Using Kineret® (anakinra)

A guide for Healthcare Professionals (HCPs)

When prescribing Kineret in Cryopyrin-Associated Periodic Syndromes (CAPS), please communicate the information outlined in this booklet to the patient/caregiver, to ensure correct patient dosing and use of the graduated syringe including injection technique.

Prescribing information can be found on back page

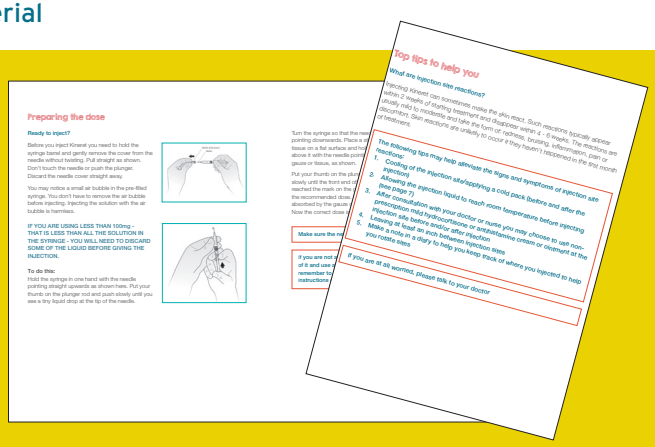
What the Kineret user will need

1. Subcutaneous (s.c.) injection training by an appropriate healthcare professional

Although patients and carers can become confident in injecting at home, it can be daunting to begin with. The right education on s.c. injection technique when Kineret is initiated will ensure correct use. It is important to tell the patient/caregiver that injecting Kineret can sometimes make the skin react (see page 7).

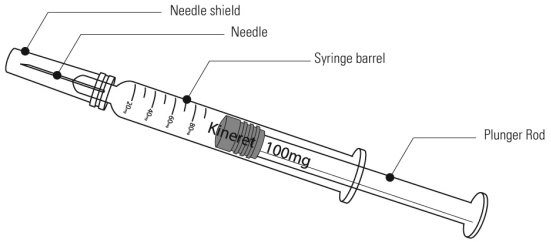
2. Approved education material

Sobi has produced a comprehensive Kineret patient/caregiver booklet which should be given to all who use Kineret for reference to ensure appropriate use. This booklet, requested and approved by the regulatory authorities, should be handed to the patient/caregiver when they start using Kineret.



3. Specific instruction on the graduated syringe

To ensure the correct dose is administered, careful guidance will need to be communicated on use of the graduated syringe (see page 5).



Facts patients and caregivers need to know about Kineret

Once you have discussed Kineret in principle with the patient/caregiver and agreed that Kineret should be prescribed, the following practical information should be covered.

1. How to give s.c. injection and appropriate sites

The patient and/or caregiver will need to receive appropriate instruction on how to give a subcutaneous injection, either to themselves or to the patient in their care.

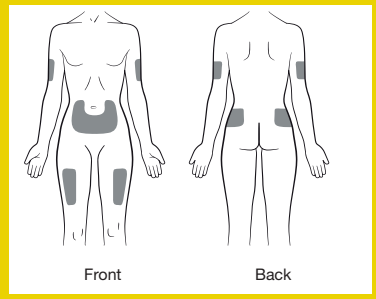
Where to inject Kineret

The most suitable places to inject are:

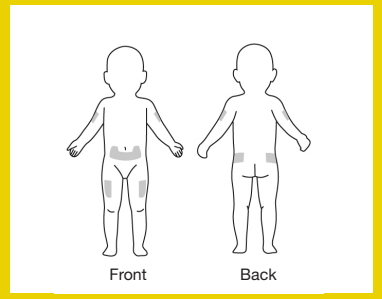
- the abdomen (except for the area around the navel)
- the top of the thighs (this is especially good for infants under a year if they have slightly chubby legs)
- the upper outer areas of the buttocks*; and
- the outer area of the upper arms*.

* Only really suitable if a caregiver is giving the injection

Adult



Child



It is also helpful to advise the patient/caregiver to change the injection site each time so the area does not become sore

- Do not inject into skin that is tender, red, bruised, or hard
- Avoid scars or stretch marks
- Do not inject close to a vein

Kineret® (anakinra)

Ensuring the appropriate dose is prescribed and delivered

The dose of Kineret should be calculated and adjusted in line with the recommended dosage in the Summary of Product Characteristics. It is vital that the patient or caregiver fully understands the dose in milligrams and graduations on the syringe. See page 5 for further instructions on delivering the appropriate dose.

Kineret CAPS initiation dose
1-2 mg/kg/day

Kineret CAPS maintenance dose	
FCAS/mild disease	Severe disease
Often not necessary to increase the dose	3-4 mg/kg/day up to 8 mg/kg/day

Starting dose:

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

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):

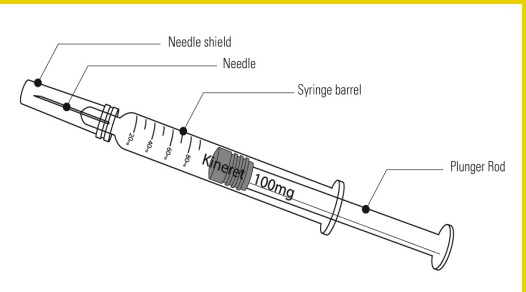
Dose increases may become necessary within 1-2 months based on therapeutic response. The usual maintenance dose in severe CAPS is 3-4 mg/kg/day, which can be adjusted to a maximum of 8 mg/kg/day.

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.

See Summary of Product Characteristics (SPC) for full dosage and follow-up details, including different patient populations.

Ensuring the appropriate dose is given

Kineret is supplied ready for use in a graduated pre-filled syringe. The marks on the side of the syringe indicate the milligrams. The graduated syringe should be used as it enables accurate dosing in CAPS patients.



The graduated pre-filled syringe allows for doses between 20 and 100 mg. As the minimum dose is 20 mg, Kineret is not approved for use in paediatric patients with a body weight below 10 kg.
If less than 100 mg is to be administered, some of the liquid will need to be discarded. Instructions for the patient on how to do this appear in the Kineret patient booklet.

As a health care professional you will need to calculate the dose to be used, based initially on the weight of the patient and later adjusted based on therapeutic response. In addition the dose will need to be adjusted to the nearest dose which can be delivered from one or more graduated syringes.
As Kineret can only be administered as 20-100 mg per injection in 10 mg increments, it is important that the prescribed dose allows for this dosing.

Dose calculation examples:

Harry suffers from severe Muckle-Wells syndrome and needs a dose of 4-5 mg/kg/day. Harry's weight is 45 kg.
Daily dose = 45 kg x 4-5mg/kg/day = 180-225 mg/day.
Here it is most practical to prescribe 200 mg per day to be given at suitable times, approximately the same every day.

Lucy is recently diagnosed with NOMID/CINCA syndrome and has ceased responding to her initial dose of 1-2 mg/kg/day. She now needs a dose increase to 2-3 mg/kg/day. Lucy's weight is 12 kg.
Daily dose = 12 kg x 2-3 mg/kg/day = 24-36 mg/day.
You could prescribe 30 mg of Kineret once daily to be used around the same time each day (preferably in the morning to have the highest concentration during the daytime period).

Kineret® (anakinra)

Safety considerations

Adverse reactions may occur when treating with Kineret.
The most severe common adverse reactions are:

- **Serious infections**
- **Neutropenia**
- **Thrombocytopenia**

Infections

It is not recommended to initiate Kineret treatment in a patient with an ongoing infection.
In CAPS patients, there is a risk of disease flares when discontinuing Kineret treatment. This should be taken into account when deciding on discontinuing Kineret during a severe infection.

Neutropenia

Kineret treatment **should not be** initiated in patients with neutropenia. As neutropenia may occur in patients treated with Kineret, it is important to monitor neutrophil counts prior to initiating Kineret treatment and monthly after initiation of therapy for the first six months and quarterly thereafter.
Should a patient develop neutropenia, Kineret treatment should be discontinued and neutrophil counts should be monitored closely.

Thrombocytopenia

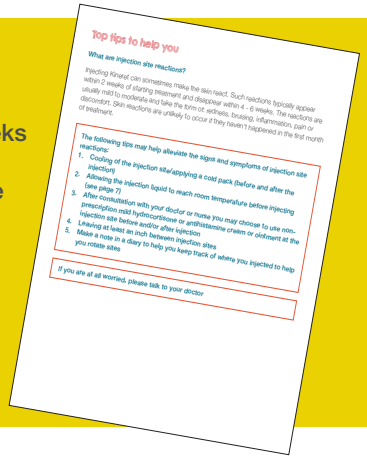
In clinical studies in RA patients, thrombocytopenia has been reported in 1.9% of treated patients compared to 0.3% in the placebo group. The thrombocytopenias have been mild, i.e. platelet counts have been >75 x10^9/L. Mild thrombocytopenia has also been observed in CAPS patients.

The most common adverse reactions are injection-site reactions, headache and increased blood cholesterol

General advice for patients and caregivers

Explain that injecting Kineret can sometimes make the skin react. Such reactions typically appear within 2 weeks of starting treatment and disappear within 4 - 6 weeks. The reactions are usually mild to moderate and take the form of: redness, bruising, inflammation, pain or discomfort. Skin reactions are unlikely to occur if they haven't happened in the first month of treatment.

Tips which may help alleviate the signs and symptoms of injection site reactions are included in the Kineret Patient booklet.


Top tips to help you

What are injection site reactions?

Injecting Kineret can sometimes make the skin react. Such reactions typically appear within 2 weeks of starting treatment and disappear within 4 - 6 weeks. The reactions are usually mild to moderate and take the form of: redness, bruising, inflammation, pain or discomfort. Skin reactions are unlikely to occur if they haven't happened in the first month of treatment.

The following tips may help alleviate the signs and symptoms of injection site reactions:

1. Cooling of the injection site/applying a cold pack (before and after the injection)
2. Allowing the injection liquid to reach room temperature before injecting (see page 7)
3. After consultation with your doctor or nurse you may choose to use non-prescription mild hydrocortisone or antihistamine cream or ointment at the injection site before and/or after injection
4. Leaving at least an inch between injection sites
5. Make a note in a diary to help you keep track of where you injected to help you rotate sites

If you are at all worried, please talk to your doctor

Tips to manage injection site reactions

Patients should be advised to cool the injection site, e.g. by using an ice pack, before and after the injection.

The syringe should be left for out for approximately 30 minutes and allowed to warm to room temperature or be warmed in the hand before injection.

The patient should be clearly instructed NOT to heat the syringe in hot water, in a microwave oven or by any other means than those specified above.

To further alleviate any injection-site reactions you may recommend anti-histamine or hydrocortisone cream or ointment if the patient's general health status allows. Prophylaxis with hydrocortisone cream, ideally 30-60 minutes before the injection, may be used in all patients for the first 3-6 months of treatment to reduce the frequency of injection-site reactions.

In summary; for optimal Kineret use by patients and caregivers please make sure you cover the following important points:

- **Training on good subcutaneous injection technique and site rotation**
- **Provide to all patients and caregivers the approved Kineret patient booklet**
- **Ensure they know how to give the right dose using the graduated syringe**

Any additional copies of educational materials can be ordered via mail.uk@sobi.com

Additional advice on safe disposal of medicines and sharps

The used pre-filled syringe and any gauze or tissue with Kineret solution should be disposed of in accordance with local requirements, about which the patient should be informed. Please also advise the patient and/or caregiver on how to dispose of medicines no longer required. These measures will help to protect the environment.

If there is a contact number to access a HCP for additional help please provide it to the patient/caregiver to support them in using Kineret in CAPS.

Kineret® (anakinra)

Abbreviated Prescribing Information

Kineret® (anakinra) Abbreviated Prescribing Information Please refer to the current Summary of Product Characteristics (SPC) for full prescribing information.

Presentation Kineret 100 mg (150 mg/ml) anakinra* solution for injection in a pre-filled syringe. *Human interleukin-1 receptor antagonist (r-metHuIL-1ra) produced in *Escherichia coli* cells by recombinant DNA technology.

Indications Kineret is indicated for the treatment of the signs and symptoms of rheumatoid arthritis (RA) in combination with methotrexate, in adults 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).

Dosage and administration Kineret treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis or CAPS. For patient convenience, Kineret is supplied ready for use in a graduated pre-filled syringe. The recommended starting dose in RA is 100 mg administered once a day by subcutaneous injection. The dose should be administered at approximately the same time each day. The recommended starting dose in all CAPS subtypes in 1-2mg/kg/day by subcutaneous injection. Maintenance dose in mild CAPS (FCAS, Mild MWS): patients are usually well controlled by maintaining the recommended starting dose (1-2mg/kg/day). Maintenance dose in severe CAPS (MWS and NOMID/CINCA): Dose increase may become necessary within 1-2 months based on therapeutic response. The usual maintenance dose in severe CAPS is 3-4 mg/kg/day to a maximum of 8mg/kg/day. Evaluation of clinical symptoms and inflammatory markers in severe CAPS are recommended at 3 months and then every 6 months after initiation. For full details please refer to SPC. *Elderly population (≥ 65 years) and those with hepatic impairment* No dose adjustment is required. *Paediatric population (< 18 years)* In children and infants aged 8 months and older with a body weight of 10 kg or above, dose and administration is the same as for adult CAPS patients, based on body weight. No data are available in children under the age of 8 months. No data are available. *Renal impairment* See SPC for full details. Kineret should not be used in patients with severe renal impairment. Dosage adjustment and caution is needed for patients with moderate renal impairment (CL_{cr} 30 to 50 ml/minute), but not in those with mild renal impairment (CL_{cr} 50 to 80 ml/minute).

Contraindications Hypersensitivity to the active substance, any of the excipients or to *E. coli* derived proteins. Patients with severe renal impairment (CL_{cr}< 30 ml/minute) or neutropenia (ANC <1.5 x10^9/l)

Warnings and precautions for use See full SPC for details. *Allergic reaction*, including anaphylactic reactions and angioedema have been reported uncommonly (majority were maculopapular or urticarial rashes). If a severe allergic reaction occurs administration of Kineret should be discontinued and appropriate treatment initiated. Kineret has been associated with an increased incidence of *serious infections* (vs placebo), which was increased further in a small number of patients with asthma. The safety and efficacy of Kineret in patients with chronic infections have not been evaluated. 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. Isolated case reports indicating non-infectious hepatitis have been received (mainly reported in patients with predisposing factors). Kineret has been associated with an increased incidence of serious infections (vs. placebo). In Kineret treated CAPS patients, there is a risk for disease flares when discontinuing Kineret treatment, which should be taken into account when deciding on discontinuing Kineret during a severe infection. Kineret treatment should not be initiated in patients with *neutropenia* (ANC < 1.5 x 10^9/l). It is recommended that neutrophil counts be assessed prior to, during (monthly during the first 6 months) and then quarterly after treatment. In patients who become neutropenic (ANC < 1.5 x 10^9/l) Kineret treatment should be discontinued. The use of Kineret in patients with pre-existing *malignancy* is not recommended. No data are available on the effects of *vaccination* with inactivated antigens in patients receiving Kineret, other than a tetanus/diphtheria toxoid vaccine, where no difference in response was observed. Due to lack of data live vaccines should not be given concurrently with Kineret. Caution should be used in treating the *elderly (≥65 years)*, due to the higher incidence of infections in the elderly population in general. The concurrent administration of Kineret and *etanercept or other TNF antagonists* is not recommended due to higher rates of serious infection and neutropenia.

Interactions During clinical trials interactions with other medicinal products (including nonsteroidal anti-inflammatory drugs, corticosteroids, and DMARDs) have not been observed. The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g. IL-1) during chronic inflammation. This would be clinically relevant for CYP450 substrates with a narrow therapeutic index (e.g.warfarin and phenytoin), which could make therapeutic monitoring and dose adjustment necessary when starting or stopping Kineret.

Fertility, pregnancy and lactation There are limited amount of data from the use anakinra in pregnant women. Kineret is not recommended during pregnancy and in women of childbearing potential not using contraception. Breast- feeding should be discontinued during treatment with Kineret.

Undesirable effects See SPC for full listing and details. The most common and consistently reported treatment-related adverse reactions associated with Kineret in trials was **injection site reactions (ISRs)**. The majority were reported as mild to moderate (95% in RA Patients) In CAPS patients no patient permanently or temporarily discontinued Kineret treatment due to ISRs, which typically appear within 2 weeks' therapy and disappear within 4-6 weeks and it is uncommon for them to develop after the first month of therapy. 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. 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. CAPS patients (n=43), 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. **Serious Infections** The subject incidence of serious adverse reactions at the recommended dose of Kineret (100 mg/day) in RA is comparable with placebo. In RA the incidence of serious infection was higher in Kineret-treated patients compared with patients receiving placebo (1.8% vs. 0.7%). The infections observed consisted primarily of bacterial events such as cellulitis, pneumonia, and bone and joint infections. Infections have been noted in all organ systems and have been reported in patients receiving Kineret alone or in combination with immunosuppressive agents. Neutrophil decreases occurred more frequently in patients receiving Kineret compared with placebo. **Neutropenia** was reported in 2 patients. Both episodes of neutropenia resolved over time with continued Kineret treatment. The safety profile seen in **paediatric patients** was similar to that seen in adult populations. *Very common* adverse events (≥ 1/10): headache and injection site reaction, blood cholesterol increase; *Common* adverse events (≥1/100 to 1/10): neutropenia and serious infections requiring hospitalization, thrombocytopenia.

Shelf-life 3 years when kept in refrigerator (2ºC - 8ºC)

Legal category POM

Marketing authorisation numbers EU/1/02/203/007 – 28-pack

Further Information is available from: Swedish Orphan Biovitrum Ltd: Suite 2, Riverside 3, Granta Park, Great Abington, Cambridgeshire, CB21 6AD. Tel: 01223 891854

Date of preparation May 2016

Company reference NP-0968

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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: HPRA Pharmacovigilance, Earlsfort Trrace, IRL- Dublin 2; Tel: +3531 6764971; Fax: +3531 6762517. Website www.hpra.ie
Adverse events should also be reported to Sobi by email: drugsafety@sobi.com

Additional copies can be ordered from:
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www.sobi-uk.co.uk

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