PRODUCT INFORMATION
KINERET®
(anakinra)

NAME OF THE MEDICINE
KINERET is the Swedish Orphan Biovitrum AB (publ) trademark for anakinra (rbe).

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 an additional 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 pre-filled syringes as a sterile, clear, colourless-to-white, preservative-free solution for daily subcutaneous (SC) administration. The solution may contain some small translucent-to-white particles of protein.

PHARMACOLOGY

KINERET blocks the biological activity of interleukin-1 (IL-1) by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI) which is expressed in a wide variety of tissues and organs.

IL-1 production is induced in response to inflammatory stimuli and mediates various physiological 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 rheumatoid arthritis (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 CAPS. CIAS1/NLRP3 encodes for cryopyrin, a component of the inflammasome. The activated inflammasome results in proteolytic maturation and secretion of IL-1β, which has a broad range of effects including systemic inflammation. Untreated CAPS patients are characterised by increased CRP, SAA and IL-6 relative to normal serum levels. Administration of KINERET results in a decrease in the acute phase reactants and a decrease in IL-6 expression level has been observed. Decreased acute phase protein levels are noted within the first weeks of treatment.

In addition to various degrees of arthritis, SJIA is characterised by systemic inflammatory features such as spiking fever, skin rash, hepatosplenomegaly, serositis, and increased acute phase reactants. An important role of IL-1 in the pathogenesis of SJIA has been demonstrated by ex vivo and gene expression studies.

Immunogenicity

In clinical trials, up to 3% of RA patients tested seropositive at least once during the study for antibodies capable of neutralising the biologic effects of anakinra. The occurrence of antibodies was typically transient and not associated with clinical adverse reactions or diminished efficacy.

In addition, in a clinical trial 6% of paediatric JIA patients tested seropositive at least once during the study for antibodies capable of neutralising the biologic effects of anakinra.

Pharmacokinetics

The absolute bioavailability of the commercial formulation has not been definitively established. However, the absolute bioavailability of development formulations was high

(> 80%) for a 70 mg SC bolus injection and the commercial formulation is likely to be comparable. In patients with RA, maximum plasma concentrations of KINERET occurred at 3 to 7 hours after SC administration of KINERET at clinically relevant doses (1 to 2 mg/kg; n = 18); the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of KINERET was observed after daily SC doses for up to 24 weeks. Evidence suggests that KINERET is predominantly metabolised in proximal renal tubules.

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

When comparing the dose-normalised concentration data in JIA patients with data in adult RA patients no major difference between the age groups were seen when comparing mean estimates, however, the variability was high in the data set (CV% 69-117).

A population PK/PD analysis in patients with SJIA and autoinflammatory syndromes (87 patients aged 8 months to 21 years including 22 SJIA patients aged 2-16 years) based on mean anakinra steady state plasma concentration of 0.4mg/L required to attain plasma C-reactive protein (CRP) level ≤ 10mg/L indicated a mean effective anakinra dose of 2 mg/kg/day for body weight 10-50 kg and 1 mg/kg up to a maximum of 100 mg/day for body weight >50 kg (see DOSAGE AND ADMINISTRATION).

The pharmacokinetics in CAPS patients is similar to that in RA patients. Anakinra exhibits approximate dose linearity with a slight tendency to higher than proportional increase.

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. The mean plasma clearance of KINERET decreased 70%-75% in normal subjects with severe or end stage renal disease (creatinine clearance < 30 mL/minute). No formal studies have been conducted examining the pharmacokinetics of KINERET administered subcutaneously in rheumatoid arthritis patients with renal impairment. The efficacy of alternative dosing regimens has not been examined in patients with renal impairment.

Patients With Hepatic Dysfunction:

No formal studies have been conducted examining the pharmacokinetics of KINERET administered subcutaneously in RA patients with hepatic impairment. However, a study including 12 patients with hepatic dysfunction (Child-Pugh Class B) given a single 1 mg/kg intravenous dose has been performed. Pharmacokinetic parameters were not substantially different from healthy volunteers, other than a decrease in clearance of approximately 30% in comparison with data from a study with healthy volunteers. A corresponding decrease in creatinine clearance was seen in the hepatic failure population. Accordingly, the decrease in clearance is most likely explained by a decrease in renal function in this population. These data support that no dose adjustment is required for patients with hepatic dysfunction of Child-Pugh Class B.

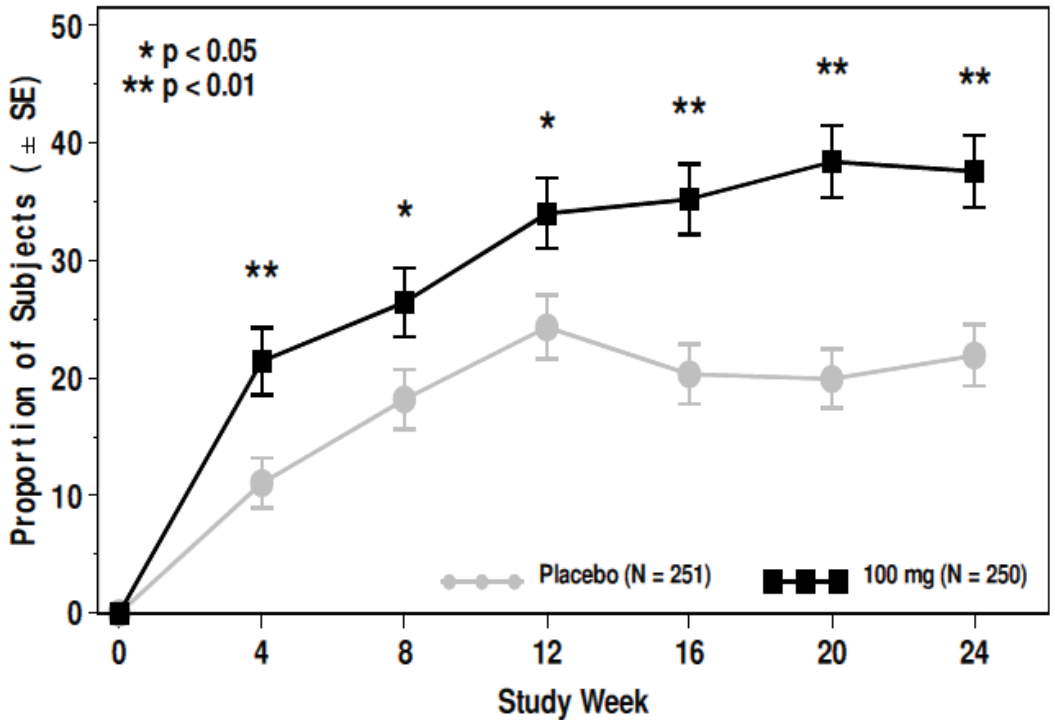
CLINICAL TRIALS

RA

The efficacy of KINERET versus placebo was studied in a phase 3 trial in 501 patients with active rheumatoid arthritis who had been on stable doses of methotrexate (10 to 25 mg/week) for at least 8 weeks. In addition, patients had at least 6 swollen/painful joints and 9 tender joints and either a C-reactive protein of ≥ 1.5 mg/dL or an ESR of ≥ 28 mm/hour. The patients were also required to have radiographic evidence of at least one bone erosion. Patients were maintained on methotrexate therapy during the study.

The primary efficacy variable was a 20% improvement in the American College of Rheumatology response criteria (ACR20) (composite score) at 24 weeks. KINERET, administered subcutaneously at a dose of 100 mg daily with background methotrexate, was shown to be more effective in achieving ACR20 (odds ratio = 2.36, 95% CI 1.55, 3.62) compared with placebo plus methotrexate. The results for sustained ACR20 (defined as achieving an ACR20 in at least 4 out of 6 study months with at least one of these ACR20 responses occurring at 12 or 24 weeks) were consistent with the primary analysis. The time course of ACR20 response is shown in Figure 1.

Figure 1. Percent of Patients[a] Achieving an ACR20 Response by Study Week (Methotrexate Co-administration)



[a]ITT population with non-responder imputation

Patients treated with KINERET were more likely to achieve an ACR20 or higher magnitude of response (ACR50 and ACR70) than patients treated with placebo (Table 1). The treatment response rates did not differ based on gender or ethnic group. Clinical responses to KINERET were seen by week 4 of enrolment.

Table 1. Percent of Patients With ACR Responses (Methotrexate Co-administration)

Response	Placebo n = 251	KINERET 100 mg/day n = 250
ACR 20		
month 3	24%	34%*
month 6	22%	38%***
ACR 50		
month 3	6%	13%**
month 6	8%	17%**
ACR 70		
month 3	0%	3%*
month 6	2%	6%*

*

p < 0.05, KINERET versus placebo
** p< 0.01, KINERET versus placebo
*** p < 0.001, KINERET versus placebo

CAPS

The safety and efficacy of KINERET have been demonstrated in 43 patients with severe CAPS aged 0.7 to 46 years (36 patients <18 years) in a prospective, long-term, open-label outcome study with a treatment duration of up to 5 years. Efficacy was demonstrated by decrease in disease-specific Diary Symptom Sum Score (DSSS), including the prominent disease symptoms fever, rash, joint pain, vomiting, and headache from baseline to 3-6 months and every 6 months thereafter while on treatment.

A significant improvement in all individual disease symptoms comprising the DSSS was seen, sustained up to Month 60. Results were consistent across age, gender, presence of CIAS1 mutation, and disease phenotype. There was also a rapid and sustained decrease in diary symptom score from baseline to Month 60 for secondary symptoms (fatigue, eye redness, sleep problems, seizures, and difficulties ambulating).

Levels of the biomarkers of inflammation serum amyloid A (SAA), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) decreased significantly from before to after 3 months of KINERET treatment and were sustained throughout the study.

Disease symptoms worsened and inflammatory serum markers increased during a treatment withdrawal phase and promptly improved again at reinstitution of KINERET therapy.

Indicators of active CNS involvement (including headache, lumbar puncture opening pressure, papilloedema, and CSF pleocytosis) and signs of inflammatory meningeal enhancement on brain MRI decreased during KINERET treatment. Manifestations of eye inflammation decreased, and visual acuity remained stable during the study. Estimated pure tone average (ePTA) data showed stable hearing during long-term treatment, and signs of cochlear inflammation on brain MRI showed significant reductions.

The number of patients on concomitant glucocorticoid treatment decreased during the study, and doses were considerably reduced for patients with continued steroid use.

Haematological lab tests at baseline showed signs of inflammation. Haemoglobin and haematocrit values were low and WBC counts, including neutrophils, were increased, reflecting active disease in the study population. All laboratory values improved after initiation of KINERET treatment.

SJIA

Limited evidence of efficacy was available from a study in which 24 SJIA patients were randomised to anakinra (2mg/kg/day SC to a maximum of 100mg/day) and placebo groups (12 patients in each group) for a double blind treatment for one month, followed by open label single arm anakinra treatment (N = 24) for 11 months.

Patients eligible for enrollment were aged 2-20 years with a diagnosis of SJIA according to Edmonton's criteria, more than 6 months' disease duration, active systemic disease (disease-related fever and/or C-reactive protein (CRP) > 20 mg/l and/or first hour erythrocyte sedimentation rate (ESR) >20) and significant overall disease activity at day 1 (D1) defined by at least three of the following Giannini's core-set items: (1) physician global assessment of disease activity ≥20/100; (2) parent/patient assessment of disease effect on overall wellbeing ≥20/100; (3) Childhood Health Assessment Questionnaire score ≥0.375/3; (4) ≥2 joints with active arthritis; (5) ≥2 joints with non-irreversible limited range of motion and (6) ESR ≥30 despite oral prednisone or prednisolone ≥0.3 mg/kg or 10 mg/day (whichever was lower). Intravenous or intra-articular steroids, immunosuppressive drugs and disease-modifying antirheumatic drugs (DMARDs) had to be stopped at least 1 month before study onset or for longer periods of time depending on their half-life.

The mean age of patients who participated was 9.5 years (SD 5.19) in anakinra group vs 7.5 years (SD 3.73) in placebo group. The mean duration of disease was 4.2 years (SD 3.3) in anakinra vs. 3.2 years (SD 1.95) in placebo group. The mean daily steroid dose was

0.52mg/kg (SD 0.237) in anakinra group vs. 0.66mg/kg (SD 0.373) in placebo group. A total of 8/12 patients in anakinra group and 11/12 patients in placebo group were on methotrexate (MTX) at baseline.

After a one month blinded phase, 8/12 patients in the KINERET treated group were identified as modified ACRpedi30 responders compared to 1/12 in the placebo group. At the same time point, 7/12 were classified as ACRpedi50 and 5/12 as ACRpedi70 responders compared to none in the placebo group. Twenty two patients entered the subsequent open-label phase in the study. Out of the patients randomised to receive KINERET throughout the study, the proportions of responders at Months 1, 2, 6 and 12 were 8/12 (67%), 5/12 (42%), 3/8 (38%) and 3/7 (43%), respectively. Out of the patients who initiated the KINERET treatment after Month 1, the proportions of responders at Months 1, 2, 6 and 12 were 1/11 (9%), 9/10 (90%), 3/9 (33%) and 4/9 (44%), respectively.

Immunogenicity results were not reported in this study.

INDICATIONS

KINERET (anakinra) is indicated

- for the treatment of active adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more other Disease Modifying Anti Rheumatic Drugs (DMARDs). KINERET should be given in combination with methotrexate.
- in adult and paediatric patients aged 8 months and older with a body weight of 10 kg or above for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS) including Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA), Muckle-Wells Syndrome (MWS), and Familial Cold Autoinflammatory Syndrome (FCAS).
- for the treatment of active Systemic Juvenile Idiopathic Arthritis (SJIA) in patients 2 years and above who have failed to respond adequately to non-biological DMARDs.

CONTRAINDICATIONS

Combination therapy with KINERET (anakinra) and TNF-alpha antagonist drugs is contraindicated.

KINERET (anakinra) is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, KINERET or any components of the product.

KINERET treatment must not be initiated in patients with neutropaenia (ANC $<1.5 \times 10^9$/l) (see PRECAUTIONS).

PRECAUTIONS

General

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

KINERET is not recommended for use in patients with severe renal impairment.

The safety and efficacy of Kineret in patients with cardiac impairment has not specifically been evaluated.

Hepatic Events

In clinical studies in RA and CAPS patients, transient elevations of liver enzymes have been seen uncommonly. These elevations have not been associated with signs or symptoms of damage. During post-marketing use isolated case reports indicating noninfectious hepatitis have been received. Hepatic events during post-marketing use have mainly been reported in patients with predisposing factors, e. g history of transaminase elevations before start of Kineret treatment.

The efficacy and safety of Kineret in patients with AST/ALT ≥1.5 x upper level of normal have not been evaluated.

Serious Infections

Physicians should exercise caution when administering KINERET to patients with a history of recurring infections or with underlying conditions which may predispose them to infections.

KINERET has been associated with an increased incidence of serious infections (1.8%) compared with placebo (0.7%). In clinical studies, the risk for serious infection was higher in patients with a history of asthma compared to patients without a history of asthma.

The safety and efficacy of KINERET in patients with chronic infections have not specifically been evaluated. Patients who develop a new infection while being treated with KINERET should be monitored closely. Administration of KINERET in RA and SJIA patients should be discontinued if a patient develops a serious infection or sepsis. Treatment with KINERET should not be initiated in patients with active infections including chronic or localised infections. Doctors should exercise caution when considering the use of KINERET in patients with a history of recurring infections or with underlying conditions that may predispose the patient to infections such as advanced or poorly controlled diabetes.

In KINERET treated CAPS patients the risk of a disease flare when discontinuing treatment should be considered.

The safety of KINERET in individuals with latent tuberculosis is unknown. There have been reports of tuberculosis in patients receiving several biological anti-inflammatory treatment regimens. Patients should be screened for latent tuberculosis prior to initiating KINERET.

Other anti-rheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed also before starting therapy with KINERET.

Neutropaenia

KINERET was commonly associated with neutropaenia (ANC <1.5 x 10^9/L) in placebo-controlled studies in RA and has been observed in CAPS and SJIA patients.

KINERET treatment should not be initiated in patients with neutropaenia (ANC <1.5 x 10^9/l). It is recommended that neutrophil counts be assessed prior to initiating KINERET treatment, and while receiving KINERET, monthly during the first 6 months of treatment and quarterly hereafter. In patients who become neutropenic (ANC <1.5 x 10^9/l) the ANC should be monitored closely and KINERET treatment should be discontinued. The safety and efficacy of KINERET in patients with neutropaenia have not been evaluated.

Concurrent Treatment With KINERET and TNF-alpha Antagonists

Combination therapy with KINERET and TNF-alpha antagonist drugs is contraindicated. Concurrent administration of KINERET with TNF-alpha antagonists has been associated with an increased risk of serious infection and neutropaenia compared to KINERET alone. The combination has not been demonstrated to produce increased clinical benefit.

Immunosuppression

It is unknown if chronic exposure to KINERET can increase the incidence of malignancies. The use of KINERET in patients with pre-existing malignancy is not recommended.

Immunisations

It is recommended that, if possible, paediatric and adult patients should complete all immunisations in accordance with current immunisation guidelines prior to initiating KINERET treatment. It is also recommended that hepatitis B status is confirmed and vaccination completed prior to therapy with KINERET. However, in patients with severe CAPS the risk of not completing all immunisations should be weighed against the risk of not starting KINERET treatment.

In a placebo-controlled clinical trial in RA patients (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.

Paediatric Use

The safety and efficacy of KINERET have been demonstrated in 36 paediatric CAPS patients. Overall, the efficacy and safety profile of KINERET is comparable in adult and paediatric CAPS patients.

KINERET was studied in a single randomised, 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 paediatric use in Juvenile Rheumatoid Arthritis.

Use in the Elderly

A total of 653 patients ≥ 65 years of age, including 135 patients ≥ 75 years of age, were studied in clinical trials in RA. No overall differences in safety or effectiveness were observed between these patients and younger patients. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Carcinogenicity, Genotoxicity and Effects on Fertility

KINERET has not been evaluated for its carcinogenic potential in animals. It is known that many different types, but not all cancer cells, express the interleukin-1 receptor. Depending on the cancer cell type, activation of the receptor by interleukin-1 can cause a variety of anti-proliferative or proliferative responses. Insufficient data are available on the effect of KINERET on sub-detectable cancer cells in animals or patients. Therefore, KINERET is not recommended for use in patients with pre-existing cancer unless clearly needed.

In rats and rabbits, KINERET at doses of up to 15-30 fold greater than the human dose (based on body surface area adjusted dose) had no adverse effects on male or female fertility.

Use in Pregnancy

Category B1

Reproductive studies have been conducted with KINERET on rats and rabbits at doses up to 15-30 fold greater (based on body surface area adjusted dose) than the human dose and have revealed no evidence of impaired fertility or harm to the foetus. There are, however, no adequate and well-controlled studies in pregnant women. As animal reproduction studies are not always predictive of human response, KINERET should be used during pregnancy only if clearly needed.

Use in Lactation

It is not known whether KINERET is secreted in human breast milk. The protein that KINERET mimics (interleukin-1 receptor antagonist) occurs naturally in human breast milk. Should KINERET or antibodies to KINERET be secreted in breast milk, the effect on the

immune competence of the neonate is unknown. Exposure of lactating rats to doses of KINERET up to 15-30 fold greater (based on body surface area adjusted dose) than the human dose did not have any apparent effect on the offspring. Caution should be exercised if KINERET is administered to women who are breastfeeding.

Effects on Laboratory Tests

In placebo-controlled studies with KINERET, treatment was associated with small reductions in the mean values for total white blood count, platelets and absolute neutrophil blood count and a small increase in the mean eosinophil differential percentage.

In the placebo-controlled studies, 8% of patients receiving KINERET had decreases in neutrophil counts of at least 1 World Health Organisation (WHO) toxicity grade, compared with 2% in the placebo control group. Six KINERET-treated patients (0.3%) experienced neutropaenia (ANC < 1 x 10^9/L).

Additional patients treated with KINERET plus etanercept (3/139, 2%) developed ANC < 1 x 10^9/L. While neutropenic, one patient developed cellulitis which recovered with antibiotic therapy.

Blood counts should be assessed prior to initiating KINERET treatment and be monitored on a regular basis while receiving KINERET.

INTERACTIONS WITH OTHER MEDICINES

Interactions between KINERET and other medicines have not been investigated in formal studies. In clinical trials, interactions between KINERET and other medicines (including nonsteroidal anti-inflammatory drugs, corticosteroids and DMARDs) have not been observed.

TNF Blocking Agent

In two studies in RA, where patients received concurrent etanercept and KINERET therapy and were treated for up to 24 weeks, a 7% rate of serious infections was observed which was higher than when either agent was used alone (see also PRECAUTIONS). Two percent of patients (3/139) treated concurrently with KINERET and etanercept developed neutropaenia (ANC < 1 x 10^9/L).

Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus, it may be expected that for an IL-1 receptor antagonist, such as anakinra, the formation of CYP450 enzymes could be normalised during treatment. This would be clinically relevant for CYP450 substrates with a narrow therapeutic index (e.g. warfarin). Upon start or end of KINERET treatment in patients on these types of medicinal products, it may be relevant to consider therapeutic monitoring of the effect or drug concentration of these products and the individual dose of the medicinal product may need to be adjusted.

ADVERSE EFFECTS

In placebo-controlled RA studies, comprising 3330 patients (KINERET: 2372, Placebo: 958), the subject incidence of serious adverse reactions at the recommended dose of KINERET (100 mg/day) was comparable with placebo (7.1% compared with 6.5% in the placebo group).

Adverse events data in CAPS patients are based on an open-label study of 43 patients with NOMID/CINCA treated with KINERET for up to 5 years, with a total KINERET exposure of 159.8 patient years. During the 5-year study 14 patients (32.6%) reported 24 serious events. Eleven serious events in 4 (9.3%) patients were considered related to KINERET. No patient withdrew from KINERET treatment due to adverse events.

Adverse events data in SJIA patients is based on a partially open-label and partially blinded, placebo-controlled study of 15 SJIA patients, treated for up to 1.5 years. In addition, post-marketing adverse event reports and published studies constitute supporting data.

There are no indications from clinical studies, or from post-marketing adverse event reports and published studies, that the overall safety profile in CAPS or SJIA patients is different from that in RA patients with the exception of MAS in SJIA patients. The adverse reactions table below therefore applies to KINERET treatment in RA, CAPS and SJIA patients. Additional information on MAS is provided below.

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2. Adverse Reactions identified from RA and CAPS clinical trials by Body System and Preferred Term

MedDRA Organ System	Frequency	Undesirable Effect
Infections and infestations	Common (≥ 1/100 to < 1/10)	Serious infections
Blood and lymphatic system disorders	Common (≥ 1/100 to < 1/10)	Neutropaenia Thrombocytopaenia
Immune system disorders	Uncommon (≥ 1/1,000 to < 1/100)	Allergic reactions including anaphylactic reactions, angioedema, urticaria and pruritus
Nervous system disorders	Very common (≥ 1/10)	Headache
Hepatobiliary system	Uncommon (≥ 1/1,000 to < 1/100)	Hepatic enzyme increased
	Not known (cannot be estimated from the available data)	Non-infectious hepatitis
Skin and subcutaneous tissue disorders	Very common (≥ 1/10)	Injection site reaction
	Uncommon (≥ 1/1,000 to < 1/100)	Rash
Investigations	Very common (≥ 1/10)	Blood cholesterol increased

Serious infections

The incidence of serious infections in RA studies conducted at the recommended dose (100 mg/day) was 1.8% in KINERET treated patients and 0.7% in placebo-treated patients. In observations up to 3 years, the serious infection rate did not increase over time. Serious infections observed consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections. Most patients continued on study drug after the infection resolved.

Although the overall rate of serious infections was low, the higher incidence rate in the KINERET-treated group relative to placebo suggests a possible association between KINERET and serious infections.

An increased incidence of serious infections was observed in patients receiving concurrent KINERET and etanercept therapies (see PRECAUTIONS).

In 15 SJIA patients followed for up to 1.5 years, one patient developed a serious hepatitis due to a cytomegalovirus infection. There are no indications from post-marketing experience that types and severity of infections in SJIA patients differs from that in RA or CAPS patients.

In clinical studies of RA and SJIA and in the 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 alone or in combination with immunosuppressive agents.

In 43 CAPS patients followed for up to 5 years, 10 patients reported serious infections, the most common being pneumonia and gastroenteritis. KINERET treatment was temporarily stopped in one patient, all other patients continued KINERET treatment during the infections. There were no deaths due to serious infections in RA or CAPS studies.

Neutropaenia

In placebo-controlled studies in RA, treatment was associated with small reductions in the mean values for total white blood count and absolute neutrophil count (ANC). Neutropaenia (ANC $<1.5 \times 10^9$/L) was reported in 2.4% of patients receiving KINERET compared with 0.4% of placebo patients.

In 43 CAPS patients followed for up to 5 years neutropaenia was reported in 2 patients. Both episodes of neutropaenia resolved over time with continued KINERET treatment.

In 15 SJIA patients followed for up to 1.5 years, one event of transient neutropaenia was reported. There have been isolated reports of neutropaenia during post-marketing use.

Thrombocytopaenia

In clinical studies in RA patients, thrombocytopaenia has been reported in 1.9% of treated patients compared to 0.3% in the placebo group. The thrombocytopaenias have been mild, i.e. platelet counts have been $>75 \times 10^9$/L. Mild thrombocytopaenia has also been observed in CAPS and SJIA patients.

During post-marketing use of KINERET, thrombocytopaenia has been reported, including occasional case reports indicating severe thrombocytopaenia (i.e. platelet counts $<10 \times 10^9$/L).

Allergic reactions

Allergic reactions including anaphylactic reactions, angioedema, urticaria, rash, and pruritus have been reported uncommonly with KINERET.

In 43 CAPS patients followed for up to 5 years, no allergic event was serious and no event required discontinuation of KINERET.

In 15 SJIA patients followed for up to 1.5 years, no allergic event was serious and no event required discontinuation of KINERET.

Hepatic Events

In clinical studies in RA, CAPS and SJIA patients, transient elevations of liver enzymes have been seen uncommonly. These elevations have not been associated with signs or symptoms of hepatocellular damage. During post-marketing use isolated case reports indicating non-infectious hepatitis have been received. Hepatic events during post-marketing use have mainly been reported in patients that have been treated for SJIA, in patients with predisposing factors, e.g. history of transaminase elevations before start of KINERET treatment, or in patients that have been treated outside of the approved label.

Injection site reactions (ISR)

In RA patients the most common and consistently reported treatment-related adverse reactions associated with KINERET treatment were ISRs. The majority (95%) of ISRs were reported as mild to moderate. These were typically characterised by 1 or more of the following: erythema, ecchymosis, inflammation, and pain. At a dose of 100 mg/day, 71% of RA patients developed an ISR compared to 28% of the placebo treated patients.

In 43 CAPS patients followed for up to 5 years, no patient permanently or temporarily discontinued KINERET treatment due to ISRs.

In 15 SJIA patients followed for up to 1.5 years, the most common and consistently reported treatment-related adverse reactions associated with KINERET treatment were ISRs. One out of 15 patients discontinued due to ISRs.

ISRs were typically reported within the first 4 weeks of therapy with a median duration in RA studies of 14 to 28 days and resolved during continued KINERET treatment. The development of ISRs in patients who had not previously experienced ISRs was uncommon after the first month of therapy.

Immunogenicity

In clinical trials, the occurrence of antibodies in RA patients was typically transient and not associated with clinical adverse reactions or diminished efficacy (see PHARMACOLOGY).

The majority of CAPS patients in Study 03-AR-0298 developed anakinra anti-drug-antibodies. This was not associated with any clinically significant effects on pharmacokinetics, efficacy, or safety.

Malignancies

RA patients may be at higher risk (on average 2-3 fold) for the development of lymphoma. In clinical trials, whilst patients treated with KINERET had a higher incidence of lymphoma than the expected rate in the general population, this rate is consistent with rates reported in general for RA patients.

In clinical trials, the incidence of malignancies was the same in KINERET-treated RA patients and placebo-treated patients and did not differ from that in the general population. Furthermore, the overall incidence of malignancies was not increased during 3 years of patient exposure to KINERET.

There is no information available on the incidence of malignancies in CAPS patients receiving KINERET.

Blood cholesterol increase

In clinical studies of RA, 775 patients treated with daily KINERET doses of 30 mg, 75 mg, 150 mg, 1 mg/kg or 2 mg/kg, there was an increase of 2.4% to 5.3% in total cholesterol levels 2 weeks after start of KINERET treatment, without a dose-response relationship. A similar pattern was seen after 24 weeks of KINERET treatment. Placebo treatment (n=213) resulted in a decrease of approximately 2.2% in total cholesterol levels at week 2 and 2.3% at week 24. No data are available on LDL or HDL cholesterol.

Macrophage activation syndrome (MAS)

During post-marketing use isolated case reports of MAS in SJIA patients have been received. SJIA patients have an increased risk of spontaneous development of MAS. A causal relationship between KINERET and MAS has not been established.

Paediatric population

KINERET has been studied in 122 paediatric patients: 36 CAPS patients, 15 SJIA patients and 71 patients with other forms of juvenile idiopathic arthritis (JIA) and CAPS patients, aged 8 months to 17 years, for up to 5 years. With the exception of infections and related symptoms that were more frequently reported in patients <2 years, the safety profile was similar in all paediatric age groups. The safety profile in paediatric patients was similar to that seen in adult populations and no clinically relevant new adverse reactions were seen.

Other Adverse Reactions in RA

Adverse events, reported in at least 2% of patients treated with KINERET who used the 100 mg/day fixed dose, are shown in Table 3.

Table 3. Patient Incidence of Most Frequent Treatment-Emergent Adverse Events (≥ 2% in KINERET 100 mg/day Group) by Body System and Preferred Term

BODY SYSTEM Preferred Term	Placebo (n = 534) %	KINERET 100 mg/day (n = 1366) %
APPLICATION SITE		
Injection Site Reaction	28.5	71.2
BODY AS A WHOLE		
Influenza-Like Symptoms	5.2	6.0
Oedema Peripheral	4.5	3.8
Injury	3.2	2.9
Fever	1.5	2.2
Pain Chest	1.3	2.2
Fatigue	3.7	3.6
CARDIOVASCULAR		
Hypertension	2.6	4.5
CNS/PNS		
Headache	8.8	12.3
Dizziness	4.3	4.5
Insomnia	2.2	3.1
GASTROINTESTINAL		
Nausea	6.4	8.4
Diarrhoea	5.2	7.1
Pain Abdominal	4.5	5.3
Dyspepsia	4.3	4.7
Vomiting	4.1	3.0
HAEMATOLOGIC		
Ecchymosis	1.1	2.0
MUSCULO-SKELETAL		
Arthritis Rheumatoid	28.5	19.1
Arthralgia	6.6	5.6
Pain Limb	2.8	4.3
Pain Back	3.2	4.2
Myalgia	2.1	3.0
Fracture	0.9	2.1
PSYCHIATRIC DISORDER		
Depression	1.7	2.0
RESISTANCE MECHANISM		
Infection	2.4	2.9
RESPIRATORY		
Infection Upper Respiratory	15.2	13.8
Sinusitis	5.6	7.1
Cough	3.6	3.7
Sore Throat	3.6	3.7
Bronchitis	4.1	3.7
Upper Respiratory Tract Congestion	2.1	2.6
Dyspnoea	2.1	2.1

BODY SYSTEM Preferred Term	Placebo (n = 534) %	KINERET 100 mg/day (n = 1366) %
SKIN AND APPENDAGES		
Rash	4.1	4.1
Pruritus	2.1	2.1
URINARY DISORDER		
Infection Urinary Tract	4.5	4.6

Other Adverse Reactions in CAPS

Table 4. Most common (≥ 10% patients) Treatment-Emergent Adverse Events during the first 6 months of KINERET Treatment

	Safety Population (N= 43) Total exposure in patient years = 20.8	
BODY SYSTEM Preferred Term	**N (%)**	**Number of events/patient year**
APPLICATION SITE		
Injection Site Reaction	7 (16.3%)	0.5
CNS/PNS		
Headache	6 (14.0%)	0.7
GASTROINTESTINAL		
Vomiting	6 (14.0%)	0.6
MUSCULO-SKELETAL		
Arthralgia	5 (11.6%)	0.6
BODY AS A WHOLE		
Pyrexia	5 (11.6%)	0.4
RESPIRATORY		
Nasopharyngitis	5 (11.6%)	0.3

DOSAGE AND ADMINISTRATION

RA

The recommended dose of KINERET in adults and the elderly is 100 mg/day administered by subcutaneous injection. The dose should be administered at approximately the same time every day.

Alternating the injection site is recommended to avoid discomfort at the site of injection.

Concurrent treatment with KINERET and TNF-alpha antagonists is contraindicated (see CONTRAINDICATIONS).

CAPS

Starting dose:
The recommended starting dose for both adults and children is 1-2 mg/kg/day by SC injection. The therapeutic response is primarily reflected by reduction in clinical symptoms such as fever, rash, joint pain, and headache, but also in inflammatory serum markers (CRP/SAA levels), or occurrence of flares.

Maintenance dose in mild CAPS (FCAS, mild MWS):
Patients are usually well-controlled by maintaining the recommended starting dose (1-2 mg/kg/day).

Maintenance dose in severe CAPS (MWS and NOMID/CINCA):
Dose increases may become necessary within 1-2 months based on therapeutic response. The usual maintenance dose in severe CAPS is 3-4 mg/kg/day, which can be adjusted to a maximum of 8 mg/kg/day.

In addition to the evaluation of clinical symptoms and inflammatory markers in severe CAPS, assessments of inflammation of the CNS, including the inner ear (MRI or CT, lumbar puncture, and audiology) and eyes (ophthalmological assessments) are recommended after an initial 3 months of treatment, and thereafter every 6 months, until effective treatment doses have been identified. When patients are clinically well-controlled, CNS and ophthalmological monitoring may be conducted yearly.

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.

SJIA

The recommended dose in SJIA is 2 mg/kg/day up to a maximum of 100 mg/day by SC injection.

Treatment should be undertaken by physicians experienced in the treatment of SJIA. Decisions should be guided by clinical outcomes including laboratory measures. The treating physician should consider whether patients without clinical improvement should continue treatment with anakinra.

Hepatic impairment

No dose adjustment is required for patients with moderate hepatic impairment (Child-Pugh Class B). KINERET should be used with caution in patients with severe hepatic impairment.

Renal impairment

Physicians should consider administration of the prescribed dose of KINERET every other day for patients who have severe renal insufficiency (defined as creatinine clearance < 30 mL/min, as estimated from serum creatinine levels), or end stage renal disease. In the absence of adequate data, KINERET should be used with caution in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/minute).

Paediatric Use

CAPS: Posology and administration in children and infants aged 8 months and older with a body weight of 10 kg or above are the same as for adult CAPS patients, based on body weight. No data are available in children under the age of 8 months.

Preparation and Administration of KINERET

KINERET contains no antimicrobial agent. KINERET is for single use in one patient on one occasion only. Discard any residue.

The graduated pre-filled syringe allows for doses between 20 and 100 mg. As the minimum dose is 20 mg the syringe is not suitable for paediatric patients with a body weight below 10 kg.

Prior to administration, visually inspect the solution for particulate matter and discolouration. There may be small translucent-to-white particles of protein in the solution. This is not unusual for proteins in solution. The solution should not be used if discoloured or cloudy or if foreign particulate matter, i.e. clumps, large or coloured particles, are present.

Avoid shaking. Allow the pre-filled syringe to reach room temperature before injecting. Invert KINERET gently prior to injection.

Alternating the injection site is recommended to avoid discomfort at the site of injection. Cooling of the injection site, warming the injection liquid, use of cold packs (before and after

the injection), and use of topical corticosteroids and antihistamines after the injection can alleviate the signs and symptoms of injection site reactions.

OVERDOSAGE

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

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

KINERET is supplied in single use pre-filled syringes with a 29 gauge needle. Each pre-filled syringe contains:

0.67 mL (100 mg) of anakinra formulated at pH 6.5 with 0.70 mg polysorbate 80, 1.29 mg sodium citrate, 5.48 mg sodium chloride, and 0.12 mg disodium EDTA in Water for Injections, USP.

KINERET is available in packs containing 28 syringes. The pre-filled syringe has an outer rigid plastic needle shield attached to an inner needle cover. None of the syringe or needle shield components are made with natural rubber latex.

Store at 2° to 8°C. (Refrigerate. Do not freeze.) Avoid shaking. Protect from light. Allow the pre-filled syringe to reach room temperature before injecting. KINERET may be removed from storage for a total period of 12 hours at room temperature (up to 25°C).

NAME AND ADDRESS OF MANUFACTURER

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

NAME AND ADDRESS OF THE SPONSOR

A.Menarini Australia Pty Limited
Level 8, 67 Albert Avenue
Chatswood NSW 2067

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

28 November 2008

DATE OF MOST RECENT AMENDMENT

26 August 2016