is 1-2 mg/kg for NOMID patients. The dose can be individually adjusted to a maximum of 8 mg/kg daily to control active inflammation.

Adjust doses in 0.5 to 1.0 mg/kg increments. Once daily administration is generally recommended, but the dose may be split into twice daily administrations. Each syringe is intended for a single use. A new syringe must be used for each dose. Any unused portion after each dose should be discarded.

### 2.3 Renal Impairment

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

### 2.4 Administration

Instructions on appropriate use should be given by the healthcare provider to the patient or caregiver. Patients or caregivers should not be allowed to administer Kineret until the patient or caregiver has demonstrated a thorough understanding of procedures and an ability to inject the product correctly. The prescribed dose of Kineret should be administered according to the instructions for use and any unused portions discarded. After administration of Kineret it is essential to follow the proper procedure for disposal of syringes and any residual drug. See the "Information for Patients" insert for detailed instructions on the handling and injection of Kineret.

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

## 3 DOSAGE FORMS AND STRENGTHS

100 mg/0.67 mL solution for subcutaneous injection. Graduated syringe allows for doses between 20 and 100 mg.

## 4 CONTRAINDICATIONS

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

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Serious Infections

Kineret has been associated with an increased incidence of serious infections (2%) vs. Placebo (< 1%) in clinical trials in RA. Administration of Kineret in RA should be discontinued if a patient develops a serious infection. In Kineret treated NOMID patients the risk of a NOMID flare when discontinuing Kineret treatment should be weighed against the potential risk of continued treatment. 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.

Drugs that affect the immune system by blocking tumor necrosis factor (TNF) have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as Kineret that blocks IL-1 increases the risk of TB or other atypical or opportunistic infections. Health care providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with Kineret.

### 5.2 Use With TNF Blocking Agents

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

### 5.3 Hypersensitivity Reactions

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

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

### 5.4 Immunosuppression

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

### 5.5 Immunizations

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

**5.6 Neutrophil Count**

Patients receiving Kineret may experience a decrease in neutrophil counts. Neutrophil counts should therefore 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.

In the placebo-controlled studies, 8% of RA patients receiving Kineret had decreases in neutrophil counts of at least one World Health Organization (WHO) toxicity grade compared with 2% in the placebo control group. Nine Kineret-treated patients (0.4%) experienced neutropenia (ANC < 1 x $10^9$/L). This is discussed in more detail in the *Adverse Reactions (6): Hematologic Events (6.1)* section.

In 43 NOMID patients followed for up to 60 months 2 patients experienced neutropenia that resolved over time during continued Kineret treatment. [see *Adverse Reactions (6.2)*]

## 6 ADVERSE REACTIONS

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

### 6.1 Clinical Studies Experience in RA

The most serious adverse reactions were:

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

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

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

***Injection-site Reactions:***

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

***Infections:***

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

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

In patients who received both Kineret and etanercept for up to 24 weeks, the incidence of serious infections was 7%. The most common infections consisted of bacterial pneumonia (4 cases) and cellulitis (4 cases). One patient with pulmonary fibrosis and pneumonia died due to respiratory failure.

***Malignancies:***

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

***Hematologic Events:***

In placebo-controlled studies with Kineret, 8% of patients receiving Kineret had decreases in total white blood counts of at least one WHO toxicity grade, compared with 2% of placebo patients. Nine Kineret-treated patients (0.4%) developed neutropenia (ANC < 1 x $10^9$/L). 9 % of patients receiving Kineret had increases in eosinophil differential percentage of at least one WHO toxicity grade, compared with 3 % of placebo patients. Of patients treated concurrently with Kineret and etanercept 2% developed neutropenia (ANC < 1 x $10^9$/L). While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy. 2% of patients receiving Kineret had decreases in platelets, all of WHO toxicity grade one, compared to 0% of placebo patients.

***Hypersensitivity Reactions:***

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

***Immunogenicity:***

As with all therapeutic proteins, there is potential for immunogenicity. In Studies 1 and 4, from which data is available for up to 36 months, 49% of patients tested positive for anti-anakinra binding antibodies at one or more time points using a biosensor assay. Of the 1615 patients with available data at Week 12 or later, 30 (2%) tested positive for neutralizing antibodies in a cell-based bioassay. Of the 13 patients with available follow-up data, 5 patients remained positive for neutralizing antibodies at the end of the studies. No correlation between antibody development and adverse events was observed.

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

***Other Adverse Events:***

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

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

| Preferred term | Placebo (n = 733) | Kineret 100 mg/day (n = 1565) |
|---|---|---|
| Injection Site Reaction | 29% | 71% |
| Worsening of RA | 29% | 19% |
| Upper Respiratory Tract Infections | 17% | 14% |
| Headache | 9% | 12% |
| Nausea | 7% | 8% |

| | | |
|---|---|---|
| Diarrhea | 5% | 7% |
| Sinusitis | 7% | 7% |
| Arthralgia | 6% | 6% |
| Flu Like Symptoms | 6% | 6% |
| Abdominal Pain | 5% | 5% |

**6.2 Clinical Study Experience in NOMID**

The data described herein reflect an open-label study in 43 NOMID patients exposed to Kineret for up to 60 months adding up to a total exposure of 159.8 patient years.

Patients were treated with a starting dose of 1 to 2 mg/kg/day and an average maintenance dose of 3-4 mg/kg/day adjusted depending on the severity of disease. Among pediatric NOMID patients, doses up to 7.6 mg/kg/day have been maintained for up to 15 months.

There were 24 serious adverse events (SAEs) reported in 14 of the 43 treated patients. The most common type of SAEs reported were infections [see *Warnings and Precautions (5.1)*]. Five SAEs were related to lumbar puncture, which was part of the study procedure.

There were no permanent discontinuations of study drug treatment due to AEs. Doses were adjusted in 5 patients because of AEs; all were dose increases in connection with disease flares.

The reporting frequency of AEs was highest during the first 6 months of treatment. The incidence of AEs did not increase over time, and no new types of AEs emerged.

The most commonly reported AEs during the first 6 months of treatment (incidence >10%) were injection site reaction (ISR), headache, vomiting, arthralgia, pyrexia, and nasopharyngitis (Table 2).

The most commonly reported AEs during the 60-month study period, calculated as the number of events/patient years of exposure, were arthralgia, headache, pyrexia, upper respiratory tract infection, nasopharyngitis, and rash (Table 2).

The AE profiles for different age groups <2 years, 2-11 years, and 12-17 years corresponded to the AE profile for patients ≥18 years, with the exception of infections and related symptoms being more frequent in patients <2 years.

***Infections***

The reporting rate for infections was higher during the first 6 months of treatment (2.3 infections/patient-year) compared to after the first 6 months (1.7 infections/patient year). The most common infections were upper respiratory tract infection, sinusitis, ear infections, and nasopharyngitis.

There were no deaths or permanent treatment discontinuations due to infections. In one patient Kineret administration was temporarily stopped during an infection and in 5 patients the dose of Kineret was increased due to disease flares in connection with infections. Thirteen infections in 7 patients were classified as serious, the most common being pneumonia and gastroenteritis occurring in 3 and 2 patients, respectively. No serious opportunistic infections were reported.

The reporting frequency for infections was highest in patients <12 years of age.

***Hematologic Events***

After start of Kineret treatment neutropenia was reported in 2 patients. One of these patients experienced an upper respiratory tract infection and an otitis media infection. Both episodes of neutropenia resolved over time with continued Kineret treatment.

***Injection Site Reactions***

In total, 17 injection site reactions (ISRs) were reported in 10 patients during the 60-month study period. Out of the 17 ISRs, 11 (65%) occurred during the first month and 13 (76%) were reported during the first 6 months. No ISR was reported after Year 2 of treatment. The majority of ISRs were reported as mild (76% mild, 24% moderate). No patient permanently or temporarily discontinued Kineret treatment due to injection site reactions.

***Immunogenicity***

The immunogenicity of Kineret in NOMID patients was not evaluated.

**Table 2. Most common (>10% of patients) treatment-emergent adverse events during the first 6 months of Kineret treatment**

| | **Safety population (N=43) Total exposure in patient years= 20.8** | |
|---|---|---|
| **Preferred term** | **N (%)** | **Number of events /patient year** |
| Injection site reaction | 7 (16.3%) | 0.5 |
| Headache | 6 (14.0%) | 0.7 |
| Vomiting | 6 (14.0%) | 0.6 |
| Arthralgia | 5 (11.6%) | 0.6 |
| Pyrexia | 5 (11.6%) | 0.4 |
| Nasopharyngitis | 5 (11.6%) | 0.3 |

The most common adverse reactions occurring after the first 6-month period of treatment with Kineret (up to 60 months of treatment) included: arthralgia, headache, pyrexia, upper respiratory tract infection, nasopharyngitis, and rash.

## 7 DRUG INTERACTIONS

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

**7.1 TNF Blocking Agents**

A higher rate of serious infections has been observed in patients treated with concurrent Kineret and etanercept therapy than in patients treated with etanercept alone [see *Warnings and Precautions (5.2)*]. Two percent of patients treated concurrently with Kineret and etanercept developed neutropenia (ANC < 1 x $10^9$/L). Use of Kineret in combination with TNF blocking agents is not recommended.

## 8 USE IN SPECIFIC POPULATIONS

**8.1 Pregnancy**

**Teratogenic effects: Pregnancy Category B**: There are no adequate and well-controlled studies of Kineret in pregnant women. Reproductive studies have been performed in rats and rabbits at doses up to 25 times the maximum recommended human dose (on a mg/kg basis at a maternal dose of 200 mg/kg/day) and have

revealed no evidence of impaired fertility or harm to the fetus due to Kineret. Because animal reproduction studies are not always predictive of human response, Kineret should be used during pregnancy only if clearly needed.

**8.3 Nursing Mothers**

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

**8.4 Pediatric Use**

The NOMID study included 36 pediatric patients: 13 below 2 years, 18 between 2 and 11 years, and 5 between 12 and 17 years of age. A subcutaneous Kineret starting dose of 1–2 mg/kg/day was administered in all age groups. An average maintenance dose of 3–4 mg/kg/day was adequate to maintain clinical response throughout the study irrespective of age but a higher dose was, on occasion, required in severely affected patients. The prefilled syringe does not allow doses lower than 20 mg to be administered.

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

**8.5 Geriatric Use**

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

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

**8.6 Renal Impairment**

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

**8.7 Hepatic Impairment**

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

## 10 OVERDOSAGE

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

## 11 DESCRIPTION

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

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

## 12 CLINICAL PHARMACOLOGY

**12.1 Mechanism of Action**

Kineret blocks the biologic activity of IL-1 alpha and beta 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.

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. The levels of the naturally occurring IL-1Ra in synovium and synovial fluid from RA patients are not sufficient to compete with the elevated amount of locally produced IL-1.

Spontaneous mutations in the CIAS1/NLRP3 gene have been identified in a majority of patients with cryopyrin-associated periodic syndromes such as NOMID. CIAS1/NLRP3 encodes for cryopyrin, a component of the inflammasome. The activated inflammasome results in proteolytic maturation and secretion of IL-1β, which has an important role in the systemic inflammation and manifestations of NOMID.

**12.3 Pharmacokinetics**

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

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

In NOMID patients, at a median SC dose of 3 mg/kg once daily and a median treatment time of 3.5 years, the median (range) steady-state serum exposure of anakinra was $C_{max}$ 3628 (655–8511) ng/mL (n=16) and $C_{24h}$ 203 (53–1979) ng/mL (n=16). The median (range) half-life of anakinra was 5.7 (3.1–28.2) hours (n=12). There was no obvious gender difference.

Patients With Renal Impairment: The mean plasma clearance of Kineret in subjects with mild (creatinine clearance 50-80 mL/min) and moderate (creatinine clearance 30-49 mL/min) renal insufficiency was reduced by 16% and 50%, respectively. In severe renal insufficiency and end stage renal disease (creatinine clearance < 30 mL/min[1]), mean plasma clearance declined by 70% and 75%, respectively. Less than 2.5% of the administered dose of Kineret was removed by hemodialysis or continuous ambulatory peritoneal dialysis. Based on these observations, a dose schedule change should be considered for subjects with severe renal insufficiency or end stage renal disease [see *Dosage and Administration (2.2)*].

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

## 13 NONCLINICAL TOXICOLOGY

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

Long-term animal studies to evaluate the carcinogenic potential of Kineret were not conducted. Using a standard in vivo and in vitro battery of mutagenesis assays, Kineret did not induce gene mutations in either bacteria or mammalian cells. Kineret had no effects on fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 25 times the maximum recommended dose).

## 14 CLINICAL STUDIES

### 14.1 Clinical Studies in RA

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

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

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

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

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

In Studies 1, 2 and 3, the improvement in signs and symptoms of RA was assessed using the American College of Rheumatology (ACR) response criteria ($ACR_{20}$, $ACR_{50}$, $ACR_{70}$). In these studies, patients treated with Kineret were more likely to achieve an $ACR_{20}$ or higher magnitude of response ($ACR_{50}$ and $ACR_{70}$) than patients treated with placebo (Table 3). 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 4.

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

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

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

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

**Table 4: Median ACR Component Scores in Study 1**

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

[a] Health Assessment Questionnaire; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking,

hygiene, reach, grip, and activities.

[b] Visual analog scale; 0 = best, 100 = worst

[c] Scale 0 to 68

[d] Scale 0 to 66

A 24-week study was conducted in 242 patients with active RA on background methotrexate who were randomized to receive either etanercept alone or the combination of Kineret and etanercept. The $ACR_{50}$ response rate was 31% for patients treated with the combination of Kineret and etanercept and 41% for patients treated with etanercept alone, indicating no added clinical benefit of the combination over etanercept alone. Serious infections were increased with the combination compared to etanercept alone [see *Warnings and Precautions (5.1)*].

In Study 1, the effect of Kineret on the progression of structural damage was assessed by measuring the change from baseline at month 12 in the Total Modified Sharp Score (TSS) and its subcomponents, erosion score, and joint space narrowing (JSN) score.[2] Radiographs of hands/wrists and forefeet were obtained at baseline, 6 months and 12 months and scored by readers who were unaware of treatment group. A difference between placebo and Kineret for change in TSS, erosion score (ES) and JSN score was observed at 12 months (Table 5).

**Table 5: Mean Radiographic Changes Over 12 Months in Study 1**

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

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

** Based on Wilcoxon rank-sum test

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

### 14.2 Clinical Studies in NOMID

The efficacy of Kineret was evaluated in a prospective, long-term, open-label and uncontrolled study which incorporated a withdrawal period in a subset of 11 patients. This study included 43 NOMID patients 0.7 to 46 years of age treated for up to 60 months. Patients were given an initial Kineret dose of 1–2.4 mg/kg body weight. During the study, the dose was adjusted by 0.5 to 1 mg/kg increments to a protocol-specified maximum of 10 mg/kg daily, titrated to control signs and symptoms of disease. The maximum dose actually studied was 7.6 mg/kg/day. The average maintenance dose was 3 to 4 mg/kg daily. In general, the dose was given once daily, but for some patients, the dose was split into twice daily administrations for better control of disease activity.

NOMID symptoms were assessed with a disease-specific Diary Symptom Sum Score (DSSS), which included the prominent disease symptoms fever, rash, joint pain, vomiting, and headache. In addition, serum amyloid A (SAA), hsCRP, and ESR levels were monitored. Changes in clinical and laboratory parameters from baseline to Months 3 to 6 and from Month 3 (before withdrawal) to the end of the withdrawal period were assessed in the subset of patients who underwent withdrawal. The estimated changes from baseline in DSSS are summarized through Month 60 in Table 6. Results were consistent across all subgroups, including age, gender, presence of CIAS1 mutation, and disease phenotype. Improvements occurred in all individual disease symptoms comprising the DSSS (Table 7), as well as in the serum markers of inflammation. For the 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of Kineret therapy. Upon withdrawal of treatment, the median time until disease flare criteria were met was 5 days.

**Table 6. Estimated change from baseline in DSSS in NOMID patients (N=29)**

| Time point | Estimated mean change from baseline in DSSS* | 95% confidence interval |
|---|---|---|
| Month 3-6 | -3.5 | -3.7 to -3.3 |
| Month 12 | -3.6 | -3.9 to -3.3 |
| Month 36 | -3.5 | -3.8 to -3.2 |
| Month 60 | -3.5 | -3.8 to -3.1 |

*Mean (SD) baseline value was 4.5 (3.2)

**Table 7. Individual diary key symptom scores by visit (ITT diary population)**

| Visit (month) | Number of patients | Fever score* | Rash score* | Joint pain score* | Vomiting score* | Headache score* |
|---|---|---|---|---|---|---|
| Baseline | 29 | 0.5 (0.8) | 1.9 (1.1) | 1.2 (1.1) | 0.1 (0.2) | 0.9 (1.0) |
| 1 | 28 | 0.1 (0.1) | 0.3 (0.5) | 0.2 (0.3) | 0.0 (0.0) | 0.2 (0.3) |
| 3 | 26 | 0.1 (0.2) | 0.1 (0.2) | 0.2 (0.4) | 0.0 (0.1) | 0.1 (0.2) |
| 6 | 25 | 0.0 (0.1) | 0.1 (0.1) | 0.2 (0.4) | 0.0 (0.1) | 0.2 (0.3) |
| 12 | 24 | 0.1 (0.1) | 0.1 (0.2) | 0.1 (0.2) | 0.0 (0.1) | 0.1 (0.2) |
| 36 | 19 | 0.0 (0.2) | 0.0 (0.2) | 0.1 (0.3) | 0.0 (0.0) | 0.2 (0.6) |
| 60 | 15 | 0.0 (0.0) | 0.1 (0.3) | 0.3 (0.7) | 0.0 (0.0) | 0.1 (0.3) |

*mean (SD)

Kineret treatment also appeared to be associated with improvement of, or stability in, assessments of other NOMID disease manifestations, such as CNS, audiogram, and visual acuity data, up to Month 60.

## 15 REFERENCES

1. Cockcroft DW and Gault HM. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31-41.
2. Sharp JT, Young DY, Bluhm GB, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? *Arthritis Rheum.* 1985; 28:1326-1335.
3. National Cancer Institute. Surveillance, Epidemiology, and End Results Database (SEER) Program. SEER Incidence Crude Rates, 11 Registries, 1992-1999.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

**Storage**

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

**Rx only**

## 17 PATIENT COUNSELING INFORMATION

Instruct patients and their caregivers on the proper dosage and administration of Kineret and provide all patients with the "Patient information and Instructions for Use" insert. While this Patient Information and Instructions for Use 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. The ability to inject subcutaneously should be assessed to ensure proper administration of Kineret. Inform patients and their caregivers that the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex. Thoroughly instruct patients and their caregivers on the importance of proper disposal and caution against the reuse of needles, syringes, and drug product. A puncture-resistant container for the disposal of used syringes should be available to the patient. The full container should be disposed of according to the directions provided by the healthcare provider.

Infections: Inform patients that Kineret may lower the ability of their immune system to fight infections. Advise patients of the importance of contacting their doctor if they develop any symptoms of infection.

Injection-site reactions: Physicians should explain to patients that almost a quarter of patients in the clinical trial experienced a reaction at the injection site. Injection-site reactions may include pain, erythema, swelling, purities, brusing, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Patients should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Allergic or other drug reactions: Inform patients about the signs and symptoms of allergic and other adverse drug reactions and the appropriate actions they should take if they experience any of these signs and symptoms.

See FDA-approved patient labeling (Patient Information and Instruction for Use)


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