

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Kineret treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Posology

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.

Elderly population (≥ 65 years)

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

Paediatric population (< 18 years)

The efficacy of Kineret in children with RA (JIA) aged 0 to 18 years has not been established.

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

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

Method of administration

Kineret is administered by subcutaneous injection.

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

Alternating the injection site is recommended to avoid discomfort at the site of injection. Cooling of the injection site, warming the injection liquid, use of cold packs (before and after the injection), and use of topical corticosteroids and antihistamines after the injection can alleviate the signs and symptoms of injection site reactions.

4.3 Contraindications

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

Kineret must not be used in patients with severe renal impairment ($CL_{cr} < 30$ ml/minute) (see section 4.2).

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

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.

The inner needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause severe allergic reactions.

Hepatic Events

In clinical studies in RA and CAPS patients, transient elevations of liver enzymes have been seen uncommonly. These elevations have not been associated with signs or symptoms of hepatocellular damage. During post-marketing use isolated case reports indicating non-infectious hepatitis have been received. Hepatic events during post marketing use have mainly been reported in patients with predisposing factors, e.g history of transaminase elevations before start of Kineret treatment. The efficacy and safety of Kineret in patients with $AST/ALT \geq 1.5$ 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%). 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 in patients with chronic infections have not been evaluated.

Kineret treatment should not be initiated in patients with active infections. Kineret treatment should be discontinued if a severe infection develops.

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.

Neutropenia

Kineret was commonly associated with neutropenia ($ANC < 1.5 \times 10^9/l$) in placebo-controlled studies in RA. For more information on neutropenia see section 4.8.

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

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.

Vaccinations

In a placebo-controlled clinical trial ($n = 126$), no difference was detected in anti-tetanus antibody response between the Kineret and placebo treatment groups when 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 patients ≥ 65 years of age, including 163 patients ≥ 75 years of age, were studied in clinical trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. 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 antagonist treatment

Concurrent administration of Kineret and etanercept has been associated with an increased risk of serious infections and neutropenia compared to etanercept alone. This treatment combination has not demonstrated increased clinical benefit.

The concurrent administration of Kineret and etanercept or other TNF antagonists is not recommended (see section 4.5).

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e. essentially 'sodium-free'.

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 trials, interactions between Kineret and other medicinal products (including nonsteroidal anti-inflammatory medicinal products, corticosteroids, and DMARDs) have not been observed.

Concurrent Kineret and TNF antagonist treatment

In a clinical trial with 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 trials 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 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

There are limited amount of data from the use of anakinra in pregnant women. However, reproductive studies have been conducted with Kineret on rats and rabbits at doses up to 100 times the human RA dose and have revealed no evidence of impaired fertility or harm to the foetus.

Kineret is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

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 patients was injection site reaction. The subject incidence of serious adverse reactions at the recommended dose of Kineret (100 mg/day) was comparable with placebo (7.1% compared with 6.5% in the placebo group). 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 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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

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.

There were no deaths due to serious infections in RA studies.

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

Neutropenia

In placebo-controlled studies with Kineret, treatment was associated with small reductions in the mean values for total white blood count and absolute neutrophil count (ANC). Neutropenia ($ANC < 1.5 \times 10^9/l$) 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.

Malignancies

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

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

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.

Immunogenicity

In clinical trials, up to 3% of adult patients tested seropositive at least once during the study for antibodies capable of neutralising the biologic effects of anakinra. The occurrence of antibodies was typically transient and not associated with clinical adverse reactions or diminished efficacy. In addition, in a clinical trial 6% of paediatric patients tested seropositive at least once during the study for antibodies capable of neutralising the biologic effects of anakinra.

Hepatic Events

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

Injection site reactions

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: erythema, ecchymosis, inflammation, and pain. At a dose of 100 mg/day, 71% of patients developed an ISR compared to 28% of the placebo treated patients. 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.

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 trials in RA patients. In studies of sepsis, 1015 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

Anakinra neutralises the biologic activity of interleukin-1 α (IL-1 α) and interleukin-1 β (IL-1 β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a

pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.

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

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

Clinical efficacy and safety

The safety and efficacy of anakinra in combination with methotrexate have been demonstrated in 1790 RA patients \geq 18 years of age with varying degrees of disease severity.

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

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

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

Safety in pediatric RA (JIA) patients

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

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.

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. 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.

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 removed from the refrigerator for 12 hours at temperature not above 25 °C, without exceeding the expiry date. At the end of this period, the product must not be put back in the refrigerator and must be disposed of.

6.5 Nature and contents of container

0.67 ml of solution for injection in a pre-filled syringe (Type I glass) with a plunger stopper (bromobutyl rubber). The pre-filled syringe has an outer rigid plastic needle shield attached to a grey inner needle cover. The inner needle cover contains dry natural rubber (a derivative of latex). See section 4.4.

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 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.

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/1/02/203/001 – 1-pack
EU/1/02/203/002 – 7-pack
EU/1/02/203/003 – 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 <http://www.ema.europa.eu>

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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 Cryopyrin-Associated Periodic Syndromes (CAPS), including:

- Neonatal-Onset Multisystem Inflammatory Disease (NOMID) / Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA)
- Muckle-Wells Syndrome (MWS)
- Familial Cold Autoinflammatory Syndrome (FCAS)

4.2 Posology and method of administration

Kineret treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis and CAPS, 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.

Elderly population (≥ 65 years)

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

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

Paediatric population (< 18 years)

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

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

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

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

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

4.3 Contraindications

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

Kineret must not be used in patients with severe renal impairment ($CL_{cr} < 30$ ml/minute) (see section 4.2).

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

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.

The inner needle cover of the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause severe allergic reactions.

Hepatic Events

In clinical studies in RA and CAPS patients, transient elevations of liver enzymes have been seen uncommonly. These elevations have not been associated with signs or symptoms of hepatocellular damage. During post-marketing use isolated case reports indicating non-infectious hepatitis have been received. Hepatic events during post marketing use have mainly been reported in patients with predisposing factors, e.g history of transaminase elevations before start of Kineret treatment. The efficacy and safety of Kineret in patients with $AST/ALT \geq 1.5$ 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 severe infection develops. In Kineret treated CAPS patients, there is a risk for disease flares when discontinuing Kineret treatment. This should be taken into account when deciding on discontinuing Kineret during a severe 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.

Neutropenia

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

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

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.

Vaccinations

In a placebo-controlled clinical trial ($n = 126$), no difference was detected in anti-tetanus antibody response between the Kineret and placebo treatment groups when 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 trials. No overall differences in safety or effectiveness were observed between these patients and younger patients. There is limited experience in treating elderly CAPS 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 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 antagonists is not recommended (see section 4.5).

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e. essentially 'sodium-free'.

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 trials, interactions between Kineret and other medicinal products (including nonsteroidal anti-inflammatory medicinal products, corticosteroids, and DMARDs) have not been observed.

Concurrent Kineret and TNF antagonist treatment

In a clinical trial 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 trials 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 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

There are limited amount of data from the use of anakinra in pregnant women. However, reproductive studies have been conducted with Kineret on rats and rabbits at doses up to 100 times the human RA dose and have revealed no evidence of impaired fertility or harm to the foetus.

Kineret is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

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. There are no indications either from this study or from post marketing adverse reaction reports that the overall safety profile in CAPS patients is different from that in RA patients.

The adverse reactions table below therefore applies to Kineret treatment both in RA and CAPS patients.

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

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

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 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.

There were no deaths due to serious infections in RA or CAPS studies.

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

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 ($ANC < 1.5 \times 10^9/l$) 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 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.

Malignancies

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

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

Allergic reactions

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

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

Immunogenicity

In clinical trials in RA, up to 3% of adult patients tested seropositive at least once during the study for antibodies capable of neutralising the biologic effects of anakinra. The occurrence of antibodies was typically transient and not associated with clinical adverse reactions or diminished efficacy. In addition, in a clinical trial 6% of paediatric patients tested seropositive at least once during the study for antibodies capable of neutralising the biologic effects of anakinra.

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

Injection site reactions

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 43 CAPS patients followed for up to 5 years no patient permanently or temporarily discontinued Kineret treatment due to 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.

Paediatric population

Kineret has been studied in 36 CAPS patients aged 8 months to < 18 years, for up to 5 years. With the exception of infections and related symptoms that were more frequently reported in patients <2 years of age, the safety profile was similar in all paediatric age groups. The safety profile in paediatric patients was similar to that seen in adult populations and no clinically relevant new adverse reactions were seen.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after 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 trials in RA or CAPS patients. In studies of sepsis, 1015 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

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

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

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

Spontaneous mutations in the CIAS1/NLRP3 gene have been identified in a majority of patients with CAPS. CIAS1/NLRP3 encodes for cryopyrin, a component of the inflammasome. The activated inflammasome results in proteolytic maturation and secretion of IL-1 β , which has a broad range of effects including systemic inflammation. Untreated CAPS patients are characterized by increased CRP, SAA and IL-6 relative to normal serum levels. Administration of Kineret 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.

Clinical efficacy and safety in RA

The safety and efficacy of anakinra in combination with methotrexate have been demonstrated in 1790 RA patients \geq 18 years of age with varying degrees of disease severity.

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

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

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

Clinical efficacy and safety in CAPS

The safety and efficacy of Kineret 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).

Paediatric population

Overall, the efficacy and safety profile of Kineret is comparable in adult and paediatric CAPS patients.

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 pediatric RA (JIA) patients

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

Immunogenicity

See section 4.8.

5.2 Pharmacokinetic properties

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

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

In general the pharmacokinetics in CAPS patients is similar to that in RA patients. In CAPS patients approximate dose linearity with a slight tendency to higher than proportional increase has been noted. Pharmacokinetic data in children < 4 years are lacking, but clinical experience is available from 8 months of age, and when started at the recommended daily dose of 1-2 mg/kg, no safety concerns have been identified. Pharmacokinetic data are lacking in older CAPS patients. Distribution into the cerebrospinal fluid has been demonstrated.

Hepatic impairment

A study including 12 patients with hepatic dysfunction (Child-Pugh Class B) given a single 1mg/kg intravenous dose has been performed. Pharmacokinetic parameters were not substantially different from healthy volunteers, other than a decrease in clearance of approximately 30% in comparison with data from a study with healthy volunteers. A corresponding decrease in creatinine clearance was seen in the hepatic failure population. Accordingly, the decrease in clearance is most likely explained by a decrease in renal function in this population. These data support that no dose adjustment is required for patients with hepatic dysfunction of Child-Pugh Class B. See section 4.2.

Renal impairment

The mean plasma clearance of Kineret 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. 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.

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 removed from the refrigerator for 12 hours at temperature not above 25 °C, without exceeding the expiry date. At the end of this period, the product must not be put back in the refrigerator and must be disposed of.

6.5 Nature and contents of container

0.67 ml of solution for injection in a graduated pre-filled syringe (Type I glass) with a plunger stopper (bromobutyl rubber). The pre-filled syringe has an outer rigid plastic needle shield attached to a grey inner needle cover. The inner needle cover contains dry natural rubber (a derivative of latex). See section 4.4.

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 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)

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 <http://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

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**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

• **Additional risk minimisation measures**

The MAH shall agree the content and format of the educational materials with the National Competent Authorities in each Member State where Kineret is marketed and prior to marketing in any additional Member State.

The MAH shall ensure that all physicians who intend to prescribe KINERET are provided with the following items:

- Educational material for health care providers
- Educational material for patients and caregivers

The educational material for health care providers shall include the following key elements:

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

The educational material for patients and caregivers will include the following key elements:

- Instructions on use of the graduated 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

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.67 ml 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 pre-filled syringe
7 pre-filled syringes
Multipack: 28 (4 x 7) 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/1/02/203/001 – 1-pack
EU/1/02/203/002 – 7-pack
EU/1/02/203/003 – 28-pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Kineret 100 mg

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 solution for injection in pre-filled syringe
Anakinra

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.67 ml 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 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/1/02/203/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Kineret 100 mg

**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 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

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
PRE-FILLED SYRINGE CARTON**

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Kineret 100 mg 0.67 ml

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Kineret 100 mg 0.67 ml

**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 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
2. What you need to know before you use Kineret
3. How to use Kineret
4. Possible side effects
5. How to store Kineret
6. Contents of the pack and other information

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. Cytokines are proteins made by your body that coordinate communication between cells and help control cell activity. In rheumatoid arthritis, your body produces too much of a cytokine called interleukin-1. This results in harmful effects such as swelling and tissue damage. 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*.

Kineret is used to treat the signs and symptoms of Rheumatoid Arthritis (RA) 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.

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 severe renal impairment (kidney damage);
- 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.

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;
- if you know you are allergic to latex. The inner needle cover of the pre-filled syringe contains a derivative of latex.

Children and adolescents

Use of Kineret in children and adolescents with Rheumatoid Arthritis has not been fully investigated and therefore cannot be recommended.

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) 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 adequate contraception must be used by women of childbearing potential when using Kineret.

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

Kineret contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e. essentially 'sodium-free'.

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) once daily. You should try to have the injection at the same time each day.

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 with Kineret, please read the 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.

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 include a fever, a cough or redness and tenderness of the skin.
- **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

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.

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.

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.

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 – 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 12 hours or disposed of.

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 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:
<http://www.ema.europa.eu>

Information on how to give yourself an injection of Kineret

This section contains information on how to give yourself an injection of Kineret. It is important that you do not try to give yourself the injection unless you have received training from your 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 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 a subcutaneous injection you will need:

- a new pre-filled syringe of Kineret; and
- alcohol wipes or similar.

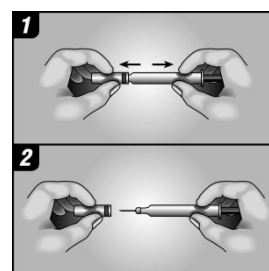
What should you do before you give yourself a subcutaneous injection of Kineret?

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.

How do you prepare your Kineret injection?

Before you inject Kineret you must do the following:

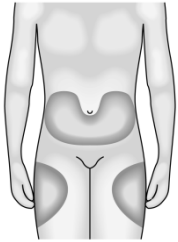
1. Hold the syringe barrel and gently take the cover from the needle without twisting. Pull straight as shown in pictures 1 and 2. Do not touch the needle or push the plunger.



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.

Where should you give your injection?

The most suitable places to inject yourself are:



- the top of your thighs; and
- the abdomen, except for the area around the navel.

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 your 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 your skin pinched.
4. After injecting the liquid, remove the needle and let go of your skin.
5. Only use each syringe for one injection.

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

- 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.
- The used pre-filled syringe 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.

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
2. What you need to know before you use Kineret
3. How to use Kineret
4. Possible side effects
5. How to store Kineret
6. Contents of the pack and other information

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)
- Cryopyrin-Associated Periodic Syndromes (CAPS) which includes the following auto-inflammatory diseases:
 - Neonatal-Onset Multisystem Inflammatory Disease (NOMID), also called Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA),
 - Muckle-Wells Syndrome (MWS),
 - Familial Cold Autoinflammatory Syndrome (FCAS)

Cytokines are proteins made by your body that co-ordinate communication between cells and help control cell activity. In Rheumatoid Arthritis and in CAPS, 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 Rheumatoid Arthritis (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 Cryopyrin-Associated Periodic Syndromes (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).

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 severe renal impairment (kidney damage);
- 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.

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;
- if you know you are allergic to latex. The inner needle cover of the pre-filled syringe contains a derivative of latex.

Children and adolescents

- RA: Use of Kineret in children and adolescents with Rheumatoid Arthritis has not been fully investigated and therefore cannot be recommended.
- CAPS: 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) 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 adequate contraception must be used by women of childbearing potential when using Kineret.

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

Kineret contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg dose, i.e. essentially 'sodium-free'.

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 100mg.

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 or CAPS.

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 include a fever, a cough or redness and tenderness of the skin.
- **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

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.

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.

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.

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 12 hours or disposed of.

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:

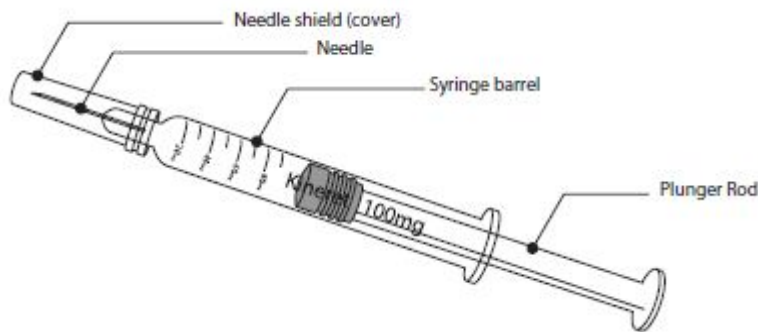
<http://www.ema.europa.eu>

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.
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.

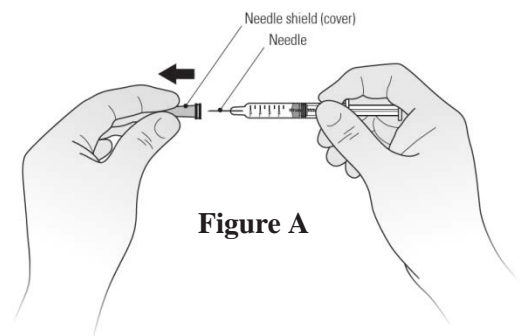


Figure A

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.
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.
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

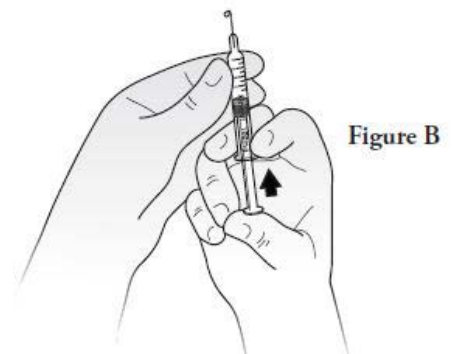


Figure B

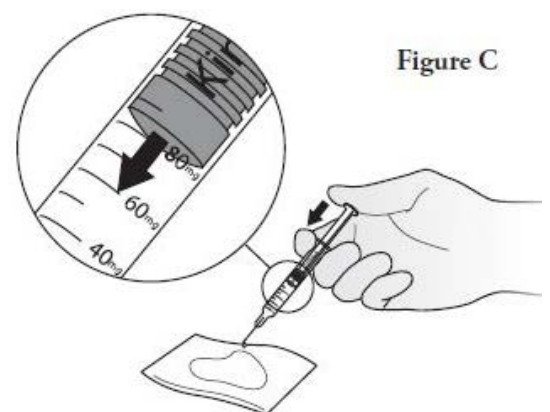


Figure C

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

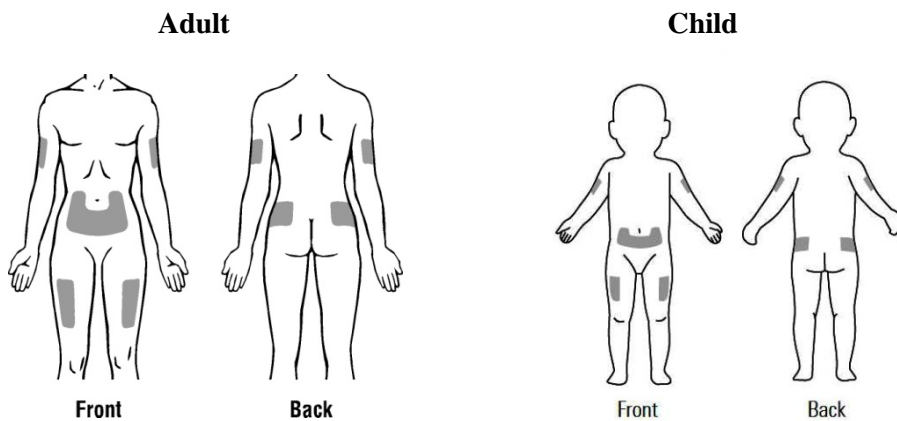


Figure D

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**.

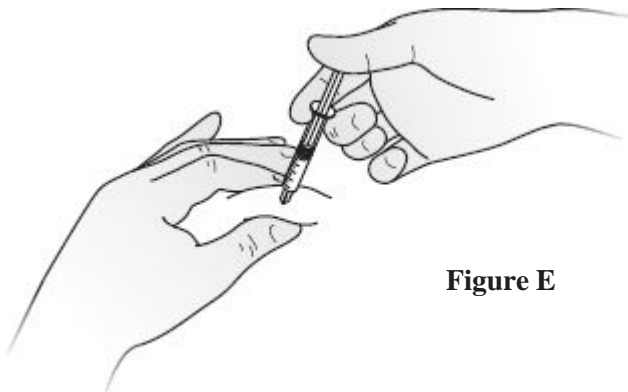


Figure E

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.