SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe.

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.

Excipient(s) with known effect

This medicinal product contains 0.70 mg of polysorbate 80 in each pre-filled syringe, which is equivalent to 1.04 mg/ml.

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

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

Periodic fever syndromes
Kineret is indicated for the treatment of the following autoinflammatory periodic fever syndromes in adults, adolescents, children and infants aged 8 months and older with a body weight of 10 kg or above:

Cryopyrin-Associated Periodic Syndromes (CAPS)
Kineret is indicated for the treatment of CAPS, including:
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)
- Muckle-Wells Syndrome (MWS)
- Familial Cold Autoinflammatory Syndrome (FCAS)

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

Still's Disease
Kineret 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 Still's disease, including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD), with active systemic features of moderate to high disease activity, or in patients with continued disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.

Kineret can be given as monotherapy or in combination with other anti-inflammatory drugs and disease-modifying antirheumatic drugs (DMARDs).

4.2 Posology and method of administration

Kineret treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of RA, CAPS, FMF and Still's disease, respectively.

Posology

RA: Adults

The recommended dose of Kineret 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

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.

Still’s disease

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 starting dose of 1-2 mg/kg/day.

Response to treatment should be evaluated after 1 month: In case of persistent systemic manifestations dose may be adjusted in children or continued treatment with Kineret should be reconsidered by the treating physician.

Elderly population (≥ 65 years)

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

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

Still's disease: Data in elderly patients are limited. No dose adjustment are expected to be required.

Paediatric population (< 18 years)

No data are available in children under the age of 8 months.

RA: The efficacy of Kineret 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.

FMF: Children weighing less than 50 kg are dosed by body weight with a recommended dose of 1-2 mg/kg/day, patients weighing 50 kg or more are dosed with 100 mg/day. In children with inadequate response the dose can be escalated up to 4 mg/kg/day.

The efficacy data of Kineret in children under 2 years of age with FMF are limited.

Still's disease: Children weighing less than 50 kg are dosed by body weight with a starting dose of 1-2 mg/kg/day, patients weighing 50 kg or more are dosed with 100 mg/day. In children with inadequate response the dose can be escalated up to 4 mg/kg/day.

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

No dose adjustment is needed for patients with mild renal impairment (CLcr 60 to 89 ml/min). Kineret 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 every other day should be considered.

Method of administration

Kineret is administered by subcutaneous injection.

Kineret is supplied ready for use in a graduated 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 to room temperature, use of cold packs (before and after the injection), and use of topical glucocorticoids 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 treatment must not be initiated in patients with neutropenia (ANC $<1.5 \times 10^9$/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 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 x upper level of normal have not been evaluated.

Serious infections

Kineret 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 treatment in patients with chronic and serious infections have not been evaluated.

Kineret 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 treated CAPS or FMF patients, there is a risk for disease flares when discontinuing Kineret treatment. With careful monitoring, Kineret treatment can be continued also during a serious infection.

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.

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. 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.

Renal impairment

Kineret is eliminated by glomerular filtration and subsequent tubular metabolism. Consequently plasma clearance of Kineret decreases with decreasing renal function.

No dose adjustment is needed for patients with mild renal impairment (CLcr 60 to 89 ml/min). Kineret 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 every other day should be considered.

Neutropenia

Kineret was commonly associated with neutropenia (ANC < 1.5 x 10^9/l) in placebo-controlled studies in RA and cases of neutropenia have been observed in patients with CAPS and Still's disease. For more information on neutropenia see section 4.8.

Kineret treatment should not be initiated in patients with neutropenia (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 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. In company-sponsored clinical studies in Still's disease no such events were reported. In a non-interventional long-term safety study in 306 paediatric patients with Still's disease one patient experienced a serious pulmonary event, an unspecified interstitial lung disease. There was no patient with pulmonary alveolar proteinosis or pulmonary hypertension in the study. A causal relationship between Kineret and pulmonary events has not been established.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

During post-marketing use drug reaction with eosinophilia and systemic symptoms (DRESS) has rarely been reported in patients treated with Kineret, predominantly in paediatric patients with Still's disease [systemic juvenile idiopathic arthritis (SJIA)]. Patients with DRESS may require hospitalization, as this condition may be fatal. If signs and symptoms of DRESS are present and an alternative aetiology cannot be established, Kineret should be discontinued and a different treatment considered.

Amyloidosis (systemic)

In patients with NOMID/CINCA who received high doses of Kineret over extended periods of time and presented with injection site amyloid deposits (see section 4.8) isolated cases of systemic AIL1RAP (IL-1 receptor antagonist protein) amyloidosis have been reported during post-marketing use.

In patients with confirmed injection site amyloid deposits, observation for symptoms of systemic amyloidosis, including close monitoring for proteinuria, is recommended.

Immunosuppression

The impact of treatment with Kineret on pre-existing malignancy has not been studied. Therefore the use of Kineret 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 studies, 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 studies, 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.

Vaccinations

In a placebo-controlled clinical study (n = 126), no difference was detected in anti-tetanus antibody response between the Kineret and placebo treatment groups when a tetanus/diphtheria toxoid 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 on the secondary transmission of infection by live vaccines in patients receiving Kineret. Therefore, live vaccines should not be given concurrently with Kineret.

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 studies. No overall differences in safety or effectiveness were observed between these patients and younger patients. There is limited experience in treating elderly CAPS, FMF and Still's 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 and TNF-α antagonist treatment

Concurrent administration of Kineret 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 and etanercept or other TNF-α antagonists is not recommended (see section 4.5).

Excipients

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

This medicinal product contains 0.70 mg of polysorbate 80 in each pre-filled syringe, which is equivalent to 1.04 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

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

Concurrent Kineret and TNF-α antagonist treatment

In a clinical study with RA patients receiving background methotrexate, patients treated with Kineret 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 studies where Kineret was used alone. Concurrent Kineret and etanercept treatment has not demonstrated increased clinical benefit.

The concurrent use of Kineret 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 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 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-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/day) was comparable with placebo (7.1% compared with 6.5% in the placebo group). The incidence of serious infection was higher in Kineret-treated patients compared to patients receiving placebo (1.8% vs. 0.7%). Neutrophil decreases occurred more frequently in patients receiving Kineret 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 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 reactions.

Adverse events data in patients with Still's disease is based on a partially open-label and partially blinded, placebo-controlled study of 15 SJIA patients, treated for up to 1.5 years and a randomised double blind placebo-controlled study of 11 adult and paediatric patients with Still's disease (6 Kineret and 5 placebo) treated for 12 weeks and followed for an additional 4 weeks. In addition, a non-interventional long-term safety study in 306 paediatric patients with Still's disease, post-marketing adverse event reports and published studies constitute supporting data.

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 postmarketing observation of a higher frequency of reported hepatic events in patients with Still's disease. The adverse reactions table below therefore applies to Kineret treatment of RA, CAPS, FMF and Still's disease. During long term treatment of RA, CAPS, and Still's disease the safety profile remains unchanged over time.

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 (≥ 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.

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
General disorders and administration site conditions	Very common (≥ 1/10)	Injection site reaction
Skin and subcutaneous tissue disorders	Uncommon (≥ 1/1,000 to < 1/100)	Rash
	Not known (cannot be estimated from the available data)	Injection site amyloid deposits Drug reaction with eosinophilia and systemic symptoms (DRESS)
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 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 a study with 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 was temporarily stopped in one patient, all other patients continued Kineret treatment during the infections.

In a study with 15 SJIA patients followed for up to 1.5 years, one patient developed a serious hepatitis in connection with a cytomegalovirus infection. In a study with 11 patients with Still's disease (SJIA and AOSD) randomized to Kineret (6 patients) or Placebo (5 patients) and followed for 16 weeks, no serious infections were reported. In a non-interventional long-term safety study of Kineret in 306 paediatric patients with Still's disease followed for up to more than 9 years (mean duration of a treatment course with Kineret was 17.0 (standard deviation 21.1) months and the median duration was 8.9 months), serious infections were reported in 13 patients. There are no indications from post-marketing adverse event reports and published studies that types and severity of infections in patients with FMF differ from those in patients with RA, CAPS or Still's disease.

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 alone or in combination with immunosuppressive agents.

Neutropenia

In placebo-controlled RA studies with Kineret, 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 10^9/l) was reported in 2.4% patients receiving Kineret compared with 0.4% of placebo patients. None of these patients had serious infections associated with the neutropenia.

In a study with 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 treatment.

In a study with 15 SJIA patients followed for up to 1.5 years, one event of transient neutropenia was reported. In a study with 11 patients with Still's disease (SJIA and AOSD) randomized to Kineret (6 patients) or Placebo (5 patients) and followed for 16 weeks, no neutropenia was reported. In a non-interventional long-term safety study in 306 paediatric patients with Still's disease followed for up to more than 9 years, (mean duration of treatment course with Kineret was 17.0 (standard deviation 21.1) months and the median duration was 8.9 months), 5 events of neutropenia including 1 event of febrile neutropenia, were 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 x10^9/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 x10^9/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 a study with 43 CAPS patients followed for up to 5 years, no allergic event was serious and no event required discontinuation of Kineret treatment.

In a study with 15 SJIA patients followed for up to 1.5 years, no allergic event was serious and no event required discontinuation of Kineret. In a study with 11 patients with Still's disease (SJIA and AOSD) randomised to Kineret (6 patients) or Placebo (5 patients) and followed for 16 weeks, no allergic reactions were reported.

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

Immunogenicity

In clinical studies 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 study 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. In a clinical study with 6 patients randomized to anakinra for 12 weeks for Still's disease (SJIA and AOSD), all patients developed ADAs but none of the patients were tested seropositive 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 were ISRs. The majority (95%) of ISRs were reported as mild to moderate. These were typically characterised by 1 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 a study with 43 CAPS patients followed for up to 5 years no patient permanently or temporarily discontinued Kineret treatment due to injection site reactions.

In a study with 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 a placebo-controlled study with 11 patients with Still's disease (SJIA and AOSD) randomized to Kineret (6 patients) or Placebo (5 patients) for 12 weeks, ISRs occurred in both treatment groups, of which all were mild in severity. No patient discontinued treatment due to ISRs. In a non-interventional long-term safety study in 306 paediatric patients with Still's disease followed for up to more than 9 years (mean duration of a treatment course with Kineret was 17.0 (standard deviation 21.1) months and the median duration was 8.9 months), ISRs of moderate or severe intensity had an incidence rate of 1.6 per 100 patient years.

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.

Injection site amyloid deposits

During post-marketing use, isolated cases of injection site amyloid deposits have been reported in patients with NOMID/CINCA who received high doses of Kineret injected subcutaneously into the same area of skin over long periods of time. Rotation of injection sites is therefore recommended.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

During post-marketing use, drug reaction with eosinophilia and systemic symptoms (DRESS) has rarely been reported in patients treated with Kineret, predominantly in paediatric patients with Still's disease [systemic juvenile idiopathic arthritis (SJIA)]. See section 4.4.

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 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.

Paediatric population

Kineret has been studied in 36 patients with CAPS, 21 patients with SJIA 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. In addition, 306 paediatric patients with Still's disease have been followed for up to more than 9 years in a non-interventional long-term safety study. 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 authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No dose-limiting toxicities were observed during clinical studies.

In studies of sepsis, 1,015 patients received Kineret 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.

5.1 Pharmacodynamic properties

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

Mechanism of action

Anakinra neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) 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 E_2 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-1β, 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 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-1β (IL-1β) in the FMF inflammasome. Untreated FMF is characterized by increased CRP and SAA. Administration of Kineret results in a decrease in acute phase reactants (e.g. CRP and SAA).

Still's disease, in addition to various degrees of arthritis, is characterised by systemic inflammatory features such as spiking fever, skin rash, hepatosplenomegaly, serositis, and increased acute phase reactants driven by IL-1 activity. Systemically, IL-1 is known to cause the hypothalamic fever response and promote hyperalgesia. The role

of IL-1 in the pathogenesis of Still's disease has been demonstrated by *ex vivo* and gene expression studies.

Clinical efficacy and safety in RA

The safety and efficacy of anakinra in combination with methotrexate have been demonstrated in 1,790 RA patients ≥ 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 ACR_{20} 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 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.

Kineret 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 4 AEs in the non-CIAS1 group (rate 0.1).

Clinical efficacy and safety in FMF

The safety and efficacy of Kineret 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 and 13 to receive placebo. The mean number of attacks

per patient per month was significantly lower in those receiving Kineret (1.7) compared to placebo (3.5). The number of patients with <1 attack per month was significantly higher in the Kineret 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 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.

Clinical efficacy and safety in Still's disease

The efficacy and safety of Kineret for the treatment of Still's disease (SJIA and AOSD) were evaluated in a randomized double-blind placebo-controlled multi-center study of 11 patients (aged 1 to 51 years) treated for 12 weeks, whereof 6 patients received Kineret. Kineret was efficacious in the treatment of Still's disease as demonstrated by superiority to placebo in the primary endpoint ACR30 response with absence of fever at Week 2 (p-value = 0.0022). The demonstrated efficacy of Kineret in ACR30, ACR50, ACR70 and ACR90 responses at Week 2 were sustained throughout the 12 weeks treatment period. No relevant unexpected safety findings were observed in the study, and the results were in line with the known safety profile of Kineret.

The safety and efficacy have been demonstrated in a published randomized controlled study in 24 SJIA patients treated with Kineret for up to 1 year. After a 1-month blinded phase, 8 of 12 patients in the Kineret treated group were identified as modified ACRpedi30 responders compared to 1 of 12 in the placebo group. At the same time point, 7 of 12 in the Kineret treated group were classified as ACRpedi50 and 5 of 12 as ACRpedi70 responders compared to none in the placebo group. 16 patients completed the subsequent open label phase and among 7 responders at month 12, 6 had stopped glucocorticoid treatment and 5 of them had inactive disease.

In a published prospective, uncontrolled, observational cohort study of 20 patients with new-onset SJIA Kineret was used as initial therapy after failure to respond to NSAIDs, but before the use of DMARDs, systemic glucocorticoids, or other biologic agents. Treatment with Kineret resulted in normalization of body temperature in 18 of 20 patients. At 1 year follow-up, 18 of 20 patients showed at least an adapted ACRpedi 70 response, and 17 of 20 patients reached an adapted ACRpedi 90 response as well as inactive disease.

A non-interventional safety study in 306 paediatric patients with Still's disease confirmed the long-term safety profile of Kineret without any new safety findings. Approximately half (46.1%) of the patients were continuously treated with Kineret for at least 1 year, and 28.1% for at least 2 years. The pattern and frequency of AEs, including SAEs, were in line with the known safety profile of Kineret. In general, the rate of AEs was highest during the first 6 months of treatment and considerably lower during later time periods. There were no deaths during Kineret treatment. Few patients discontinued due to AEs. The main reason for Kineret discontinuation was inefficacy however, the second most common reason for discontinuation was disease remission. Long-term treatment with Kineret in SJIA patients was well tolerated, with no overall increase in incidence rate of AEs, including MAS, over time.

The safety and efficacy of Kineret versus DMARD have been reported in a published 24-week multicenter, randomized, open-label study of 22 patients with glucocorticoid-dependent refractory AOSD. At Week 24, 6 of 12 patients on Kineret were in remission versus 2 of 10 patients on DMARDs. During an open-label

extension phase, switching or add-on treatment with the comparator drug was possible if improvement did not occur within 24 weeks. 17 patients completed the open-label extension phase (Week 52), of which 7 of 14 Kineret-treated patients, and 2 of 3 patients on DMARDs, were in remission at that time point.

Additional published data in Still's disease indicate that Kineret induces a rapid resolution of systemic features such as fever, rash, and elevation of acute phase reactants. Glucocorticoid doses can in many cases be reduced after initiation of Kineret therapy.

Paediatric population

Overall, the efficacy and safety profile of Kineret is comparable in adult and paediatric patients with CAPS or Still's disease.

The European Medicines Agency has waived the obligation to submit the results of studies with Kineret 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 was studied in a single randomized, blinded multi-center study 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 (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 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.

The median steady-state dose-normalized anakinra concentration in SJIA patients (aged 3 to 17 years) over 28 weeks was comparable to that observed in RA patients.

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 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 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 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

Citric acid, anhydrous
Sodium chloride
Disodium edetate dihydrate
Polysorbate 80
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

3 years

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 may be kept at room temperature up to 25 °C for a maximum of 72 hours. After removal from the refrigerator, Kineret must be used within 72 hours or discarded. Once stored at room temperature, Kineret should not be placed back in the refrigerator.

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

Kineret 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

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

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 30941/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/01/2021

10 DATE OF REVISION OF THE TEXT

24/11/2025