

1. NAME OF THE MEDICINAL PRODUCT

Kineret 100 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each graduated pre-filled syringe contains 100 mg of anakinra* per 0.67 ml (150 mg/ml).

* Human interleukin-1 receptor antagonist (r-metHuIL-1ra) produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless-to-white solution for injection that may contain some product-related translucent-to-white amorphous particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kineret 100 mg solution for injection is indicated in adults for the treatment of the signs and symptoms of Rheumatoid Arthritis (RA) in combination with methotrexate, in patients with an inadequate response to methotrexate alone.

Kineret 100 mg solution for injection is indicated in adults, adolescents, children and infants 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)
- Familial Cold Autoinflammatory Syndrome (FCAS)

Kineret 100 mg solution for injection is indicated for the treatment of Familial Mediterranean Fever (FMF). Kineret 100 mg solution for injection should be given in combination with colchicine, if appropriate.

4.2 Posology and method of administration

Kineret 100 mg solution for injection treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of Rheumatoid Arthritis, FMF and CAPS, respectively.

Posology

RA: Adults

The recommended dose of Kineret 100 mg solution for injection is 100 mg administered once a day by subcutaneous injection. The dose should be administered at approximately the same time each day.

CAPS: Adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above.

Starting dose:

The recommended starting dose in all CAPS subtypes is 1-2 mg/kg/day by subcutaneous 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.

FMF - Adults, adolescents and children aged 2 years and older

The recommended dose for patients weighing 50 kg or more is 100 mg/day by subcutaneous injection. Patients weighing less than 50 kg should be dosed by body weight with a recommended dose of 1- 2 mg/kg/day.

Elderly population (≥ 65 years)

No dose adjustment is required in RA patients. Posology and administration are the same as for adults 18 to 64 years of age.

Data in elderly CAPS patients are limited. No dose adjustments are expected to be required.

Paediatric population (< 18 years)

RA: The efficacy of Kineret 100 mg solution for injection in children with RA (JIA) aged 0 to 18 years has not been established.

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.

FMF: No data are available in children under 2 years of age with FMF.

Hepatic impairment

No dose adjustment is required for patients with moderate hepatic impairment (Child-Pugh Class B). Kineret 100 mg solution for injection should be used with caution in patients with severe hepatic impairment.

Renal impairment

No dosage adjustment is needed for patients with mild renal impairment (CL_{cr} 50 to 80 ml/minute). In the absence of adequate data, Kineret should be used with caution in patients with moderate renal impairment (CL_{cr} 30 to 50 ml/minute). Kineret must not be used in patients with severe renal impairment (CL_{cr} < 30 ml/minute). See section 4.3.

Method of administration

Kineret 100 mg solution for injection is administered by subcutaneous injection.

Kineret 100 mg solution for injection is supplied ready for use in graduated a pre-filled syringe. 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. The pre-filled syringe should not be shaken. The instructions for use and handling are given in section 6.6.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to *E. coli* derived proteins.

Kineret 100 mg solution for injection treatment must not be initiated in patients with neutropenia (ANC <1.5 x 10⁹/l). See section 4.4.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Allergic reactions

Allergic reactions, including anaphylactic reactions and angioedema have been reported uncommonly. The majority of these reactions were maculopapular or urticarial rashes.

If a severe allergic reaction occurs, administration of Kineret 100 mg solution for injection should be discontinued and appropriate treatment initiated.

Hepatic Events

In clinical studies transient elevations of liver enzymes have been seen. These elevations have not been associated with signs or symptoms of hepatocellular damage, except for one patient with SJIA that developed a serious hepatitis in connection with a cytomegalovirus infection.

During post-marketing use hepatic events, not affecting liver function, have been reported. The majority of patients have been treated for Still's disease or have had predisposing factors, e.g. a history of transaminase elevations. In addition cases of non-infectious hepatitis, including occasional events of acute liver failure, have been reported in patients with Still's disease during Kineret treatment. Hepatic events in patients with Still's disease predominantly occur during the first month of Kineret treatment. Routine testing of hepatic enzymes during the first month should be considered, especially if the patient has pre-disposing factors or develops symptoms indicating liver dysfunction. The efficacy and safety of Kineret in patients with $AST/ALT \geq 1.5 \times$ upper level of normal have not been evaluated.

Serious infections

Kineret 100 mg solution for injection has been associated with an increased incidence of serious infections (1.8%) vs. placebo (0.7%) in RA patients. For a small number of patients with asthma, the incidence of serious infection was higher in Kineret-treated patients (4.5%) vs. placebo-treated patients (0%); these infections were mainly related to the respiratory tract.

The safety and efficacy of Kineret 100 mg solution for injection treatment in patients with chronic and serious infections have not been evaluated.

Kineret 100 mg solution for injection treatment should not be initiated in patients with active infections. Kineret treatment should be discontinued in RA patients if a serious infection develops. In Kineret 100 mg solution for injection treated CAPS or FMF patients, there is a risk for disease flares when discontinuing Kineret 100 mg solution for injection treatment. With careful monitoring, Kineret 100 mg solution for injection treatment can be continued also during a serious infection.

Physicians should exercise caution when administering Kineret 100 mg solution for injection to patients with a history of recurring infections or with underlying conditions which may predispose them to infections.

The safety of Kineret 100 mg solution for injection 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 100 mg solution for injection. The available medical guidelines should also be taken into account.

Other anti-rheumatic therapies have been associated with hepatitis B reactivation. Therefore, screening for viral hepatitis should be performed in accordance with published guidelines also before starting therapy with Kineret 100 mg solution for injection.

Renal impairment

Kineret 100 mg solution for injection is eliminated by glomerular filtration and subsequent tubular metabolism. Consequently, plasma clearance of Kineret 100 mg solution for injection decreases with decreasing renal function.

No dose adjustment is needed for patients with mild renal impairment (CL_{cr} 60 to 89 ml/min). Kineret 100 mg solution for injection should be used with caution in patients with moderate renal

impairment (CLcr 30 to 59 ml/min). In patients with severe renal impairment (CLcr <30 ml/min) or end stage renal disease, including dialysis, administration of the prescribed dose of Kineret 100 mg solution for injection every other day should be considered.

Neutropenia

Kineret 100 mg solution for injection was commonly associated with neutropenia (ANC < $1.5 \times 10^9/l$) in placebo-controlled studies in RA and cases of neutropenia have been observed in patients with CAPS. For more information on neutropenia see section 4.8.

Kineret 100 mg solution for injection treatment should not be initiated in patients with neutropenia (ANC < $1.5 \times 10^9/l$). It is recommended that neutrophil counts be assessed prior to initiating Kineret 100 mg solution for injection treatment, and while receiving Kineret 100 mg solution for injection, monthly during the first 6 months of treatment and quarterly hereafter. In patients who become neutropenic (ANC < $1.5 \times 10^9/l$) the ANC should be monitored closely and Kineret 100 mg solution for injection treatment should be discontinued. The safety and efficacy of Kineret 100 mg solution for injection in patients with neutropenia have not been evaluated.

Pulmonary Events

During post-marketing use events of interstitial lung disease, pulmonary alveolar proteinosis and pulmonary hypertension have been reported mainly in paediatric patients with Still's disease treated with IL-6 and IL-1 inhibitors, including Kineret. Patients with trisomy 21 seem to be overrepresented. A causal relationship with Kineret has not been established.

Immunosuppression

The impact of treatment with Kineret 100 mg solution for injection on pre-existing malignancy has not been studied. Therefore, the use of Kineret 100 mg solution for injection in patients with pre-existing malignancy is not recommended.

Malignancies

RA patients may be at a higher risk (on average 2-3 fold) for the development of lymphoma. In clinical trials, whilst patients treated with Kineret 100 mg solution for injection 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 crude incidence rate of malignancy was the same in the Kineret-treated patients and the 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 100 mg solution for injection.

Vaccinations

In a placebo-controlled clinical trial (n = 126), no difference was detected in anti-tetanus antibody response between the Kineret 100 mg solution for injection and placebo treatment groups when a tetanus/diphtheria toxoid vaccine was administered concurrently with Kineret 100 mg solution for injection. No data are available on the effects of vaccination with other inactivated antigens in patients receiving Kineret 100 mg solution for injection.

No data are available on either the effects of live vaccination or on the secondary transmission of infection by live vaccines in patients receiving Kineret 100 mg solution for injection. Therefore, live vaccines should not be given concurrently with Kineret 100 mg solution for injection.

Elderly population (> 65 years)

A total of 752 RA patients ≥ 65 years of age, including 163 patients ≥ 75 years of age, were studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. There is limited experience in treating elderly CAPS and FMF disease patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating elderly patients.

Concurrent Kineret 100 mg solution for injection and TNF- α antagonist treatment

Concurrent administration of Kineret 100 mg solution for injection and etanercept has been associated with an increased risk of serious infections and neutropenia compared to etanercept alone in RA patients. This treatment combination has not demonstrated increased clinical benefit.

The concurrent administration of Kineret 100 mg solution for injection and etanercept or other TNF- α antagonists is not recommended (see section 4.5).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions between Kineret 100 mg solution for injection and other medicinal products have not been investigated in formal studies. In clinical trials, interactions between Kineret 100 mg solution for injection and other medicinal products (including nonsteroidal anti-inflammatory medicinal products, glucocorticoids, and DMARDs) have not been observed.

Concurrent Kineret 100 mg solution for injection and TNF- α antagonist treatment

In a clinical trial with RA patients receiving background methotrexate, patients treated with Kineret 100 mg solution for injection and etanercept were observed to have a higher rate of serious infections (7%) and neutropenia than patients treated with etanercept alone and higher than observed in previous trials where Kineret 100 mg solution for injection was used alone. Concurrent Kineret 100 mg solution for injection and etanercept treatment has not demonstrated increased clinical benefit.

The concurrent use of Kineret 100 mg solution for injection with etanercept or any other TNF- α antagonist is not recommended (see section 4.4).

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 normalized during treatment. This would be clinically relevant for CYP450 substrates with a narrow therapeutic index (e.g. warfarin and phenytoin). Upon start or end of Kineret 100 mg solution for injection treatment in patients on these types of medicinal products, it may be relevant to consider therapeutic monitoring of the effect or concentration of these products and the individual dose of the medicinal product may need to be adjusted.

For information on vaccinations see section 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of anakinra in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of anakinra during pregnancy and in woman of childbearing potential not using contraception.

Breast-feeding

It is unknown whether anakinra/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with Kineret.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

In placebo-controlled studies in RA patients, the most frequently reported adverse reactions with Kineret 100 mg solution for injection were injection site reactions (ISRs), which were mild to moderate in the majority of patients. The most common reason for withdrawal from study in Kineret 100 mg solution for injection -treated RA patients was injection site reaction. The subject incidence of serious adverse reactions in RA studies at the recommended dose of Kineret 100 mg solution for injection (100 mg/day) was comparable with placebo (7.1% compared with 6.5% in the placebo group). The incidence of serious infection was higher in Kineret 100 mg solution for injection -treated patients compared to patients receiving placebo (1.8% vs. 0.7%). Neutrophil decreases occurred more frequently in patients receiving Kineret 100 mg solution for injection compared with placebo.

Adverse reactions data in CAPS patients are based on an open-label study of 43 patients with NOMID/CINCA treated with Kineret 100 mg solution for injection for up to 5 years, with a total Kineret 100 mg solution for injection exposure of 159.8 patient years. During the 5-year study, 14 patients (32.6%) reported 24 serious events. Eleven serious events in four (9.3%) patients were considered related to Kineret 100 mg solution for injection. No patient withdrew from Kineret 100 mg solution for injection treatment due to adverse reactions.

Adverse events data in patients with FMF are based on post-marketing adverse event reports and published studies.

There are no indications either from these studies or from post-marketing adverse reaction reports that the overall safety profile in patients with CAPS, FMF or Still's disease is different from that in patients with RA, with the exception of the risk for development of MAS in patients with Still's disease. The adverse reactions table below therefore applies to Kineret treatment of RA, CAPS, FMF and Still's disease.

Tabulated list of adverse reactions

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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.

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)	Neutropenia Thrombocytopenia
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 disorders	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 100 mg solution for injection treated patients and 0.7% in placebo-treated patients. In observations up to 3 years, the serious infection rate remained stable over time. The infections observed consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections. Most patients continued on study medicinal product after the infection resolved.

In 43 CAPS patients followed for up to 5 years the frequency of serious infections was 0.1/year, the most common being pneumonia and gastroenteritis. Kineret 100 mg solution for injection was temporarily stopped in one patient, all other patients continued Kineret 100 mg solution for injection treatment during the infections.

In 15 SJIA patients followed for up to 1.5 years, one patient developed a serious hepatitis in connection with a cytomegalovirus infection. There are no indications from post-marketing experience that types and severity of infections in patients with Still's disease differ from those in RA or CAPS patients.

In clinical studies and during post-marketing use, rare cases of opportunistic infections have been observed and have included fungal, mycobacterial, bacterial, and viral pathogens. Infections have been noted in all organ systems and have been reported in patients receiving Kineret 100 mg solution for injection alone or in combination with immunosuppressive agents.

Neutropenia

In placebo-controlled RA studies with Kineret 100 mg solution for injection, treatment was associated with small reductions in the mean values for total white blood count and absolute neutrophil count (ANC). Neutropenia (ANC < 1.5 x 10⁹/l) was reported in 2.4% patients receiving Kineret 100 mg solution for injection compared with 0.4% of placebo patients. None of these patients had serious infections associated with the neutropenia.

In 43 CAPS patients followed for up to 5 years neutropenia was reported in 2 patients. Both episodes of neutropenia resolved over time with continued Kineret 100 mg solution for injection treatment.

In 15 SJIA patients followed for up to 1.5 years, one event of transient neutropenia was reported.

Thrombocytopenia

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

During post-marketing use of Kineret, thrombocytopenia has been reported, including occasional case reports indicating severe thrombocytopenia (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. The majority of these reactions were maculopapular or urticarial rashes.

In 43 CAPS patients followed for up to 5 years, no allergic event was serious and no event required discontinuation of Kineret 100 mg solution for injection treatment.

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

In 12 FMF patients treated 4 months with Kineret 100 mg solution for injection in a published randomized controlled study no allergic event was reported as serious and no event required discontinuation of Kineret.

Immunogenicity

In clinical trials in RA, up to 3% of adult patients tested seropositive at least once during the study for neutralizing anti-anakinra antibodies. 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 86 paediatric patients with JIA, whereof none of the 15 SJIA subtype patients, tested seropositive at least once during the study for neutralizing anti-anakinra antibodies.

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.

Hepatic Events

In clinical studies transient elevations of liver enzymes have been seen. These elevations have not been associated with signs or symptoms of hepatocellular damage, except for one patient with SJIA that developed serious hepatitis in connection with a cytomegalovirus infection.

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 Still's disease and in patients with predisposing factors, e.g. a history of transaminase elevations before start of Kineret treatment.

Injection site reactions

ISRs typically appear within 2 weeks of therapy and disappear within 4-6 weeks. The development of ISRs in patients who had not previously experienced ISRs was uncommon after the first month of therapy.

In RA patients the most common and consistently reported treatment-related adverse reactions associated with Kineret 100 mg solution for injection were ISRs. The majority (95%) of ISRs were reported as mild to moderate. These were typically characterised by one or more of the following: erythaema, 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 100 mg solution for injection treatment due to injection site reactions.

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 the 15 patients discontinued due to ISRs.

In patients with FMF the types and frequencies of ISRs are similar to those seen in RA *and* SJIA. Discontinuations due to ISRs have occurred also in patients with FMF.

Blood cholesterol increase

In clinical studies of RA, 775 patients treated with daily Kineret 100 mg solution for injection 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 100 mg solution for injection treatment, without a dose-response relationship. A similar pattern was seen after 24 weeks Kineret 100 mg solution for injection 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.

Paediatric population

Kineret 100 mg solution for injection has been studied in 36 CAPS patients, 15 SJIA patients and 71 patients with other forms of JIA, aged 8 months to <18 years, for up to 5 years. With the exception of infections and related symptoms that were more frequently reported in patients <2 years of age, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

4.9 Overdose

No dose-limiting toxicities were observed during clinical studies.

In studies of sepsis, 1,015 patients received Kineret 100 mg solution for injection at doses up to 2 mg/kg/hour i.v. (~35 times the recommended dose in RA) over a 72-hour treatment period. The adverse event profile from these studies show no overall difference from that seen in the rheumatoid arthritis studies.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors, ATC code: L04AC03

Mechanism of action

Anakinra neutralises the biologic activity of interleukin-1 α (IL-1 α) and interleukin-1 β (IL-1 β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.

Pharmacodynamic effects

IL-1 is found in the plasma and synovial fluid of patients with rheumatoid arthritis, and a correlation has been reported between IL-1 concentrations in the plasma and the activity of the disease.

Anakinra inhibits responses elicited by IL-1 *in vitro*, including the induction of nitric oxide and prostaglandin E₂ and/or collagenase production by synovial cells, fibroblasts, and chondrocytes.

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-1 β , which has a broad range of effects including systemic inflammation. Untreated CAPS patients are characterized by increased CRP, SAA and IL-6 relative to normal serum levels. Administration of Kineret 100 mg solution for injection 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 patients with FMF, mutation of the MEFV gene encoding for pyrin is leading to malfunctioning and overproduction of interleukin-1 β (IL-1 β) in the FMF inflammasome. Untreated FMF is characterized by increased CRP and SAA. Administration of Kineret 100 mg solution for injection results in a decrease in acute phase reactants (e.g. CRP and SAA).

Clinical efficacy and safety in RA

The safety and efficacy of anakinra in combination with methotrexate have been demonstrated in 1,790 RA patients $\geq$ 18 years of age with varying degrees of disease severity.

A clinical response to anakinra generally appeared within 2 weeks of initiation of treatment and was sustained with continued administration of anakinra. Maximal clinical response was generally seen within 12 weeks after starting treatment.

Combined anakinra and methotrexate treatment demonstrates a statistically and clinically significant reduction in the severity of the signs and symptoms of RA in patients who have had an inadequate response to methotrexate alone (38% vs. 22% responders as measured by ACR₂₀ criteria). Significant improvements are seen in the pain, tender joint count, physical function (HAQ score), acute phase reactants and in the patient's and physician's global assessment.

X-ray examinations have been undertaken in one clinical study with anakinra. These have shown no deleterious effect on joint cartilage.

Clinical efficacy and safety in CAPS

The safety and efficacy of Kineret 100 mg solution for injection have been demonstrated in CAPS patients with varying degrees of disease severity. In a clinical study including 43 adult and paediatric patients (36 patients aged 8 months to < 18 years) with severe CAPS (NOMID/CINCA and MWS), a clinical response to anakinra was seen within 10 days after initiation of treatment in all patients and was sustained for up to 5 years with the continued administration of Kineret 100 mg solution for injection.

Kineret 100 mg solution for injection treatment significantly decreases the manifestations of CAPS, including a reduction in frequently occurring symptoms as fever, rash, joint pain, headache, fatigue, and eye redness. A rapid and sustained decrease in the levels of the inflammatory biomarkers; serum amyloid A (SAA), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and a normalization of inflammatory hematological changes are seen. In the severe form of CAPS, long-term treatment improves the systemic inflammatory organ manifestations of the eye, inner ear, and CNS. Hearing and visual acuity did not deteriorate further during anakinra treatment.

Analysis of treatment-emergent AEs classified by presence of CIAS1 mutation showed that there were no major differences between the CIAS1 and non-CIAS1 groups in overall AE reporting rates, 7.4 and 9.2, respectively. Similar rates were obtained for the groups on the SOC level, except for eye disorders with 55 AEs (rate 0.5), whereof 35 ocular hyperemia (which could also be a symptom of CAPS) in the CIAS1 group, and four AEs in the non-CIAS1 group (rate 0.1).

Clinical efficacy and safety in FMF

The safety and efficacy of Kineret 100 mg solution for injection in the treatment of patients with colchicine resistant FMF has been demonstrated in a randomized, double blind, and placebo-controlled published study with a treatment period of 4 months. Primary efficacy outcomes were number of attacks per month, and number of patients with a mean of <1 attack per month. 25 patients with colchicine resistant FMF were enrolled; 12 randomized to receive Kineret 100 mg solution for injection and 13 to receive placebo. The mean number of attacks per patient per month was significantly lower in those receiving Kineret 100 mg solution for injection (1.7) compared to placebo (3.5). The number of patients with <1 attack per month was significantly higher in the Kineret 100 mg solution for injection group; 6 patients, compared to none in the placebo group.

Additional published data in patients with FMF, intolerant to colchicine or with colchicine resistant FMF, demonstrate that the clinical effect of Kineret 100 mg solution for injection is evident in both clinical symptoms of attacks as well as in reduced levels of inflammatory markers, such as CRP and SAA. In the published studies the safety profile of anakinra in patients with FMF was generally similar to that in other indications.

Paediatric population

Overall, the efficacy and safety profile of Kineret 100 mg solution for injection is comparable in adult and paediatric patients with CAPS.

The European Medicines Agency has waived the obligation to submit the results of studies with Kineret 100 mg solution for injection in one or more subsets of the paediatric population in CAPS and RA (JIA) (see section 4.2 for information on paediatric use).

Safety in paediatric RA (JIA) patients

Kineret 100 mg solution for injection was studied in a single randomized, blinded multi-center trial in 86 patients with polyarticular course JIA (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 100 mg solution for injection (25 patients) or placebo (25 patients), administered daily for an additional 16 weeks. A subset of these patients continued open-label treatment with Kineret 100 mg solution for injection 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 100 mg solution for injection is not recommended for paediatric use in JIA.

Immunogenicity

See section 4.8.

5.2 Pharmacokinetic properties

The absolute bioavailability of anakinra after a 70 mg subcutaneous bolus injection in healthy subjects ($n = 11$) is 95%. The absorption process is the rate-limiting factor for the disappearance of anakinra from the plasma after subcutaneous injection. In subjects with RA, maximum plasma concentrations of anakinra occurred at 3 to 7 hours after subcutaneous administration of anakinra at clinically relevant doses (1 to 2 mg/kg; $n = 18$). The plasma concentration decreased with no discernible distribution phase and the terminal half-life ranged from 4 to 6 hours. In RA patients, no unexpected accumulation of anakinra was observed after daily subcutaneous doses for up to 24 weeks. Mean (SD) estimates of clearance (CL/F) and volume of distribution (Vd/F) by population analysis of data from two PK studies in 35 RA patients were 105(27) ml/min and 18.5(11) l, respectively. Human and animal data demonstrated that the kidney is the major organ responsible for elimination of anakinra. The clearance of anakinra in RA patients increased with increasing creatinine clearance.

The influence of demographic covariates on the pharmacokinetics of anakinra was studied using population pharmacokinetic analysis encompassing 341 patients receiving daily subcutaneous injection of anakinra at doses of 30, 75, and 150 mg for up to 24 weeks. The estimated anakinra clearance increased with increasing creatinine clearance and body weight. Population pharmacokinetic analysis demonstrated that the mean plasma clearance value after subcutaneous bolus administration was approximately 14% higher in men than in women and approximately 10% higher in subjects < 65 years than in subjects ≥ 65 years. However, after adjusting for creatinine clearance and body weight, gender and age were not significant factors for mean plasma clearance. No dose adjustment is required based on age or gender.

In general, the pharmacokinetics in CAPS patients is similar to that in RA patients. In CAPS patients approximate dose linearity with a slight tendency to higher than proportional increase has been noted. Pharmacokinetic data in children < 4 years are lacking, but clinical experience is

available from 8 months of age, and when started at the recommended daily dose of 1-2 mg/kg, no safety concerns have been identified. Pharmacokinetic data are lacking in older CAPS patients. Distribution into the cerebrospinal fluid has been demonstrated.

Hepatic impairment

A study including 12 patients with hepatic dysfunction (Child-Pugh Class B) given a single 1mg/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. See section 4.2.

Renal impairment

The mean plasma clearance of Kineret 100 mg solution for injection 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), mean plasma clearance declined by 70% and 75%, respectively. Less than 2.5% of the administered dose of Kineret 100 mg solution for injection was removed by hemodialysis or continuous ambulatory peritoneal dialysis. These data support that no dose adjustment is needed for patients with mild renal impairment (CLcr 50 to 80 ml/minute). See section 4.2.

5.3 Preclinical safety data

Anakinra had no observed effect on the fertility, early development, embryo-foetal development, or peri- and postnatal development in the rat at doses up to 100 times the human dose (2 mg/kg/day). No effects on embryo-foetal development in the rabbit were observed at doses 100 times the human dose.

In a standard battery of tests designed to identify hazards with respect to DNA, anakinra did not induce bacterial or mammalian cell gene mutations. Neither did anakinra increase the incidence of chromosomal abnormalities or micronuclei in bone marrow cells in mice. Long-term studies have not been performed to evaluate the carcinogenic potential of anakinra. Data from mice over expressing IL-1ra and IL-1ra mutant knock-out mice, did not indicate an increased risk of tumour development.

A formal toxicologic and toxicokinetic interaction study in rats revealed no evidence that Kineret 100 mg solution for injection alters the toxicologic or pharmacokinetic profile of methotrexate.

Juvenile rats treated at doses up to 100 times the human dose from day 7 postparturition up to adolescence did not show any signs of adverse effects of the treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Citric acid, anhydrous
Polysorbate 80
Disodium, EDTA, dehydrate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Store in the original container in order to protect from light.

For the purpose of ambulatory use, Kineret 100 mg solution for injection may be removed from the refrigerator for 12 hours at temperature not above 25 °C, without exceeding the expiry date. At the end of this period, the product must not be put back in the refrigerator and must be disposed of.

6.5 Nature and contents of container

0.67 ml of solution for injection in a graduated pre-filled syringe (Type I glass) with a plunger stopper (bromobutyl rubber) and 29 gauge needle. 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.

Pack sizes of 1, 7 or 28 (multipack containing 4 packs of 7 pre-filled syringes) pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Kineret 100 mg solution for injection is a sterile unpreserved solution. For single use only.

Do not shake. Allow the pre-filled syringe to reach room temperature before injecting.

Before administration, visually inspect the solution for particulate matter and discolouration. Only clear, colourless-to-white solutions that may contain some product-related translucent-to-white amorphous particles should be injected.

The presence of these particles does not affect the quality of the product.

The pre-filled syringe is for single use only. Discard any unused medicinal product.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MEGAPHARM LTD, POB 519, HOD HASHARON 4510501

8. MANUFACTURER

Swedish Orphan Biovitrum AB (publ)

SE-112 76 Stockholm

Sweden

9. MARKETING AUTHORISATION NUMBER(S)

145-79-33059

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