ANNEX I

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.

COVID-19
Kineret is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk of progressing to severe respiratory failure determined by plasma concentration of soluble urokinase plasminogen activator receptor (suPAR) ≥ 6 ng/ml (see sections 4.2, 4.4 and 5.1).

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, COVID-19, CAPS, FMF and Still's disease, respectively.

suPAR testing
If specified in the indication, patient selection for treatment with Kineret based on suPAR level ≥ 6 ng/ml should be measured by a validated test (see sections 4.1, 4.4, and 5.1).

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.

COVID-19: Adults
The recommended dose of Kineret is 100 mg administered once a day by subcutaneous injection for 10 days.

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 and COVID-19: 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.

COVID-19: The efficacy of Kineret in children with COVID-19 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. Treatment with Kineret for COVID-19 can be continued despite (secondary) infections.

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

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 COVID-19, CAPS and Still's disease. For more information on neutropenia see section 4.3 and 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, or COVID-19 vaccines, 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, and 173 COVID-19 patients ≥ 65 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).

COVID-19 Patients
The effect of treatment with Kineret has not been established in COVID-19 patients with suPAR < 6 ng/ml.

Kineret treatment should not be initiated in patients requiring non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) as efficacy has not been established in these patient populations.

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 COVID-19 are based on a randomized placebo-controlled study of 405 Kineret-treated patients with COVID-19 pneumonia (SAVE-MORE study). The incidence of serious adverse reactions in the anakinra-treatment group was comparable with the placebo group. Neutropenia, elevation of liver function test, rash and injection site reactions were reported more frequently in patients receiving Kineret compared with placebo. The overall safety profile in patients with COVID-19 treated with Kineret is similar to that in Kineret-treated patients with RA.

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 the clinical study in COVID-19, secondary serious infections were common, however less frequently observed in patients treated with Kineret compared to placebo-treated patients.

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 the clinical study in COVID-19, events of neutropenia were reported in 3.0% of Kineret-treated patients and 0.5% of patients receiving placebo. All adverse events of neutropenia were mild or moderate in severity.

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.

In the clinical study in COVID-19, no allergic reaction was considered related to 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.

In patients with COVID-19 treated with Kineret, injection site reactions were reported with low frequency.

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 listed in Appendix V.

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. PHARMACOLOGICAL PROPERTIES

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.

In COVID-19 patients, progression from lower respiratory tract infection (LRTI) to severe respiratory failure (SRF) is dependent on the early release of IL-1α from virally infected lung epithelial cells, which in turn stimulates further cytokine production including IL-1β from alveolar macrophages.

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 COVID-19

The safety and efficacy of Kineret was evaluated in patients with COVID-19 pneumonia ≥ 18 years of age with a risk of developing severe respiratory failure in a randomized double-blind placebo-controlled study. The patient population enrolled into the SAVE-MORE study was hospitalized with confirmed COVID-19 pneumonia (LRTI radiologically confirmed by chest X-ray or CT) and was considered to be at risk of developing SRF, determined by an elevation in suPAR (≥ 6 ng/ml). Patients had suPAR level ≥ 6 ng/ml measured by the suPARnostic Quick Triage kit. These patients had not yet progressed to SRF (i.e., exclusion criteria were: pO2/FiO2 ratio less than 150 mmHg or the requirement of mechanical ventilation, NIV, or ECMO). The majority of patients received low- or high-flow supplementary oxygen at screening (81.6%). The study enrolled 606 patients and efficacy analysis was performed in the intention-to-treat (ITT) population comprising of 594 patients of whom 189 patients were randomized to the placebo+SoC arm and 405 patients to the anakinra+SoC arm. The majority of the patients (91.4%) had severe COVID-19 pneumonia and 8.6 % of patients had moderate COVID-19 pneumonia at start of treatment. 85.9% of patients received dexamethasone. The mean (SD) duration of Kineret treatment was 8.4 (2.1) days. The primary endpoint of the study was the comparative 11-point WHO Clinical Progression ordinal Scale (CPS) between the two arms of treatment by Day 28. The 11-point WHO CPS provides a measure of illness severity across a range from 0 (not infected); 1-3 (mild disease), 4-5 (hospitalized – moderate disease), 6-9 (hospitalized – severe disease with increasing degrees of NIV, MV and ECMO) to 10 (dead). Of the patients randomised in the SAVE-MORE study 8.6% had a baseline WHO-CPS of 4; 84.7% had a baseline WHO-CPS of 5 and 6.7% had a baseline WHO-CPS of 6.

In patients treated with Kineret for up to 10 days a significant improvement of the clinical status according to the WHO-CPS was demonstrated by Day 28 compared to placebo (OR: 0.36 [95% CI 0.26 to 0.50] P<0.001). Improvement of the patients' clinical status was seen by Day 14. The treatment benefit of Kineret was supported by increase in the number of patients fully recovered and reduction in the number of patients who progressed to severe respiratory failure or death compared to placebo. No new safety signals or safety concerns were observed from the use of Kineret for treatment of COVID-19.

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 Macrophage activation syndrome (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.

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 is a sterile 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)

EU/1/02/203/005 – 1-pack
EU/1/02/203/006 – 7-pack
EU/1/02/203/007 – 28-pack

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8 March 2002
Date of latest renewal: 20 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Boehringer Ingelheim RCV GmbH & Co KG
Dr. Boehringer-Gasse 5-11
A-1121 Vienna
Austria

Pfizer Health AB
Mariefredsvägen 37
SE-645 41 Strängnäs
Sweden

Name and address of the manufacturer responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Kineret is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe or use Kineret have access to/are provided with the following educational package:

- Physician educational material
- Patient and caregiver information pack

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The Guide for healthcare professionals shall contain the following key elements:

- The importance of explaining the use of the syringe and correct injection technique to patients and/or caregivers
- The importance of providing patients and/or caregivers with the educational material

The patient and caregiver information pack should contain:

- Patient information leaflet
- The patient and caregiver guide

The patient and caregiver guide shall contain the following key elements:

- Instructions on use of the syringe
- Instructions on correct injection procedures and disposal of used syringes
- How to manage injection site reactions

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON (CONTAINS BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.67 ml graduated pre-filled syringe contains 100 mg of anakinra.

3. LIST OF EXCIPIENTS

Excipients: anhydrous citric acid, sodium chloride, disodium edetate dihydrate, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 GRADUATED pre-filled syringe
7 GRADUATED pre-filled syringes
Multipack: 28 (4 x 7) GRADUATED pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original container in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/203/005 – 1-pack
EU/1/02/203/006 – 7-pack
EU/1/02/203/007 – 28-pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kineret 100 mg 0.67 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 7 PRE-FILLED SYRINGES AS AN INTERMEDIATE PACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.67 ml graduated pre-filled syringe contains 100 mg of anakinra.

3. LIST OF EXCIPIENTS

Excipients: anhydrous citric acid, sodium chloride, disodium edetate dihydrate, polysorbate 80, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
7 GRADUATED pre-filled syringes
This box containing 7 pre-filled syringes is part of a 28-multipack.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use.
For subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze.
Store in the original container in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/203/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Kineret 100 mg 0.67 ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC {number}
SN {number}
NN {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGES

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Kineret 100 mg/0.67 ml injection
Anakinra

SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.67 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kineret is and what it is used for

Kineret contains the active substance anakinra. This is a type of cytokine (an immunosuppressive agent) that is used to treat:
- Rheumatoid Arthritis (RA)
- COVID-19 in patients who have pneumonia, need extra oxygen and are at risk of lung failure
- Periodic fever syndromes:
  - Cryopyrin-Associated Periodic Syndromes (CAPS)
    - Neonatal-Onset Multisystem Inflammatory Disease (NOMID), also called Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
    - Muckle-Wells Syndrome (MWS),
    - Familial Cold Autoinflammatory Syndrome (FCAS)
  - Familial Mediterranean Fever (FMF)
- Still's disease including Systemic Juvenile Idiopathic Arthritis (SJIA) and Adult-Onset Still's Disease (AOSD)

Cytokines are proteins made by your body that co-ordinate communication between cells and help control cell activity. In RA, CAPS, FMF, Still's disease, and in COVID-19 pneumonia, your body produces too much of a cytokine called interleukin-1. This results in harmful effects leading to inflammation, causing the symptoms of the disease. Normally, your body produces a protein that blocks the harmful effects of interleukin-1. The active substance of Kineret is anakinra, this works in the same way as your natural interleukin-1 blocking protein. Anakinra is produced by DNA technology using the micro-organism *E. coli*.

For RA, Kineret is used to treat the signs and symptoms of the disease in adults (age 18 years and over) in combination with another medicine called methotrexate. Kineret is for patients whose response to methotrexate on its own is not good enough to control the rheumatoid arthritis.

For COVID-19, Kineret is used to treat the hyperinflammation (stronger than the usual inflammation) associated with the disease in adults (age 18 years and over) who have pneumonia, need extra oxygen to help them breathe (low- or high-flow oxygen) and are at risk of lung failure.

For CAPS, Kineret is used to treat the signs and symptoms of inflammation associated with the disease such as rash, joint pain, fever, headache and fatigue in adults and children (age 8 months and older).

For FMF, Kineret is used to treat the signs and symptoms of inflammation associated with the disease such as recurrent fever, fatigue, abdominal pain, muscle or joint pain and rash. Kineret can be used together with colchicine, if appropriate.

For Still's disease, Kineret is used to treat the signs and symptoms of inflammation associated with the disease such as rash, joint pain and fever.

2. What you need to know before you use Kineret

Do not use Kineret
- if you are allergic to anakinra or any of the other ingredients of this medicine, listed in section 6;
- if you are allergic to other products that are produced by DNA technology using the micro-organism *E. coli*;
- if you have neutropenia (low white blood cell count) determined after a blood test.

Contact your doctor immediately
- if you get a rash all over your body, shortness of breath, wheezing, fast pulse or sweating after your Kineret injection. These may be signs that you are allergic to Kineret.
- if you have ever developed an atypical, widespread rash or skin peeling after taking Kineret.

Warnings and precautions
Talk to your doctor before using Kineret:
- if you have a history of recurring infections, or if you suffer from asthma. Kineret may worsen these conditions;
- if you have cancer. Your doctor will have to decide if you can still be given Kineret;
- if you have a history of increased levels of liver enzymes;
- if you require vaccinations. You must not be given live vaccines while being treated with Kineret.

Still's disease
- In rare cases patients with Still's disease, mainly children, may develop lung disease, also during Kineret treatment. The risk may be increased in patients with Down's syndrome (trisomy 21). Symptoms of lung disease can be e.g. shortness of breath during light exercise, morning cough, and difficulties breathing. If you develop signs of lung disease you should contact your health care provider as soon as possible.
- The serious skin reaction, DRESS (drug reaction with eosinophilia and systemic symptoms), has rarely been reported in association with Kineret treatment, predominantly in children with Still's disease [systemic juvenile idiopathic arthritis (SJIA)]. Seek medical attention immediately if you notice an atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.

CAPS
- Few cases of systemic amyloidosis (a condition where abnormal proteins build up in tissues and organs) have been reported in patients with NOMID/CINCA, who first developed lumps under the skin at the injection sites (amyloid deposits). These patients had been using anakinra in high doses for several years. Symptoms of systemic amyloidosis can include swelling (particularly in the legs and ankles), foamy urine, increased or decreased urination, muscle cramps, unexplained weight loss, diarrhoea or constipation, and fatigue. Tell your doctor if you notice any of these symptoms.

Children and adolescents
- RA: Use of Kineret in children and adolescents with Rheumatoid Arthritis has not been fully investigated and therefore cannot be recommended.
- COVID-19: Use of Kineret in children and adolescents with COVID-19 has not been investigated and therefore cannot be recommended.
- CAPS, FMF, Still's disease: Kineret is not recommended for children younger than 8 months of age because there is no data in this age group.

Other medicines and Kineret
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Medicines called tumour necrosis factor (TNF-α) inhibitors, such as etanercept should not be used with Kineret because this may increase the risk of infections.

When you start taking Kineret the chronic inflammation in your body will decrease. This could mean that the doses of some other medicines, e.g. warfarin or phenytoin, have to be adjusted.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Kineret has not been tested in pregnant women. Use of Kineret is not recommended during pregnancy and in women of childbearing potential not using contraception. It is important to tell your doctor if you are pregnant, if you think you may be pregnant or are planning to have a baby. Your doctor will discuss with you the potential risks of taking Kineret during pregnancy.

It is not known whether anakinra is excreted in human milk. You must not breast-feed if you use Kineret.

Kineret contains sodium and polysorbate 80
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially 'sodium-free'.

This medicine 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. Tell your doctor if you have any known allergies.

3. How to use Kineret

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Kineret must be injected under your skin (subcutaneous) daily. You should try to have the injection at the same time each day.

The recommended dose is either 20 to 90 mg or 100 mg. Your doctor will tell you the dose that you need or whether you need a dose higher than 100 mg.

COVID-19: The recommended dose is 100 mg injected under your skin (subcutaneous) daily for 10 days.

Injecting Kineret yourself
Your doctor may decide that it would be more convenient for you to inject Kineret yourself. Your doctor or nurse will show you how to inject yourself. Do not try to inject yourself if you have not been trained.

For instructions on how to inject yourself or your child with Kineret, please read the "Instructions for preparing and giving an injection of Kineret" section at the end of this leaflet.

If you use more Kineret than you should
You should have no serious problems if you accidentally take more Kineret than you need. However, you should contact your doctor, nurse or pharmacist if this does happen. If you feel unwell in any way you should contact your doctor or nurse immediately.

If you forget to use Kineret
If you have forgotten to take a dose of Kineret, you should contact your doctor to discuss when you should take the next dose.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Possible side effects are similar regardless if you are treated with Kineret for RA, CAPS, FMF, Still's disease, or COVID-19.

If any of the following happen, tell your doctor immediately:

- **Serious infections** such as pneumonia (a chest infection) or infections of the skin can occur during Kineret treatment. Symptoms might be persistent high fever, shivers, cough, headache, and redness and tenderness of the skin. Also persistent low-grade fever, weight loss, and persistent cough can be signs of an infection.

- **Serious allergic reactions** are uncommon. However, any of the following symptoms may indicate an allergic reaction to Kineret, so you should seek immediate medical attention. Do not inject more Kineret.
  - Swelling of the face, tongue or throat
  - Trouble swallowing or breathing
  - Suddenly feeling fast pulse or sweating
  - Itchy skin or rash

- Drug reaction with eosinophilia and systemic symptoms (**DRESS)**, the serious skin reaction, has rarely been reported in association with Kineret treatment, predominantly in children with Still's disease (systemic juvenile idiopathic arthritis). Signs of DRESS may include an atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.

Very common side effects (may affect more than 1 in 10 people):
- Redness, swelling, bruising or itching at the injection site. These symptoms are generally mild to moderate and are more common at the start of your treatment.
- Headaches.
- Increased total blood cholesterol levels.

Common side effects (may affect up to 1 in 10 people):
- Neutropenia (low white blood cell count) determined after a blood test. This might increase the risk of you getting an infection. Symptoms of infection might include a fever or a sore throat.
- Serious infections such as pneumonia (a chest infection) or infections of the skin.
- Thrombocytopenia (low level of blood platelets).

Uncommon side effects (may affect up to 1 in 100 people):
- Serious allergic reactions including swelling of the face, tongue or throat, trouble swallowing or breathing, suddenly feeling fast pulse or sweating and itchy skin or rash.
- Elevated levels of liver enzymes determined after a blood test.

Side effects with frequency not known (frequency cannot be estimated from the available data):
- Signs of liver disorders such as yellow skin and eyes, nausea, loss of appetite, dark-coloured urine and light-coloured stools.
- If Kineret is injected repeatedly at the same place, there is a risk of a lump (amyloid deposit) forming under the skin. Rotate the injection site to avoid this.
- Signs of atypical, widespread rash, which may occur in conjunction with high body temperature and enlarged lymph nodes.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Kineret

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.
Store in a refrigerator (2 °C to 8 °C). Do not freeze.
Store in original carton in order to protect from light.

Do not use Kineret if you think it has been frozen. Once a syringe has been removed from the refrigerator and has reached room temperature (up to 25 °C) it must either be used within 72 hours or discarded. Do not place it back in the refrigerator if it has been stored at room temperature.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Kineret contains
- The active substance is anakinra. Each graduated pre-filled syringe contains 100 mg of anakinra.
- The other ingredients are anhydrous citric acid, sodium chloride, disodium edetate dihydrate, polysorbate 80 and sodium hydroxide and water for injections.

What Kineret looks like and contents of the pack
Kineret is a clear, colourless-to-white solution for injection and is supplied ready for use in a pre-filled syringe. It may contain some translucent-to-white particles of protein. The presence of these particles does not affect the quality of the product.

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.

Marketing Authorisation Holder and Manufacturer
Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

This leaflet was last revised in

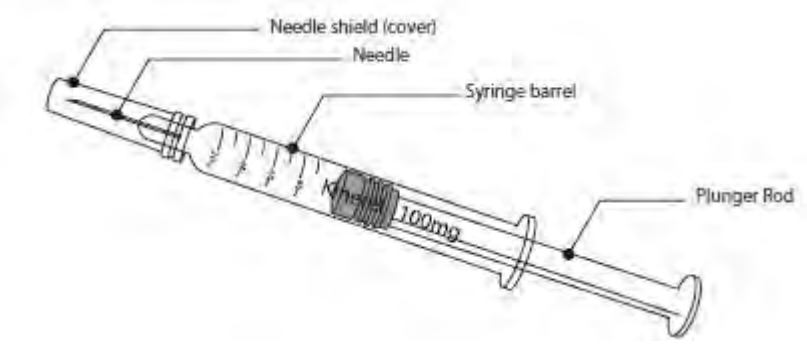
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF KINERET

This section contains information on how to give yourself or your child an injection of Kineret. It is important that you do not try to give yourself or your child the injection unless you have received training from a doctor, nurse or pharmacist. If you have questions about how to inject, please ask your doctor, nurse or pharmacist for assistance.

How do you or the person injecting you, use the Kineret pre-filled syringe?

You will need to give yourself or your child an injection at the same time every day. Kineret is injected just under the skin. This is called a subcutaneous injection.



Equipment:

To give yourself or your child a subcutaneous injection you will need:

- a pre-filled syringe of Kineret
- alcohol wipes or similar; and
- a sterile gauze or tissue

What should you do before you give yourself or your child a subcutaneous injection of Kineret?

1. Take your Kineret pre-filled syringe out of the refrigerator.
2. Do not shake the pre-filled syringe.
3. Check the expiry date on the pre-filled syringe label (EXP). Do not use it if the date has passed the last day of the month shown.
4. Check the appearance of Kineret. It must be a clear, colourless-to-white solution. There may be some translucent-to-white particles of protein in the solution. The presence of these particles does not affect the quality of the product. The solution should not be used if it is discoloured or cloudy, or if any particles other than translucent-to-white particles are present.
5. For a more comfortable injection, leave at room temperature for approximately 30 minutes or hold the pre-filled syringe gently in your hand for a few minutes. **Do not** warm Kineret in any other way (for example, do not warm it in a microwave or in hot water).
6. **Do not** remove the cover from the syringe until you are ready to inject.
7. **Wash your hands thoroughly**.
8. Find a comfortable, well-lit, clean surface and put all the equipment you need within reach.

9. Make sure you know what Kineret dose your doctor has prescribed; 20 to 90 mg, 100 mg or higher.
   - If your doctor has prescribed a 100 mg dose you should continue to the "**How to prepare a 100 mg dose**" section.
   - If your doctor has prescribed a lower dose you should continue to the "**How to prepare a 20 to 90 mg dose**" section.

How to prepare a 100 mg dose

Before you inject Kineret you must do the following:

1. Hold the syringe barrel and gently remove the cover from the needle without twisting. Pull straight as shown in **Figure A**. Do not touch the needle or push the plunger. Immediately discard the needle cover.

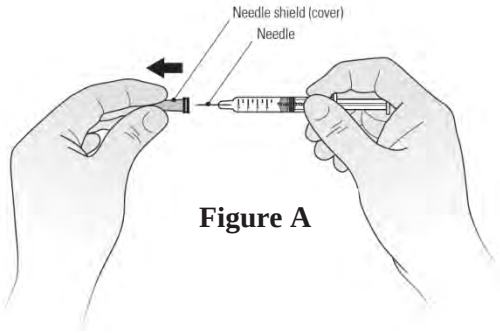


Figure A

2. You may notice a small air bubble in the pre-filled syringe. You do not have to remove the air bubble before injecting. Injecting the solution with the air bubble is harmless.

3. You can now use the pre-filled syringe as described in the "**Where should you give your injection?**" section and "**How do you give your injection?**" section.

How to prepare a 20 to 90 mg dose

Before you inject Kineret you must do the following:

1. Hold the syringe barrel and gently remove the cover from the needle without twisting. Pull straight as shown in **Figure A**. Do not touch the needle or push the plunger. Immediately discard the needle cover.

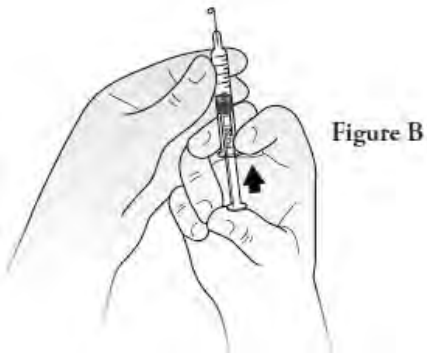


Figure B

2. You should position the syringe in one hand with the needle pointing straight upwards as shown in **Figure B**. Put your thumb on the plunger rod and push slowly until you see a tiny liquid drop at the tip of the needle.

3. Turn the syringe so that the needle is now pointing downwards. Place a sterile gauze or tissue on a flat surface and hold the syringe above it with the needle pointing towards the gauze or tissue, as shown in **Figure C**. Make sure the needle does not touch the gauze or tissue.

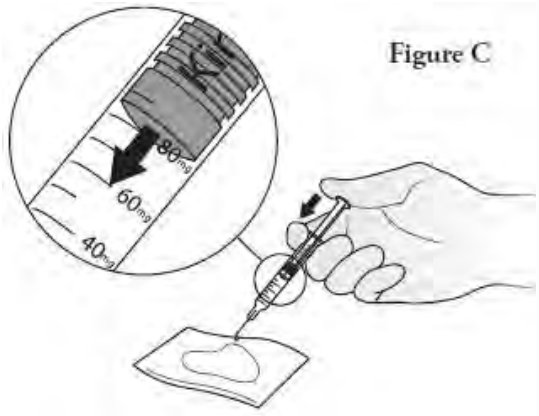


Figure C

4. Put your thumb on the plunger rod and push slowly until the plunger front has reached the scale mark of your Kineret dose. (Your doctor will have told you what dose you need to use.) The ejected liquid will be absorbed by the gauze or tissue as shown in **Figure C**.

5. If you are not able to set the correct dose, dispose of the syringe and use a new one.

6. You can now use the pre-filled syringe as described in the "**Where should you give your injection?**" section and the "**How do you give your injection?**" section.

Where should you give your injection?

The most suitable places to inject yourself or your child are (See **Figure D**):

- the abdomen (except for the area around the navel)
- the top of the thighs
- the upper outer areas of the buttocks; and
- the outer area of the upper arms

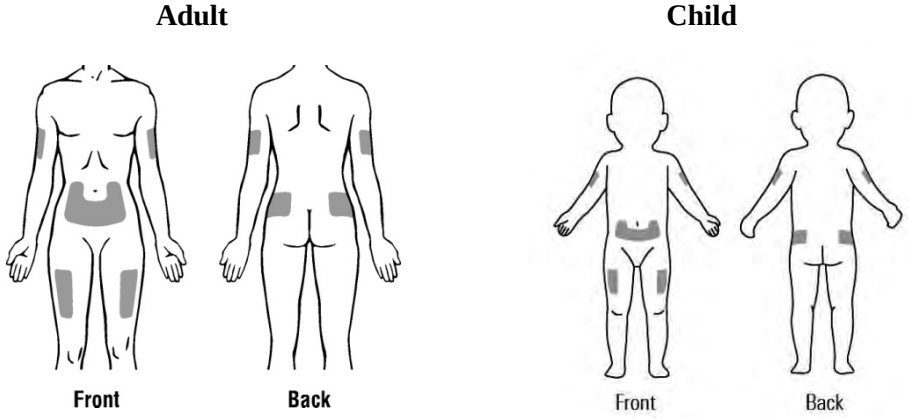


Figure D

Change the place that you inject each time so you don't become sore in one area. If someone else is injecting for you, they can also use the back of your arms.

How do you give your injection?

1. Disinfect the skin by using the alcohol wipe and pinch the skin between your thumb and forefinger, without squeezing it.

2. Put the needle fully into the skin as shown by your nurse or doctor.

3. Inject the liquid slowly and evenly, always keeping the skin pinched as in **Figure E**.

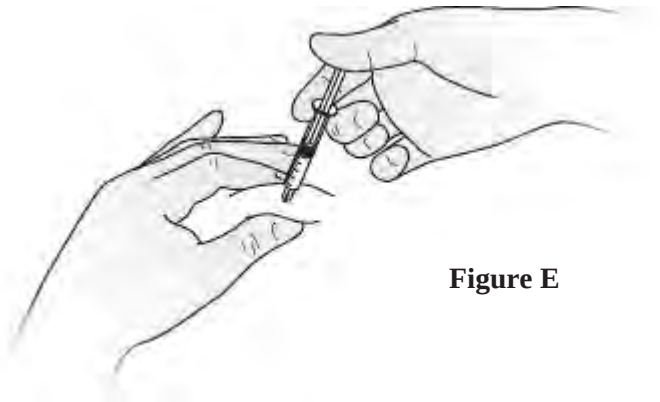


Figure E

4. After injecting the liquid, remove the needle and let go of the skin.

5. Any unused medicine must be discarded. Only use each syringe for one injection. Do not reuse a syringe as this can cause infection.

Remember

If you have any problems, please do not be afraid to ask your doctor or nurse for help and advice.

Disposing of used syringes and supplies

- Do not put the cover back on used needles.
- Keep used syringes out of reach and sight of children.
- Never put the pre-filled syringes that you have used into your normal household rubbish bin.
- If you had a dose lower than 100 mg you will have been told to eject liquid from the syringe onto a gauze or tissue. After your injection discard the wet gauze or tissue with your syringe and clean the surface with a fresh tissue.
- The used pre-filled syringe and any gauze or tissue with Kineret solution should be disposed of in accordance with local requirements. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.