ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kevzara 150 mg solution for injection in pre-filled syringe
Kevzara 150 mg solution for injection in pre-filled pen
Kevzara 200 mg solution for injection in pre-filled syringe
Kevzara 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kevzara 150 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

Kevzara 150 mg solution for injection in pre-filled pen

Each pre-filled pen contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

Kevzara 200 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

Kevzara 200 mg solution for injection in pre-filled pen

Each pre-filled pen contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

Sarilumab is a human monoclonal antibody produced in Chinese Hamster Ovary 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 pale yellow sterile solution of approximately pH 6.0.

Kevzara 150 mg solution for injection

298-346 mmol/kg

Kevzara 200 mg solution for injection

306-371 mmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

Kevzara in combination with methotrexate (MTX) is indicated for the treatment of moderately to severely active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Kevzara can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see section 5.1).

Polymyalgia rheumatica

Kevzara is indicated for the treatment of polymyalgia rheumatica (PMR) in adult patients who have had an inadequate response to corticosteroids or who experience a relapse during corticosteroid taper.

4.2 Posology and method of administration

Treatment should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of the condition for which this medicinal product is intended (see section 4.1). Patients must be given the patient card.

Posology

Rheumatoid arthritis
The recommended dose of sarilumab is 200 mg once every 2 weeks administered as a subcutaneous injection.

Polymyalgia rheumatica
The recommended dose of sarilumab is 200 mg once every 2 weeks administered as a subcutaneous injection, in combination with a tapering course of systemic corticosteroids, after which sarilumab can be continued as monotherapy.

Data are available in patients that were treated for up to 1 year. Therefore treatment beyond 52 weeks should be guided by disease activity, physician discretion, and patient choice.

Dose modification

Rheumatoid arthritis
Reduction of dose from 200 mg once every 2 weeks to 150 mg once every 2 weeks is recommended for management of neutropenia, thrombocytopenia, and liver enzyme elevations.

Treatment with sarilumab must be withheld in patients who develop a serious infection until the infection is controlled.

Initiating treatment with sarilumab is not recommended in patients with a low neutrophil count, i.e. absolute neutrophil count (ANC) less than 2 x 10^9/L.

Initiating treatment with sarilumab is not recommended in patients with a platelet count below 150 x 10^3/µL.

Table 1: Recommended dose modifications in case of neutropenia, thrombocytopenia, or liver enzyme elevations for rheumatoid arthritis (see sections 4.4 and 4.8):

Low Absolute Neutrophil Count (see section 5.1)	
Lab Value (cells x 10^9/L)	**Recommendation**
ANC greater than 1	Current dose of sarilumab to be maintained.
ANC 0.5-1	Treatment with sarilumab to be withheld until >1 x 10^9/L. Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ANC less than 0.5	Treatment with sarilumab to be discontinued.

Low Platelet Count	
Lab Value (cells x 10^3/µL)	**Recommendation**

50 to 100	Treatment with sarilumab to be withheld until >100 x 10^3/μL. Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
Less than 50	If confirmed by repeat testing, treatment with sarilumab to be discontinued.

Liver Enzyme Abnormalities	
Lab Value	**Recommendation**
ALT > 1 to 3 x Upper Limit of Normal (ULN)	Clinically appropriate dose modification of concomitant DMARDs or immunomodulatory agents to be considered.
ALT > 3 to 5 x ULN	Treatment with sarilumab to be withheld until <3 x ULN. Sarilumab can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ALT > 5 x ULN	Treatment with sarilumab to be discontinued.

Polymyalgia rheumatica (PMR)
Laboratory Abnormalities: Discontinue sarilumab in patients with PMR who develop the following laboratory abnormalities *(see section 4.4 and 5.1)*:

- neutropenia (ANC below 1 x 10^9/L at the end of the dosing interval)
- thrombocytopenia (platelet count below 100 x 10^3 μL)
- AST or ALT elevations (3 times above the ULN)

Dosage modifications have not been studied in patients with PMR with these conditions. For treatment initiation criteria, refer to the posology for PMR.

Missed dose

If a dose of sarilumab is missed and it has been 3 days or less since the missed dose, the next dose should be administered as soon as possible. The subsequent dose should be administered at the regularly scheduled time. If it has been 4 days or more since the missed dose, the subsequent dose should be administered at the next regularly scheduled time, the dose should not be doubled.

Special populations

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment. Sarilumab has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment
The safety and efficacy of sarilumab have not been studied in patients with hepatic impairment, including patients with positive hepatitis B virus (HBV) or hepatitis C virus (HCV) serology (see section 4.4).

Elderly
No dose adjustment is required in patients over 65 years of age (see section 4.4).

Paediatric population
The safety and efficacy of sarilumab pre-filled syringe and pre-filled pen in children less than 18 years of age have not been established. No data are available.

Method of administration

Subcutaneous use.

Injection sites (abdomen, thigh and upper arm) should be rotated with each injection. Sarilumab should not be injected into skin that is tender, damaged, or has bruises or scars.

Pre-filled syringe and pre-filled pen
The total content (1.14 ml) of the pre-filled syringe/pre-filled pen should be administered as a subcutaneous injection.

For the pre-filled syringe/pre-filled pen, a patient may self-inject sarilumab or the patient's caregiver may administer sarilumab if their healthcare professional determines that it is appropriate. Proper training should be provided to patients and/or caregivers on the preparation and administration of sarilumab prior to use.

The pre-filled syringe or pen has not been studied in paediatric patients.

Comprehensive instructions for administration of this medicinal product are given in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Serious infections

Patients must be closely monitored for the development of signs and symptoms of infection during treatment with sarilumab (see sections 4.2 and 4.8). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Sarilumab must not be administered in patients with an active infection, including localised infections. The risks and benefits should be considered prior to initiating treatment in patients who have:
- chronic or recurrent infection;
- a history of serious or opportunistic infections;
- HIV infection;
- underlying conditions that may predispose them to infection;
- been exposed to tuberculosis; or
- lived in or travelled to areas of endemic tuberculosis or endemic mycoses.

Treatment with sarilumab must be withheld if a patient develops a serious infection or an opportunistic infection. Once the infection is controlled, treatment with sarilumab may be re-initiated at the discretion of the healthcare professional.

A patient who develops an infection during treatment should also undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents. The most frequently observed serious infections with sarilumab in RA patients included pneumonia and cellulitis (see section 4.8). Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with sarilumab in RA. In some patients with RA with concomitant tuberculosis, disseminated rather than localised infections were observed, most of whom were taking

concomitant immunosuppressants such as MTX or corticosteroids, which may increase the risk of infection.

Tuberculosis
Patients must be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating treatment with sarilumab. Patients with latent or active tuberculosis must be treated with standard antimycobacterial therapy before initiating treatment. Anti-tuberculosis therapy must be considered prior to initiation of treatment in patients with a past medical history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Healthcare professionals are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised. When considering anti-tuberculosis therapy, consultation with a physician with expertise in tuberculosis may be appropriate.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral reactivation
Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with sarilumab (see section 4.8). No cases of Hepatitis B reactivation were reported in the clinical studies; however patients who were at risk for reactivation were excluded.

Laboratory parameters

Neutrophil count
Treatment with sarilumab was associated with a higher incidence of decrease in ANC (see section 4.8). Decrease in ANC was not associated with higher incidence of infections, including serious infections.

- Initiating treatment with sarilumab is not recommended in patients with a low neutrophil count, i.e., ANC less than 2 x 10^9/L. In patients who develop an ANC less than 0.5 x 10^9/L, it is recommended to discontinue treatment with sarilumab (see section 4.2).
- Neutrophil count must be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on ANC results, see section 4.2.
- Based on the pharmacodynamics of the changes in ANC, results obtained at the end of the dosing interval should be used when considering dose modification (see section 5.1).

Platelet count
Treatment with sarilumab was associated with a reduction in platelet counts in clinical studies. Reduction in platelets was not associated with bleeding events (see section 4.8).

- Initiating treatment with sarilumab is not recommended in patients with a platelet count below 150 x10^3/µL. In patients who develop a platelet count less than 50 x 10^3/ µL, treatment with sarilumab must be discontinued.
- Platelet count must be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on platelet counts, see section 4.2.

Liver enzymes
Treatment with sarilumab was associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies (see section 4.8). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic medicinal products (e.g., MTX) were used in combination with sarilumab.

Initiating treatment with sarilumab is not recommended in patients with elevated transaminases, ALT or AST greater than 1.5 x ULN. In patients who develop elevated ALT greater than 5 x ULN, treatment with sarilumab must be discontinued (see section 4.2).

ALT and AST levels must be monitored 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, consider other liver function tests such as bilirubin. For recommended dose modifications based on transaminase elevations, see section 4.2.

Lipid abnormalities
Lipid levels may be reduced in patients with chronic inflammation. Treatment with sarilumab was associated with increases in lipid parameters such as LDL cholesterol, HDL cholesterol, and/or triglycerides (see section 4.8). Lipid parameters should be assessed approximately 4 to 8 weeks following initiation of treatment with sarilumab, then at approximately 6 month intervals.
Patients should be managed according to clinical guidelines for the management of hyperlipidaemia.

Gastrointestinal perforation and diverticulitis

Cases of gastrointestinal perforation and diverticulitis have been reported in association with sarilumab. Gastrointestinal perforation has been reported in patients with and without diverticulitis. Patients presenting with symptoms potentially indicative of diverticulitis, such as abdominal pain, gastrointestinal haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation. Sarilumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis (see section 4.8).

Malignancies

Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with sarilumab on the development of malignancies is not known but malignancies were reported in clinical studies (see section 4.8).

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with sarilumab (see section 4.8). Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Patients must be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, administration of Sarilumab must be stopped immediately (see section 4.3).

Hepatic impairment

Treatment with sarilumab is not recommended in patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Vaccinations

Concurrent use of live vaccines as well as live attenuated vaccines should be avoided during treatment with sarilumab as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving sarilumab. Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. The interval between live vaccinations and initiation of therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk

RA patients have an increased risk for cardiovascular disorders and risk factors (e.g. hypertension, hyperlipidaemia) should be managed as part of usual standard of care.

Polysorbate 20 (E 432)

This medicinal product contains 2.28 mg of polysorbate 20 in each 1.14 ml of solution for injection which is equivalent to 2 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Sarilumab exposure was not affected when coadministered with MTX based on the population pharmacokinetic analyses and across study comparisons. MTX exposure is not expected to be changed by sarilumab coadministration; however, no clinical data was collected. Sarilumab has not been investigated in combination with Janus kinase (JAK) inhibitors or biological DMARDs such as tumour necrosis factor (TNF) antagonists.

Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) and therefore have the potential to alter the pharmacokinetics of concomitantly administered medicinal products that are substrates of these enzymes. Elevated levels of interleukin-6 (IL-6) may down-regulate CYP activity such as in patients with RA or PMR and hence increase drug levels compared to subjects without RA or PMR. Blockade of IL-6 signalling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered medicinal products concentrations.

The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of sarilumab in patients being treated with CYP substrate medicinal products, therapeutic monitoring of effect (e.g., warfarin) or concentration of the medicinal product (e.g., theophylline) should be performed and the individual dose of the medicinal product should be adjusted as needed.

Caution should be exercised in patients who start sarilumab treatment while on therapy with CYP3A4 substrates (e.g., oral contraceptives or statins), as sarilumab may reverse the inhibitory effect of IL-6 and restore CYP3A4 activity, leading to decreased exposure and activity of CYP3A4 substrate (see section 5.2). Interaction of sarilumab with substrates of other CYPs (CYP2C9, CYP 2C19, CYP2D6) has not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during and up to 3 months after treatment (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of sarilumab in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Sarilumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab.

Breast-feeding

It is unknown whether sarilumab is excreted in human milk or absorbed systemically after ingestion. The excretion of sarilumab in milk has not been studied in animals (see section 5.3).
Because IgG1 are excreted in human milk**,** a decision must be made whether to discontinue breast-feeding or to discontinue sarilumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available on the effect of sarilumab on human fertility. Animal studies showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Kevzara has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions in RA (n=661) and PMR (n=59) patients are neutropenia (14.3%), upper respiratory infections (6.8%), increased ALT (6.3%), urinary tract infections (5.3%), and injection site erythema (5.0%). The most common serious adverse reactions are infections (3.1%) (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions listed in the table have been reported in controlled clinical studies. The frequency of adverse reactions listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions in patients with RA and PMR

MedDRA System Organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection
		Urinary tract infection
		Oral herpes
		Cellulitis
		Pneumonia
	Uncommon	Nasopharyngitis
		Diverticulitis
Blood and lymphatic system disorders	Very common	Neutropenia*
	Common	Leukopenia*
		Thrombocytopenia
Metabolism and nutrition disorders	Common	Hypertriglyceridemia
		Hypercholesterolemia
Gastrointestinal disorders	Rare	Gastrointestinal perforation
Hepatobiliary disorders	Common	Transaminases increased
General disorders and administration site conditions	Common	Injection site erythema
		Injection site pruritus*

*In the SAPHYR study, the reported ADRs in PMR patients are neutropenia, leukopenia and injection site pruritus.

Description of selected adverse reactions

Rheumatoid arthritis

Infections

In the placebo-controlled population, the rates of infections were 84.5, 81.0, and 75.1 events per 100 patient-years, in the 200 mg and 150 mg sarilumab + DMARDs and placebo + DMARDs groups respectively. The most commonly reported infections (5% to 7% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis. The rates of serious infections were 4.3, 3.0, and 3.1 events per 100 patient-years, in the 200 mg, 150 mg sarilumab + DMARDs, and placebo + DMARDs groups, respectively.

In the sarilumab +DMARDs long-term safety population, the rates of infections and serious infection were 57.3 and 3.4 events per 100-patient years, respectively.

The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infection have been reported (see section 4.4).

The overall rates of infections and serious infections in the sarilumab monotherapy population were consistent with rates in the sarilumab + DMARDs population.

Gastrointestinal perforation

Gastrointestinal perforation was reported in patients with and without diverticulitis. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medicinal products (NSAIDs), corticosteroids, or MTX. The contribution of these concomitant medicinal products relative to sarilumab in the development of gastrointestinal perforations is not known (see section 4.4).

Hypersensitivity reactions

In the placebo-controlled population, the proportion of patients who discontinued treatment due to hypersensitivity reactions was higher among those treated with sarilumab (0.9% in 200 mg group, 0.5% in 150 mg group) than placebo (0.2%). The rates of discontinuations due to hypersensitivity in the sarilumab + DMARDs long-term safety population and the sarilumab monotherapy population were consistent with the placebo-controlled population. In the placebo-controlled population, 0.2% of the patients treated with sarilumab 200 mg every two weeks (q2w) + DMARD reported serious adverse reactions of hypersensitivity reactions, and none from sarilumab 150 mg q2w + DMARD group.

Injection site reactions

In the placebo-controlled population, injection site reactions were reported in 9.5%, 8%, and 1.4% of patients receiving sarilumab 200 mg, 150 mg, and placebo respectively. These injection site reactions (including erythema and pruritus) were mild to moderate in severity for the majority of patients (99.5%, 100%, and 100%, for sarilumab 200 mg, 150 mg, and placebo respectively). Two patients on sarilumab (0.2%) discontinued treatment due to injection site reactions.

Laboratory abnormalities

To allow for a direct comparison of frequency of laboratory abnormalities between placebo and active treatment, data from weeks 0-12 were used as this was prior to patients being permitted to switch from placebo to sarilumab.

Neutrophil count

Decreases in neutrophil counts below 1 x 10^9/L occurred in 6.4% and 3.6% of patients in the 200 mg and 150 mg sarilumab + DMARDs group, respectively, compared to no patients in the placebo + DMARDs group. Decreases in neutrophil counts below 0.5 x 10^9/L occurred in 0.8% and 0.6% of patients in the 200 mg and 150 mg sarilumab+ DMARDs groups, respectively. In patients experiencing a decrease in absolute neutrophil count (ANC), modification of treatment regimen such as interruption of sarilumab or reduction in dose resulted in an increase or normalisation of ANC (see section 4.2). Decrease in ANC was not associated with higher incidence of infections, including serious infections.

In the sarilumab + DMARDs long-term safety population and the sarilumab monotherapy population, the observations on neutrophil counts were consistent with those seen in the placebo-controlled population (see section 4.4).

Platelet count
Decreases in platelet counts below 100 x 10^3/µL occurred in 1.2% and 0.6% of patients on 200 mg and 150 mg sarilumab + DMARDs, respectively, compared to no patients on placebo + DMARDs**.**

In the sarilumab + DMARDs long-term safety population and the sarilumab monotherapy population, the observations on platelet counts were consistent with those seen in the placebo-controlled population.

There were no bleeding events associated with decreases in platelet count.

Liver enzymes
Liver enzyme abnormalities are summarised in Table 3. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as interruption of treatment or reduction in dose, resulted in decrease or normalisation of liver enzymes (see section 4.2). These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency (see section 4.4).

Table 3: Incidence of liver enzyme abnormalities in controlled clinical studies

	Placebo + DMARD N = 661	**Sarilumab 150 mg + DMARD N = 660**	**Sarilumab 200 mg + DMARD N = 661**	**Sarilumab monotherapy any Dose N = 467**
AST				
>3 x ULN – 5 x ULN	0%	1.2%	1.1%	1.1%
>5 x ULN	0%	0.6%	0.2%	0%
ALT				
>3 x ULN – 5 x ULN	0.6%	3.2%	2.4%	1.9%
>5 x ULN	0%	1.1%	0.8%	0.2%

Lipids
Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of sarilumab+ DMARDs in the placebo-controlled population. At week 4 the mean LDL increased by 14 mg/dL; mean triglycerides increased by 23 mg/dL; and mean HDL increased by 3 mg/dL. After week 4 no additional increases were observed. There were no meaningful differences between doses.

In the sarilumab + DMARDs long-term safety population and the sarilumab monotherapy population, the observations in lipid parameters were consistent with those seen in the placebo-controlled population.

Malignancies
In the placebo-controlled population, malignancies occurred at the same rate in patients receiving either sarilumab + DMARDs or placebo + DMARDs (1.0 events per 100 patient-years).

In the sarilumab + DMARDs long-term safety population and the sarilumab monotherapy population, the rates of malignancies were consistent with the rate observed in the placebo-controlled population (see section 4.4).

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with sarilumab.

In the placebo-controlled population, 4.0%, 5.6%, and 2.0% of patients treated with sarilumab 200 mg + DMARDs, sarilumab 150 mg + DMARDs and placebo + DMARDs respectively, exhibited a positive response in the antidrug antibody (ADA) assay. Positive responses in the neutralising antibody (NAb) assay were detected in 1.0%, 1.6%, and 0.2% of patients on sarilumab 200 mg, sarilumab 150 mg, and placebo respectively.

In the sarilumab monotherapy population, observations were consistent with the sarilumab + DMARDs population.

Antidrug antibodies (ADA) formation may affect pharmacokinetics of sarilumab. No correlation was observed between ADA development and either loss of efficacy or adverse reactions.

Polymyalgia Rheumatica
The safety of sarilumab was studied in one Phase 3 study (SAPHYR) in 117 PMR patients of whom 59 received subcutaneous sarilumab 200 mg (see section 5.1). The total patient years duration in the sarilumab PMR population was 47.37 patient years during the 12-month double blind, placebo-controlled study. Safety data are available for up to 1 year.

Infections
In the SAPHYR study, the proportion of patients with infections was lower in the sarilumab 200 mg with 14-week prednisone taper group (37.3%) compared to the placebo with 52-week prednisone taper group (50.0%). Serious infections were reported in 3 (5.1%) patients in the sarilumab 200 mg with 14-week prednisone taper group (all of which were cases of bacterial infections) and 3 (5.2%) patients in the placebo with 52-week prednisone taper group (all of which were cases of COVID-19 infection).
Laboratory abnormalities

Neutrophil count
In the SAPHYR study, decreases in neutrophil counts below 1 x 10^9/L occurred in 7 (12%) patients in the sarilumab group of which 2 (3.4%) were serious (decreases in neutrophil counts below 0.5 x 10^9/L).

Liver enzymes
In the SAPHYR study, no sarilumab treated patients had an ALT or AST greater than 3 times the upper limit of normal (ULN). In the placebo group, 2 patients had ALT elevations greater than 3x ULN.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with sarilumab.

In the PMR population, 1 (1.8%) patient treated with sarilumab 200 mg exhibited a persistent anti-drug antibody (ADA) response and none of the patients in the placebo group exhibited an ADA response. Positive response in the neutralising antibody assay was detected in the PMR patient with ADA response on sarilumab 200 mg. Because of the low occurrence of ADA, the effect of these antibodies on the safety, and/or efficacy of sarilumab is unknown.

Paediatric population

The safety and efficacy of sarilumab pre-filled syringe and pre-filled pen in children less than 18 years of age have not been established. No data are available.

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

There is no specific treatment for Kevzara overdose. In the event of an overdose, the patient should be closely monitored, treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors, ATC code: L04AC14

Mechanism of action

Sarilumab is a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling which involves ubiquitous signal-transducing glycoprotein 130 (gp130) and the Signal Transducer and Activator of Transcription-3 (STAT-3).

In functional human cell-based assays, sarilumab was able to block the IL-6 signalling pathway, measured as STAT-3 inhibition, only in the presence of IL-6.

IL-6 is a pleiotropic cytokine that stimulates diverse cellular responses such as proliferation, differentiation, survival, and apoptosis and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP) and serum amyloid A. Elevated levels of IL-6 are found in the synovial fluid of patients with rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA) and play an important role in both the pathologic inflammation and joint destruction which are hallmarks of RA and pJIA. IL-6 is involved in diverse physiological processes such as migration and activation of T-cells, B-cells, monocytes, and osteoclasts leading to systemic inflammation, synovial inflammation, and bone erosion in patients with RA and pJIA.

The activity of sarilumab in reducing inflammation is associated with laboratory changes such as decrease in ANC and elevation in lipids (see section 4.4).

Pharmacodynamic effects

Following single-dose subcutaneous (SC) administration of sarilumab 200 mg and 150 mg in patients with RA rapid reduction of CRP levels was observed. Levels were reduced to normal as early as 4 days after treatment initiation. Following single-dose sarilumab administration, in patients with RA, ANC decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline (see section 4.4). Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in haemoglobin and serum albumin. Sarilumab treatment for PMR patients taking 200 mg once every 2 weeks has a similar effect compared to RA patients on the PD biomarker profiles (CRP and ANC) over time.

Clinical efficacy

Rheumatoid arthritis (RA)
The efficacy and safety of sarilumab were assessed in three randomised, double-blind, controlled multicentre studies (MOBILITY and TARGET were placebo-controlled studies and MONARCH was an active comparator-controlled study) in patients older than 18 years with moderately to severely active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline.

Placebo-controlled studies

MOBILITY evaluated 1197 patients with RA who had inadequate clinical response to MTX. Patients received sarilumab 200 mg, sarilumab 150 mg, or placebo every 2 weeks with concomitant MTX. The primary endpoints were the proportion of patients who achieved an ACR20 response at week 24, changes from baseline in Health Assessment Questionnaire – Disability Index (HAQ-DI) score at week 16, and change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at week 52.

TARGET evaluated 546 patients with RA who had an inadequate clinical response or were intolerant to one or more TNF-α antagonists. Patients received sarilumab 200 mg, sarilumab 150 mg, or placebo every 2 weeks with concomitant conventional DMARDs (cDMARDs). The primary endpoints were the proportion of patients who achieved an ACR20 response at week 24 and the changes from baseline HAQ-DI score at week 12.

Clinical response

The percentages of sarilumab + DMARDs-treated patients achieving ACR20, ACR50, and ACR70 responses in MOBILITY and TARGET are shown in Table 4. In both studies, patients treated with either 200 mg or 150 mg of sarilumab + DMARDs every two weeks had higher ACR20, ACR50, and ACR70 response rates versus placebo-treated patients at week 24. These responses persisted through 3 years of therapy in an open-label extension study.

In MOBILITY, a greater proportion of patients treated with sarilumab 200 mg or 150 mg every two weeks plus MTX achieved remission, defined as Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) < 2.6 compared with placebo + MTX at week 52. Results at 24 weeks in TARGET were similar to the results at 52 weeks in MOBILITY (see Table 4).

Table 4: Clinical response at weeks 12, 24, and 52 in placebo-controlled studies, MOBILITY and TARGET

	Percentage of patients					
	MOBILITY MTX inadequate responders			**TARGET TNF inhibitor inadequate responders**		
	Placebo + MTX N = 398	**Sarilumab 150 mg + MTX N = 400**	**Sarilumab 200 mg + MTX N = 399**	**Placebo + cDMARDs[*] N = 181**	**Sarilumab 150 mg + cDMARDs[*] N = 181**	**Sarilumab 200 mg + cDMARDs[*] N = 184**
Week 12						
DAS28-CRP remission (< 2.6)	4.8%	18.0%[†††]	23.1%[†††]	3.9%	17.1%[†††]	17.9%[†††]
ACR20	34.7%	54.0%[†††]	64.9%[†††]	37.6%	54.1%[†]	62.5%[†††]
ACR50	12.3%	26.5%[†††]	36.3%[†††]	13.3%	30.4%[†††]	33.2%[†††]
ACR70	4.0%	11.0%[††]	17.5%[†††]	2.2%	13.8%[†††]	14.7%[†††]
Week 24						
DAS28-CRP remission (< 2.6)	10.1%	27.8%[†††]	34.1%[†††]	7.2%	24.9%[†††]	28.8%[†††]
ACR20[‡]	33.4%	58.0%[†††]	66.4%[†††]	33.7%	55.8%[†††]	60.9%[†††]
ACR50	16.6%	37.0%[†††]	45.6%[†††]	18.2%	37.0%[†††]	40.8%[†††]
ACR70	7.3%	19.8%[†††]	24.8%[†††]	7.2%	19.9%[††]	16.3%[†]
Week 52						
DAS28-CRP remission (< 2.6)	8.5%	31.0%[†††]	34.1%[†††]	NA[§]	NA[§]	NA[§]
ACR20	31.7%	53.5%[†††]	58.6%[†††]			
ACR50	18.1%	40.0%[†††]	42.9%[†††]			
ACR70	9.0%	24.8%	26.8%			

Major clinical response[¶]	3.0%	12.8%[†††]	14.8%[†††]			

[*]cDMARDs in TARGET included MTX, sulfasalazine, leflunomide and hydroxychloroquine

[†]p-value <0.01 for difference from placebo

[††]p-value <0.001 for difference from placebo

[†††]p-value <0.0001 for difference from placebo

[‡] Primary endpoint

[§] NA=Not Applicable as TARGET was a 24-week study

[¶]Major clinical response = ACR70 for at least 24 consecutive weeks during the 52-week period

In both MOBILITY and TARGET, higher ACR20 response rates were observed within 2 weeks compared to placebo and were maintained for the duration of the studies (see Figures 1 and 2).

Figure 1: Percent of ACR20 response by visit for MOBILITY

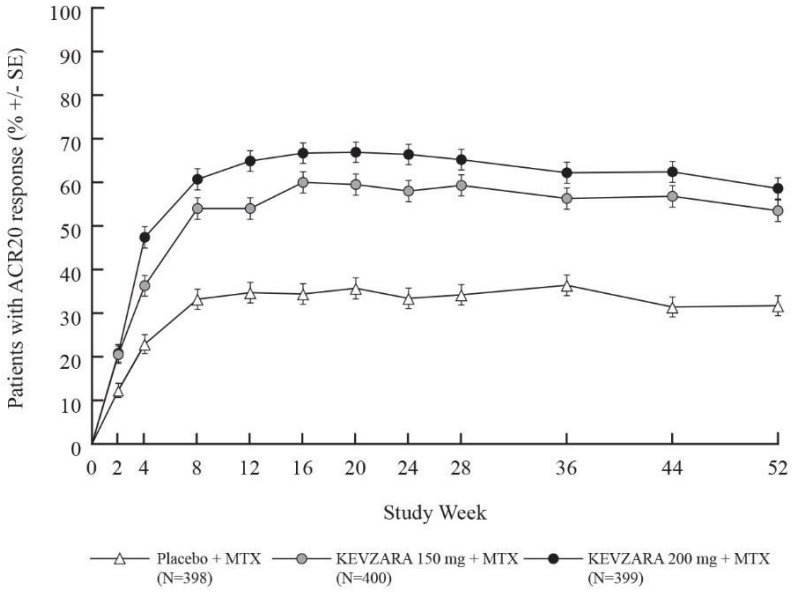
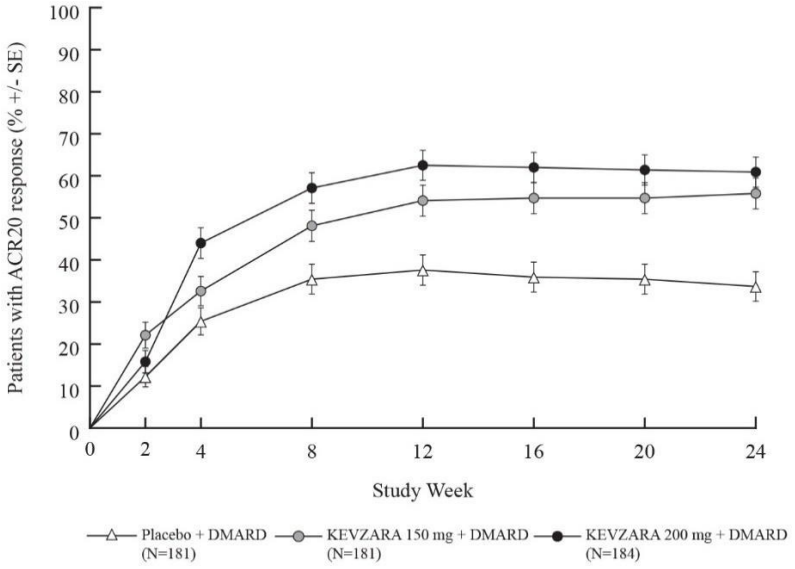


Figure 2: Percent of ACR20 response by visit for TARGET



The results of the components of the ACR response criteria at week 24 for MOBILITY and TARGET are shown in Table 5. Results at 52 weeks in MOBILITY were similar to the results at 24weeks for TARGET.

Table 5: Mean reductions from baseline to week 24 in components of ACR score

	MOBILITY			TARGET		
Component (range)	**Placebo + MTX (N = 398)**	**Sarilumab 150 mg q2w* + MTX (N = 400)**	**Sarilumab 200 mg q2w* + MTX (N = 399)**	**Placebo + cDMARDs (N = 181)**	**Sarilumab 150 mg q2w* + cDMARDs (N = 181)**	**Sarilumab 200 mg q2w* + cDMARDs (N = 184)**
Tender Joints (0-68)	-14.38	-19.25†††	-19.00†††	-17.18	-17.30†	-20.58†††
Swollen Joints (0-66)	-8.70	-11.84†††	-12.43†††	-12.12	-13.04††	-14.03†††
Pain VAS† (0-100 mm)	-19.43	-30.75†††	-34.35†††	-27.65	-36.28††	-39.60†††
Physician global VAS‡ (0-100 mm)	-32.04	-40.69†††	-42.65†††	-39.44	-45.09†††	-48.08†††
Patient global VAS‡ (0-100 mm)	-19.55	-30.41†††	-35.07†††	-28.06	-33.88††	-37.36†††
HAQ-DI (0-3)	-0.43	-0.62†††	-0.64†††	-0.52	-0.60†	-0.69††
CRP	-0.14	-13.63†††	-18.04†††	-5.21	-13.11†††	-29.06†††

*q2w = every 2 weeks

‡ Visual analogue scale

†p-value <0.01 for difference from placebo

††p-value <0.001 for difference from placebo

†††p-value <0.0001 for difference from placebo

Radiographic response

In MOBILITY, structural joint damage was assessed radiographically and expressed as change in van der Heijde-modified Total Sharp Score (mTSS) and its components, the erosion score, and joint space narrowing score at week 52. Radiographs of hands and feet were obtained at baseline, 24 weeks, and 52 weeks and scored independently by at least two well-trained readers who were blinded to treatment group and visit number.

Both doses of sarilumab + MTX were superior to placebo + MTX in the change from baseline in mTSS at 24 and 52 weeks (see Table 6). Less progression of both erosion and joint space narrowing scores at 24 and 52 weeks was reported in the sarilumab treatment groups compared to the placebo group.

Treatment with sarilumab + MTX was associated with significantly less radiographic progression of structural damage as compared with placebo. At week 52, 55.6% of patients receiving sarilumab 200 mg and 47.8% of patients receiving sarilumab 150 mg had no progression of structural damage (as defined by a change in the TSS of zero or less) compared with 38.7% of patients receiving placebo.

Treatment with sarilumab 200 mg and 150 mg + MTX inhibited the progression of structural damage by 91% and 68%, respectively, compared to placebo + MTX at week 52.

The efficacy of sarilumab with concomitant DMARDs on inhibition of radiographic progression that was assessed as part of the primary endpoints at week 52 in MOBILITY was sustained up to three years from the start of treatment.

Table 6: Mean radiographic change from baseline at week 24 and week 52 in MOBILITY

	MOBILITY MTX Inadequate responders		
	Placebo + MTX (N = 398)	**Sarilumab 150 mg q2w* + MTX (N = 400)**	**Sarilumab 200 mg q2w* + MTX (N = 399)**
Mean change at week 24			
Modified Total Sharp Score (mTSS)	1.22	0.54†	0.13††
Erosion score (0-280)	0.68	0.26†	0.02††
Joint space narrowing score	0.54	0.28	0.12†
Mean change at week 52			
Modified Total Sharp Score (mTSS) ‡	2.78	0.90††	0.25††
Erosion score (0-280)	1.46	0.42††	0.05††
Joint space narrowing score	1.32	0.47†	0.20††

*q2w=every two weeks

†p-value <0.001

††p-value <0.0001

‡Primary end point

Physical function response

In MOBILITY and TARGET, physical function and disability were assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI). Patients receiving sarilumab 200 mg or 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline in physical function compared to placebo at week 16 and week 12 in MOBILITY and TARGET, respectively.

MOBILITY demonstrated significant improvement in physical function, as measured by the HAQ-DI at week 16 compared to placebo (-0.58, -0.54, and -0.30 for sarilumab 200 mg + MTX, sarilumab 150 mg + MTX, and placebo + MTX, every two weeks, respectively). TARGET demonstrated significant improvement in HAQ-DI scores at week 12 compared to placebo (-0.49, -0.50, and -0.29 for sarilumab 200 mg + DMARDs, sarilumab 150 mg + DMARDs, and placebo + DMARDs, every two weeks, respectively).

In MOBILITY, the improvement in physical functioning as measured by HAQ-DI was maintained up to week 52 (-0.75, -0.71, and -0.46 for sarilumab 200 mg + MTX, sarilumab 150 mg + MTX, and placebo + MTX treatment groups, respectively).

Patients treated with sarilumab + MTX (47.6% in the 200 mg treatment group and 47.0% in the 150 mg treatment group) achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥0.3 units) at week 52 compared to 26.1% in the placebo + MTX treatment group.

Patient reported outcomes

General health status was assessed by the Short Form health survey (SF-36). In MOBILITY and TARGET, patients receiving sarilumab 200 mg + DMARDs every two weeks or sarilumab 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline compared to placebo + DMARDs in physical component summary (PCS) and no worsening on the mental component

summary (MCS) at week 24. Patients receiving sarilumab 200 mg + DMARDs reported greater improvement relative to placebo in the domains of *Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, and Mental Health.*

Fatigue was assessed by the FACIT-Fatigue scale. In MOBILITY and TARGET, patients receiving sarilumab 200 mg + DMARDs every two weeks or sarilumab 150 mg + DMARDs every two weeks demonstrated greater improvement from baseline compared to placebo + DMARDs.

Active Comparator-controlled Study
MONARCH was a 24–week randomised double-blind, double-dummy study that compared sarilumab 200 mg monotherapy with adalimumab 40 mg monotherapy administered subcutaneously every two weeks in 369 patients with moderately to severely active RA who were inappropriate for treatment with MTX including those who were intolerant of or inadequate responders to MTX.

Sarilumab 200 mg was superior to adalimumab 40 mg in reducing disease activity and improving physical function, with more patients achieving clinical remission over 24weeks (see Table 7).

Table 7: Efficacy results for MONARCH

	Adalimumab 40 mg q2w* (N=185)	**Sarilumab 200 mg q2w (N=184)**
DAS28-ESR (primary endpoint) p-value versus adalimumab	-2.20 (0.106)	-3.28 (0.105) < 0.0001
DAS28-ESR remission (< 2.6), n (%) p-value versus adalimumab	13 (7.0%)	49 (26.6%) < 0.0001
ACR20 response, n (%) p-value versus adalimumab	108 (58.4%)	132 (71.7%) 0.0074
ACR50 response, n (%) p-value versus adalimumab	55 (29.7%)	84 (45.7%) 0.0017
ACR70 response, n (%) p-value versus adalimumab	22 (11.9%)	43 (23.4%) 0.0036
HAQ-DI p-value versus adalimumab	-0.43(0.045)	-0.61(0.045) 0.0037

*Includes patients who increased the frequency of dosing of adalimumab 40 mg to every week because of an inadequate response

Polymyalgia rheumatica (PMR)
The efficacy and safety of sarilumab were assessed in a randomised, double-blind, placebo-controlled multicentre study (SAPHYR) in patients 50 years and older with PMR, diagnosed according to American College of Rheumatology/European Union League against Rheumatism (ACR/EULAR) classification criteria. Patients had at least one episode of unequivocal PMR flare while attempting to taper corticosteroids.

In the SAPHYR study, patients with active PMR were randomised to receive sarilumab 200 mg every two weeks with a pre-defined 14-week taper of prednisone (n= 60) or placebo every two weeks with a pre-defined 52-week taper of prednisone (n=58). One patient was randomized but not treated in the sarilumab 200 mg arm. The number of patients who completed the study treatment period was 42 (70%) and 36 (62.1%) in the sarilumab group and placebo group, respectively. Patients experiencing a disease flare or unable to adhere to the assigned prednisone tapering schedule could receive corticosteroids as rescue therapy.

By design, the prednisone tapers in the treatment arms differed. The total actual cumulative prednisone equivalent corticosteroid dose in the sarilumab arm (median 777 mg) was lower compared to placebo (median 2044 mg).

The primary end point was the proportion of patients with sustained remission at Week 52. Sustained remission was defined as achievement of disease remission no later than Week 12, absence of disease flare from Week 12 through Week 52, sustained reduction of CRP (to <10 mg/L) from Week 12 through Week 52 and successful adherence to prednisone taper from Week 12 through Week 52. Other endpoints included total cumulative corticosteroid dose over 52 weeks, time to first PMR flare, and patient reported outcomes.

Clinical Response
A greater proportion of patients in the sarilumab arm achieved sustained remission at Week 52 compared to the placebo arm (p=0.0193). At 52 weeks, a higher proportion of patients in the sarilumab arm achieved each component of the sustained remission endpoint compared to placebo. The cumulative corticosteroid dose during the 52-week treatment period was lower in the sarilumab arm compared to placebo (see Table 8).

Table 8: Clinical Response in Adults with Active PMR (SAPHYR study)

			Placebo (N=58)	Sarilumab (N=60)	p value vs placebo
Sustained remission at Week 52					
	Number of patients with sustained remission	n (%)	6 (10.3)	17 (28.3)	
	Proportion difference (95% CI) vs. placebo			18.0 (4.15, 31.82)	0.0193
Components of sustained remission at Week 52					
	Absence of signs and symptoms and CRP < 10 mg/L (disease remission*) no later than Week 12	n (%)	22 (37.9)	28 (46.7)	NC[†]
	Absence of disease flare[‡] from Week 12 through Week 52	n (%)	19 (32.8)	33 (55.0)	NC
	Sustained reduction of CRP (<10 mg/L) from Week 12 through Week 52	n (%)	26 (44.8)	40 (66.7)	NC
	Successful adherence to prednisone taper from Week 12 through Week 52	n (%)	14(24.1)	30 (50.0)	NC

*Disease remission is defined as the resolution of signs and symptoms of PMR, and normalization of CRP (<10 mg/L).
[†]NC: Not calculated
[‡]Flare is defined as recurrence of signs and symptoms attributable to active PMR requiring an increase in corticosteroid dose, or elevation of ESR attributable to active PMR plus an increase in corticosteroid dose.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Kevzara (sarilumab) in all subsets of the paediatric population in polymyalgia rheumatica (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Kevzara (sarilumab) in one or more subsets of the paediatric population in chronic idiopathic arthritis (including rheumatoid arthritis, spondylarthritis, psoriatic arthritis and juvenile idiopathic arthritis) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Rheumatoid arthritis

The pharmacokinetics of sarilumab were characterised in 2186 adult patients with RA treated with sarilumab which included 751 patients treated with 150 mg and 891 patients treated with 200 mg subcutaneous doses every two weeks for up to 52 weeks.

Absorption
The absolute bioavailability for sarilumab after SC injection was estimated to be 80% by population PK analysis. The median t_{max} after a single subcutaneous dose was observed in 2 to 4 days. After multiple dosing of 150 to 200 mg every two weeks, steady state was reached in 12 to 16 weeks with a 2- to 3-fold accumulation compared to single dose exposure.

For the 150 mg every two weeks dose regimen, the estimated mean (± standard deviation, SD) steady-state area under curve (AUC), C_{min}, and C_{max} of sarilumab were 210 ± 115 mg.day/L, 6.95 ± 7.60 mg/L, and 20.4 ± 8.27 mg/L, respectively.

For the 200 mg every two weeks dose regimen, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 396 ± 194 mg.day/L, 16.7 ± 13.5 mg/L, and 35.4 ± 13.9 mg/L, respectively. In a usability study sarilumab exposure after 200 mg Q2W was slightly higher (C_{max} + 24-34%, $AUC_{(0-2w)}$ +7-21%) after use of a pre-filled pen compared to the pre-filled syringe.

Distribution
In patients with RA, the apparent volume of distribution at steady state was 8.3 L.

Biotransformation
The metabolic pathway of sarilumab has not been characterised. As a monoclonal antibody sarilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination
Sarilumab is eliminated by parallel linear and non-linear pathways. At higher concentrations, the elimination is predominantly through the linear, non-saturable proteolytic pathway, while at lower concentrations, non-linear saturable target-mediated elimination predominates. These parallel elimination pathways result in an initial half-life of 8 to 10 days, and at steady-state an effective half-life of 21 days is estimated.

After the last steady state dose of 150 mg and 200 mg sarilumab, the median times to non-detectable concentration are 30 and 49 days, respectively.
Monoclonal antibodies are not eliminated via renal or hepatic pathways.

Linearity/non-linearity
A more than dose-proportional increase in pharmacokinetic exposure was observed in patients with RA. At steady state, exposure over the dosing interval measured by AUC increased approximately 2-fold with a 1.33-fold increase in dose from 150 to 200 mg every two weeks.

Interactions with CYP450 substrates

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 17 patients with RA, one week following a single 200-mg subcutaneous administration of sarilumab, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively (see section 4.5).

Polymyalgia rheumatica

The pharmacokinetic characteristics of subcutaneous sarilumab in PMR patients was determined using a population pharmacokinetic analysis including sparse C_{trough} observations collected from 58 PMR

patients treated with repeated subcutaneous administration of sarilumab 200 mg every two weeks. For this dose regimen, the estimated mean (± SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 551 ± 321 mg.day/L, 27.0 ± 21.5 mg/L, and 46.5 ± 23.0 mg/L, respectively.PK data analyses suggest the median time to steady state in PMR patients to be approximately 24 weeks. There was accumulation of sarilumab following subcutaneous administration, with an accumulation ratio of 5-6-fold based on the mean trough concentrations.

Special populations

Age, gender, ethnicity and body weight
Population pharmacokinetic analyses in adult patients with RA (ranging in age from 18 to 88 years with 14% over 65 years) showed that age, gender and race did not meaningfully influence the pharmacokinetics of sarilumab.

Body weight influenced the pharmacokinetics of sarilumab in adult patients. In patients with higher body weight (>100 kg) both 150 mg and 200 mg doses demonstrated efficacy; however, patients weighing >100 kg had greater therapeutic benefit with the 200 mg dose.

Renal impairment
No formal study of the effect of renal impairment on the pharmacokinetics of sarilumab was conducted. Mild to moderate renal impairment did not affect the pharmacokinetics of sarilumab. No dose adjustment is required in patients with mild to moderate renal impairment. Patients with severe renal impairment were not studied.

Hepatic impairment
No formal study of the effect of hepatic impairment on the pharmacokinetics of sarilumab was conducted (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, carcinogenic risk assessment and toxicity to reproduction and development.

No long-term animal studies have been performed to establish the carcinogenicity potential of sarilumab. The weight of evidence for IL-6Rα inhibition mainly indicates anti-tumour effects mediated by multiple mechanisms predominantly involving STAT-3 inhibition. *In vitro* and *in vivo* studies with sarilumab using human tumour cell lines showed inhibition of STAT-3 activation and inhibition of tumour growth in human tumour xenograft animal models.

Fertility studies conducted in male and female mice using a murine surrogate antibody against mouse IL-6Rα showed no impairment of fertility.

In an enhanced pre-/postnatal developmental toxicity study, pregnant Cynomolgus monkeys were administered sarilumab once-weekly intravenously from early gestation to natural birth (approximately 21 weeks) Maternal exposure up to approximately 83 times the human exposure based on AUC after subcutaneous doses of 200 mg every 2 weeks, did not cause any maternal or embryo-foetal effects. Sarilumab had no effect on maintenance of pregnancy or on the neonates evaluated up to 1 month after birth in body weight measurements, in parameters of functional or morphological development including skeletal evaluations, in immunophenotyping of peripheral blood lymphocytes, and in microscopic evaluations. Sarilumab was detected in the serum of neonates up to 1 month. The excretion of sarilumab in Cynomolgus monkey’s milk has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Arginine
Polysorbate 20 (E 432)
Sucrose
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

Kevzara 150 mg solution for injection in pre-filled syringe, Kevzara 150 mg solution for injection in pre-filled pen, Kevzara 200 mg solution for injection in pre-filled syringe, and Kevzara 200 mg solution for injection in pre-filled pen

3 years

Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC). Do not freeze.

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

6.5 Nature and contents of container

The pre-filled pen and pre-filled syringes contain a 1.14 ml solution in a syringe (type 1 glass) equipped with a stainless steel staked needle and an elastomer plunger stopper.

Kevzara 150 mg solution for injection in pre-filled syringe

The single-use pre-filled syringe has a styrene-butadiene elastomer needle cap and is equipped with a white polystyrene plunger rod and a light-orange polypropylene finger flange.

Kevzara 200 mg solution for injection in pre-filled syringe

The single-use pre-filled syringe has a styrene-butadiene elastomer needle cap and is equipped with a white polystyrene plunger rod and a dark-orange polypropylene finger flange.

Kevzara 150 mg solution for injection in pre-filled pen

The syringe components are pre-assembled into a single-use pre-filled pen with a yellow needle cover and light-orange cap.

Kevzara 200 mg solution for injection in pre-filled pen

The syringe components are pre-assembled into a single-use pre-filled pen with a yellow needle cover and dark-orange cap.

Pack sizes:

- 1 pre-filled syringe
- 2 pre-filled syringes
- Multipack containing 6 (3 packs of 2) pre-filled syringes
- 1 pre-filled pen
- 2 pre-filled pens
- Multipack containing 6 (3 packs of 2) pre-filled pens

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should be inspected before use. The solution should not be used if it is cloudy, discoloured, or contains particles, or if any part of the device appears to be damaged.

After removing the pre-filled syringe/pre-filled pen from the refrigerator, it should be allowed to reach room temperature (<25°C) by waiting 30 minutes for the pre-filled syringe or 60 minutes for the pre-filled pen as applicable, before injecting Kevzara.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. After use, the pre-filled syringe/pre-filled pen should be placed into a puncture-resistant container and discarded as required by local regulations.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1196/001
EU/1/17/1196/002
EU/1/17/1196/003
EU/1/17/1196/004
EU/1/17/1196/005
EU/1/17/1196/006
EU/1/17/1196/007
EU/1/17/1196/008
EU/1/17/1196/009
EU/1/17/1196/010
EU/1/17/1196/011
EU/1/17/1196/012

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 June 2017
Date of latest renewal: 25 April 2022

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Kevzara 175 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kevzara 175 mg/ml solution for injection

Each vial contains 270 mg sarilumab in 1.54 ml solution (175 mg/ml).

Sarilumab is a human monoclonal antibody produced in Chinese Hamster Ovary 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 pale yellow sterile solution of approximately pH 6.0.

Kevzara 175 mg/ml solution for injection

306-371 mmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Polyarticular juvenile idiopathic arthritis

Kevzara is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA; rheumatoid factor positive or negative polyarthritis and extended oligoarthritis) in patients 2 years of age and older, who have responded inadequately to previous therapy with conventional synthetic DMARDs (csDMARDs). Kevzara may be used as monotherapy or in combination with MTX.

4.2 Posology and method of administration

Treatment should be initiated and supervised by healthcare professionals experienced in the diagnosis and treatment of the condition for which this medicinal product is intended (see section 4.1) Patients must be given the patient card.

Posology

pJIA

The recommended posology in patients 2 years of age and older is 4 mg/kg subcutaneously once every 2 weeks in patients weighing 10 to less than 30 kg or 3 mg/kg subcutaneously once every 2 weeks in patients weighing greater than or equal to 30 kg.

Sarilumab can be used alone or in combination with MTX.

Sarilumab should be administered by subcutaneous injection and the dose should be calculated based on the patient's body weight (kg) at each administration. A change in dose should only be based on a consistent change in the patient's body weight over time (see Table 1).

Patients must have a minimum body weight of 10 kg when receiving sarilumab.

Patients that transition from 4 mg/kg to 3 mg/kg given once every 2 weeks
For patients who initially receive the 4 mg/kg dose and weigh between 27.5 to <39.5 kg, the 0.65 ml volume of injection must be maintained until the patient reaches 39.5 kg. At 39.5 kg, the patient must transition to the 3 mg/kg dose (see Table 1).

The dose is capped at 200 mg given once every 2 weeks for patients weighing at or above 63 kg.

Table 1: Subcutaneous sarilumab doses based on body weight range

Body weight (kg)	**Volume per injection (ml)**
Patients 10 to less than 30 kg weight (4 mg/kg q2w)	
≥10 and <12.5	0.25
≥12.5 and <14.5	0.30
≥14.5 and <16.5	0.35
≥16.5 and <19	0.40
≥19 and <21	0.45
≥21 and <23.5	0.50
≥23.5 and <25.5	0.55
≥25.5 and <27.5	0.60
≥27.5 and <30	0.65
Patients at or above 30 kg weight (3 mg/kg q2w)	
≥30 and <31	0.50
≥31 and <34	0.55
≥34 and <37	0.60
≥37 and <39.5	0.65
≥39.5 and <42.5	0.70
≥42.5 and <45	0.75
≥45 and <48.5	0.80
≥48.5 and <51.5	0.85
≥51.5 and <54.5	0.90
≥54.5 and <57	0.95
≥57 and <63	1.00
≥63	1.1

Table 2: Recommendation in case of neutropenia, thrombocytopenia, or liver enzyme elevations for pJIA (see sections 4.4 and 4.8):

Low Absolute Neutrophil Count	
Lab Value (cells x 10^9/L)	**Recommendation**
ANC greater than 1	Current dose of sarilumab to be maintained.
• ANC ≥ 0.5 - <1 with or without infection • ANC < 0.5 without infection	Treatment with sarilumab to be withheld until clinical condition has been evaluated.
ANC < 0.5 associated with infection	Treatment with sarilumab to be discontinued.
Low Platelet Count	
Lab Value (cells x 10^3/µL)	**Recommendation**
50 to 100	Treatment with sarilumab to be withheld until >100 x 10^3/µL and

	until clinical condition has been evaluated.
Less than 50	Treatment with sarilumab to be discontinued.
Liver Enzyme Abnormalities	
Lab Value	**Recommendation**
ALT > 1 to 3 x Upper Limit of Normal (ULN)	Clinically appropriate dose modification of concomitant MTX and/or other medicinal products to be considered.
ALT > 3 to 5 x ULN	Treatment with sarilumab to be withheld until < 3 x ULN and until clinical condition has been evaluated.
ALT > 5 x ULN	Treatment with sarilumab to be discontinued.

Dose reduction of sarilumab has not been studied in the pJIA population. The decision to resume or discontinue sarilumab should be based upon the medical assessment of the individual patient. If appropriate, the dose of concomitant MTX and/or other treatment should be modified or stopped.

Missed dose

If a dose of sarilumab is missed and it has been 3 days or less since the missed dose, the next dose should be administered as soon as possible. The subsequent dose should be administered at the regularly scheduled time. If it has been 4 days or more since the missed dose, the subsequent dose should be administered at the next regularly scheduled time, the dose should not be doubled.

Special populations

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment. Sarilumab has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment
The safety and efficacy of sarilumab have not been studied in patients with hepatic impairment, including patients with positive hepatitis B virus (HBV) or hepatitis C virus (HCV) serology (see section 4.4).

Elderly
No dose adjustment is required in patients over 65 years of age (see section 4.4).

Paediatric population
The safety and efficacy of sarilumab in children less than 2 years of age have not been established. No data are available.

Method of administration

Subcutaneous use.

Injection sites (abdomen, thigh and upper arm) should be rotated with each injection. Sarilumab should not be injected into skin that is tender, damaged, or has bruises or scars.

Vial
The vial is intended for administration by a healthcare professional only. The 175 mg/ml vial is a ready to use solution for injection which does not need to be diluted. Withdrawal of the dose from the vial using a sterile needle and syringe. The needle or syringe should not be re-used.

The contents of the sarilumab vial should not be mixed with, or transferred into, the content of another vial of sarilumab. The vial is for single use only. The unused portion must be discarded (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
Active, severe infections (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

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

Serious infections

Patients must be closely monitored for the development of signs and symptoms of infection during treatment with sarilumab (see sections 4.2 and 4.8). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Sarilumab must not be administered in patients with an active infection, including localised infections. The risks and benefits should be considered prior to initiating treatment in patients who have:

- chronic or recurrent infection;
- a history of serious or opportunistic infections;
- HIV infection;
- underlying conditions that may predispose them to infection;
- been exposed to tuberculosis; or
- lived in or travelled to areas of endemic tuberculosis or endemic mycoses.

Treatment with sarilumab must be withheld if a patient develops a serious infection or an opportunistic infection. Once the infection is controlled, treatment with sarilumab may be re-initiated at the discretion of the healthcare professional.

A patient who develops an infection during treatment should also undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including sarilumab for RA. The most frequently observed serious infections with sarilumab in RA patients included pneumonia and cellulitis (see section 4.8). Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with sarilumab. In isolated cases, disseminated rather than localised infections were observed in patients often taking concomitant immunosuppressants such as MTX or corticosteroids, which in addition to RA may predispose them to infections.

Tuberculosis
Patients must be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating treatment with sarilumab. Patients with latent or active tuberculosis must be treated with standard antimycobacterial therapy before initiating treatment. Anti-tuberculosis therapy must be considered prior to initiation of treatment in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Healthcare professionals are reminded of the risk of false negative tuberculin skin and interferon-gamma TB blood test results, especially in patients who are severely ill or immunocompromised. When considering anti-tuberculosis therapy, consultation with a physician with expertise in tuberculosis may be appropriate.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral reactivation
Viral reactivation has been reported with immunosuppressive biologic therapies. Cases of herpes zoster were observed in clinical studies with sarilumab (see section 4.8). No cases of Hepatitis B reactivation were reported in the clinical studies; however patients who were at risk for reactivation were excluded.

Laboratory parameters

Neutrophil count
Treatment with sarilumab was associated with a higher incidence of decrease in ANC (see section 4.8). Decrease in ANC was not associated with higher incidence of infections, including serious infections.

- Initiating treatment with sarilumab is not recommended in patients with a low neutrophil count, i.e., ANC less than 2 x 10^9/L. In patients who develop an ANC less than 0.5 x 10^9/L, it is recommended to discontinue treatment with sarilumab (see section 4.2).
- Neutrophil count must be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on ANC results, see section 4.2.
- Based on the pharmacodynamics of the changes in ANC, results obtained at the end of the dosing interval should be used when considering dose modification (see section 5.1).

Platelet count
Treatment with sarilumab was associated with a reduction in platelet counts in clinical studies. Reduction in platelets was not associated with bleeding events (see section 4.8).

- Initiating treatment with sarilumab is not recommended in patients with a platelet count below 150 x10^3/µL. In patients who develop a platelet count less than 50 x 10^3/ µL, treatment with sarilumab must be discontinued.
- Platelet count must be monitored 4 to 8 weeks after start of therapy and according to clinical judgment thereafter. For recommended dose modifications based on platelet counts, see section 4.2.

Liver enzymes
Treatment with sarilumab was associated with a higher incidence of transaminase elevations. These elevations were transient and did not result in any clinically evident hepatic injury in clinical studies (see section 4.8). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic medicinal products (e.g., MTX) were used in combination with sarilumab.

Initiating treatment with sarilumab is not recommended in patients with elevated transaminases, ALT or AST greater than 1.5 x ULN. In patients who develop elevated ALT greater than 5 x ULN, treatment with sarilumab must be discontinued (see section 4.2).

ALT and AST levels must be monitored 4 to 8 weeks after start of therapy and every 3 months thereafter. When clinically indicated, consider other liver function tests such as bilirubin. For recommended dose modifications based on transaminase elevations, see section 4.2.

Lipid abnormalities
Lipid levels may be reduced in patients with chronic inflammation. Treatment with sarilumab was associated with increases in lipid parameters such as LDL cholesterol, HDL cholesterol, and/or triglycerides (see section 4.8). Lipid parameters should be assessed approximately 4 to 8 weeks following initiation of treatment with sarilumab, then at approximately 6 month intervals.
Patients should be managed according to clinical guidelines for the management of hyperlipidaemia.

Gastrointestinal perforation and diverticulitis

Cases of gastrointestinal perforation and diverticulitis have been reported in association with sarilumab. Gastrointestinal perforation has been reported in patients with and without diverticulitis. Patients presenting with symptoms potentially indicative of diverticulitis, such as abdominal pain,

gastrointestinal haemorrhage and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with gastrointestinal perforation. Sarilumab should be used with caution in patients with previous history of intestinal ulceration or diverticulitis (see section 4.8).

Malignancies

Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with sarilumab on the development of malignancies is not known but malignancies were reported in clinical studies (see section 4.8).

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with sarilumab (see section 4.8). Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Patients must be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, administration of Sarilumab must be stopped immediately (see section 4.3).

Hepatic impairment

Treatment with sarilumab is not recommended in patients with active hepatic disease or hepatic impairment (see sections 4.2 and 4.8).

Vaccinations

Concurrent use of live vaccines as well as live attenuated vaccines should be avoided during treatment with sarilumab as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving sarilumab. Prior to initiating treatment, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. The interval between live vaccinations and initiation of therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

Cardiovascular risk

RA patients have an increased risk for cardiovascular disorders and risk factors (e.g. hypertension, hyperlipidaemia) should be managed as part of usual standard of care.

Polysorbate 20 (E 432)

This medicinal product contains 2.28 mg of polysorbate 20 in each 1.14 ml of solution for injection which is equivalent to 2 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Sarilumab exposure was not affected when coadministered with MTX based on the population pharmacokinetic analyses and across study comparisons. MTX exposure is not expected to be changed by sarilumab coadministration; however, no clinical data was collected. Sarilumab has not been investigated in combination with Janus kinase (JAK) inhibitors or biological DMARDs such as tumour necrosis factor (TNF) antagonists.

Various *in vitro* and limited *in vivo* human studies have shown that cytokines and cytokine modulators can influence the expression and activity of specific cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) and therefore have the potential to alter the pharmacokinetics of concomitantly administered medicinal products that are substrates of these enzymes. Elevated levels of interleukin-6 (IL-6) may down-regulate CYP activity such as in patients with RA and hence increase

drug levels compared to subjects without RA. Blockade of IL-6 signalling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered medicinal products concentrations.

The modulation of IL-6 effect on CYP enzymes by sarilumab may be clinically relevant for CYP substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of sarilumab in patients being treated with CYP substrate medicinal products, therapeutic monitoring of effect (e.g., warfarin) or concentration of the medicinal product (e.g., theophylline) should be performed and the individual dose of the medicinal product should be adjusted as needed.

Caution should be exercised in patients who start sarilumab treatment while on therapy with CYP3A4 substrates (e.g., oral contraceptives or statins), as sarilumab may reverse the inhibitory effect of IL-6 and restore CYP3A4 activity, leading to decreased exposure and activity of CYP3A4 substrate (see section 5.2). Interaction of sarilumab with substrates of other CYPs (CYP2C9, CYP 2C19, CYP2D6) has not been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during and up to 3 months after treatment (see section 4.5).

Pregnancy

There are no or limited amount of data from the use of sarilumab in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

Sarilumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with sarilumab.

Breast-feeding

It is unknown whether sarilumab is excreted in human milk or absorbed systemically after ingestion. The excretion of sarilumab in milk has not been studied in animals (see section 5.3).
Because IgG1 are excreted in human milk**,** a decision must be made whether to discontinue breast-feeding or to discontinue sarilumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available on the effect of sarilumab on human fertility. Animal studies showed no impairment of male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Kevzara has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Paediatric population

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

Summary of the safety profile

The most common adverse reactions were nasopharyngitis (36.6%), neutropenia (31.2%), upper respiratory tract infection (14.0%), injection site erythema (9.7%), pharyngitis (9.7%) and alanine aminotransferase increased (9.7%).

The most common adverse reaction that resulted in permanent discontinuation of therapy with sarilumab was neutropenia (5.4%).

Tabulated list of adverse reactions

Adverse reactions listed in the table have been reported in a clinical study. The frequency of adverse reactions listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions in pJIA patients who received at least one administration of the recommended dose of sarilumab

MedDRA System Organ Class	Frequency	Adverse reaction
Infections and infestations	Very Common	Upper respiratory tract infection*
		Nasopharyngitis‡
Blood and lymphatic system disorders	Very common	Neutropenia†
Hepatobiliary disorders	Common	Alanine aminotransferase increased
General disorders and administration site conditions	Very Common	Injection site reaction††

* Includes upper respiratory tract infection and viral upper respiratory tract infection
‡ Includes nasopharyngitis and pharyngitis
† Includes neutropenia and neutrophil count decreased
†† Including injection site erythema, injection site pruritus, injection site swelling, injection site bruising, injection site inflammation, injection site reaction, injection site urticaria, injection site warmth

Infections
In the pJIA study, the rate of infections was 146.6 events per 100 patient-years. The most common infections observed were nasopharyngitis (36.6%) and upper respiratory tract infections (URTI) (14.0%). The majority of nasopharyngitis and URTI events were mild.

Injection Site Reactions
In the pJIA study, injection site reactions (ISRs) occurred in 13 (14.0%) patients and the most commonly reported ISR was injection site erythema (9.7%). The majority of these events were mild and none of the ISRs required patient withdrawal from treatment or dose interruption.

Laboratory abnormalities
Neutrophil count
In the pJIA study, decreases in neutrophil counts below 1 x 10^9/L occurred in 10/52 (19.2%) patients weighing in ≥30 kg and 20/41 (48.8%) patients weighing 10 to <30 kg. The frequency of decreased neutrophil count was higher until Week 12. Decrease in ANC was not associated with an occurrence of infections, including serious infections.

Monocyte count
In the pJIA study, decrease in monocyte counts occurred in 4 (4.3%) patients and were mild in severity and non-serious.

Liver enzymes
In the pJIA study, one (1.1%) patient had ALT greater than 3 times the upper limit of normal (ULN). Nine (9.7%) patients overall had ALT increase and majority were mild in severity and all were non-serious

Lipids
In the pJIA study, triglyceride levels of ≥150 mg/dL (1 x ULN) were observed in one (1.1%) patient. Three (3.2%) patients overall had elevation in triglycerides, and all were mild in severity and non-serious. No significant changes in mean LDL, HDL or total cholesterol were observed during the entire 156-week treatment period.

Immunogenicity
In the pJIA population, 3 (4.3%) patients treated with the recommended dose exhibited an antidrug antibody (ADA) response. Neutralizing antibodies were detected in one pJIA patient with ADA response. Because of the low occurrence of anti-drug antibodies, the effect of antibodies on the safety, and/or effectiveness of sarilumab is unknown.

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

There is no specific treatment for Kevzara overdose. In the event of an overdose, the patient should be closely monitored, treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, Interleukin inhibitors, ATC code: L04AC14

Mechanism of action

Sarilumab is a human monoclonal antibody (IgG1 subtype) that specifically binds to both soluble and membrane-bound IL-6 receptors (IL-6Rα), and inhibits IL-6-mediated signalling which involves ubiquitous signal-transducing glycoprotein 130 (gp130) and the Signal Transducer and Activator of Transcription-3 (STAT-3).

In functional human cell-based assays, sarilumab was able to block the IL-6 signalling pathway, measured as STAT-3 inhibition, only in the presence of IL-6.

IL-6 is a pleiotropic cytokine that stimulates diverse cellular responses such as proliferation, differentiation, survival, and apoptosis and can activate hepatocytes to release acute-phase proteins, including C-reactive protein (CRP) and serum amyloid A. Elevated levels of IL-6 are found in the synovial fluid of patients with rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA) and play an important role in both the pathologic inflammation and joint destruction which are hallmarks of RA and pJIA. IL-6 is involved in diverse physiological processes such as migration and

activation of T-cells, B-cells, monocytes, and osteoclasts leading to systemic inflammation, synovial inflammation, and bone erosion in patients with RA and pJIA.

The activity of sarilumab in reducing inflammation is associated with laboratory changes such as decrease in ANC and elevation in lipids (see section 4.4).

Pharmacodynamic effects

Following single-dose subcutaneous (SC) administration of sarilumab 200 mg and 150 mg in patients with RA rapid reduction of CRP levels was observed. Levels were reduced to normal as early as 4 days after treatment initiation. Following single-dose sarilumab administration, in patients with RA, ANC decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline (see section 4.4). Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in haemoglobin and serum albumin. In patients with pJIA, decreases in CRP, erythrocyte sedimentation rate (ESR) and neutrophil count were observed after sarilumab administration.

Clinical efficacy

Polyarticular juvenile idiopathic arthritis (pJIA)

Supportive efficacy and safety data were assessed in a multicentre, open-label, two-phase study in patients aged 2 to 17 years of age with polyarticular- juvenile idiopathic arthritis (pJIA) diagnosed according to American College Rheumatology (ACR) classification criteria who had an inadequate response to current therapy. This study was divided into a dose range finding portion and a confirmatory portion. Three doses were investigated in the 12-week core treatment phase of the dose range finding portion. Following the dose selection, patients were enrolled to receive the recommended dose [3 mg/kg every 2 weeks (q2w) in 42 patients weighing ≥30 kg (Group A) and 4 mg/kg q2w in 31 patients weighing ≥10 kg and <30 kg (Group B)]. A total of 101 patients were treated, including 73 patients who received the recommended dose regimen from baseline and 20 patients who had their dose switched to the recommended dose during the study.

The efficacy of sarilumab in paediatric patients with pJIA is based on pharmacokinetic (PK) extrapolation and the established efficacy of sarilumab in RA patients. The extrapolation is further supported by the efficacy evaluation that was conducted and based on JIA ACR 70 and 90 response rate, change from baseline for Juvenile Arthritis Disease Activity Score-27 (JADAS), and proportion of patients with clinical remission. Efficacy was assessed up to 48 weeks in the 73 patients that received the recommended dose from baseline.

Of these 73 patients, baseline mean disease duration and JADAS-27 were 2.48 years and 22.73, respectively. At baseline, 84.9% of patients had received at least one csDMARD (mainly MTX), 13.7% received systemic glucocorticoids, and 19.2% had prior treatment with biological DMARDs (mainly TNFi). The patients treated had subtypes of JIA that, at disease onset, included rheumatoid factor positive (17.8%), negative polyarticular JIA (65.8%), or extended oligoarticular JIA (16.4%).

Clinical response
JIA ACR responses were seen as early as Week 2. The proportion of patients with JIA ACR 70 response rate were 76.7% and 87.7% at Week 12 and Week 48, respectively, and JIA ACR 90 response rate were 42.5% and 69.9% at Week 12 and Week 48, respectively.

Change from baseline in JADAS-27 CRP was -17.46 at Week 12 and -20.75 at Week 48 for the patients on the recommended dose. At Week 48, 51.6% of patients on the recommended dose were in remission (inactive disease per Wallace criteria for 6 consecutive months).

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Kevzara (sarilumab) in one or more subsets of the paediatric population in chronic idiopathic arthritis

(including rheumatoid arthritis, spondylarthritis, psoriatic arthritis and juvenile idiopathic arthritis) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Paediatric population

Polyarticular- juvenile idiopathic arthritis (pJIA)
The pharmacokinetics of sarilumab in pJIA patients was characterized by observed and population pharmacokinetic analysis which included 101 paediatric patients 2 to 17 years of age who were treated with repeated subcutaneous doses of sarilumab.

For 3 mg/kg sarilumab (patients with a body weight ≥30 kg) given every 2 weeks, the estimated mean (±SD) steady-state AUC, C_{min}, and C_{max} of sarilumab were 294 ± 148 mg.day/L, 9.84 ± 6.35 mg/L, and 29.2 ± 15.0 mg/L, respectively by population PK analysis.

For 4 mg/kg sarilumab (patients with a body weight 10 to <30 kg) given every 2 weeks, the estimated mean (± SD) steady-state AUC, C_{min}, and C_{max} of sarilumab were 375 ± 102 mg.day/L, 14.5 ± 8.56 mg/L, and 37.3 ± 8.10 mg/L, respectively by population PK analysis.

Consistent with RA adult patients, sarilumab is eliminated by parallel linear and non-linear pathways, in pJIA patients, these parallel elimination pathways result in an initial half-life of 5 to 7 days. Time to steady state was about 10 weeks longer compared to RA adult patients. Following subcutaneous administration at Week 48, accumulation ratio was approximately 5-fold based on the observed mean trough concentrations (11.6 mg/L and 14.2 mg/L) compared to single dose exposure (2.24 mg/L and 3.10 mg/L) for 3 and 4 mg/kg q2w, respectively. Steady state concentrations were within the range of exposures in adult RA patients following 200 mg every 2 weeks.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, carcinogenic risk assessment and toxicity to reproduction and development.

No long-term animal studies have been performed to establish the carcinogenicity potential of sarilumab. The weight of evidence for IL-6Rα inhibition mainly indicates anti-tumour effects mediated by multiple mechanisms predominantly involving STAT-3 inhibition. *In vitro* and *in vivo* studies with sarilumab using human tumour cell lines showed inhibition of STAT-3 activation and inhibition of tumour growth in human tumour xenograft animal models.

Fertility studies conducted in male and female mice using a murine surrogate antibody against mouse IL-6Rα showed no impairment of fertility.

In an enhanced pre-/postnatal developmental toxicity study, pregnant Cynomolgus monkeys were administered sarilumab once-weekly intravenously from early gestation to natural birth (approximately 21 weeks) Maternal exposure up to approximately 83 times the human exposure based on AUC after subcutaneous doses of 200 mg every 2 weeks, did not cause any maternal or embryo-foetal effects. Sarilumab had no effect on maintenance of pregnancy or on the neonates evaluated up to 1 month after birth in body weight measurements, in parameters of functional or morphological development including skeletal evaluations, in immunophenotyping of peripheral blood lymphocytes, and in microscopic evaluations. Sarilumab was detected in the serum of neonates up to 1 month. The excretion of sarilumab in Cynomolgus monkey's milk has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Arginine
Polysorbate 20 (E 432)
Sucrose
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

Kevzara 175 mg/ml solution for injection
2 years

Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC). Do not freeze.

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

6.5 Nature and contents of container

Kevzara 175 mg/ml solution for injection
The vial (type 1 glass) containing 1.54 ml solution is closed with ETFE-coated bromobutyl stoppers and crimped with an aluminium seal with a flip-off cap.

Pack sizes:
- 2 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The solution should be inspected before use. The solution should not be used if it is cloudy, discoloured, or contains particles, or if any part of the device appears to be damaged.

Each vial contains an overfill to ensure sufficient extractable volume.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. After use, the syringe for the vial should be placed into a puncture-resistant container and discarded as required by local regulations.

7. MARKETING AUTHORISATION HOLDER

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1196/013

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 June 2017
Date of latest renewal: 25 April 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

Name and address of the manufacturers of the biological active substance

Regeneron Pharmaceuticals Inc.
81 Columbia Turnpike
Rensselaer
12144
United States

Sanofi Winthrop Industrie
9 quai Jules Guesde
94403 Vitry-sur-Seine Cedex
France

Name and address of the manufacturers responsible for batch release

Sanofi Winthrop Industrie
Boulevard Industriel, Zone Industrielle,
Le Trait, 76580,
France

Sanofi-Aventis Deutschland GmbH
Brueningstrasse 50
Industriepark Hochst
65926 Frankfurt am Main
Germany

Genzyme Ireland Ltd
IDA Industrial Park
Old Kilmeaden Road
Waterford,
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

- **Additional risk minimisation measures**

Prior to launch of Kevzara in each Member State the MAH must agree about the content and format of patient card, including communication media, distribution modalities, and any other aspects, with the National Competent Authority.

The MAH shall ensure that in each Member State where Kevzara is marketed, all healthcare professionals who are expected to prescribe Kevzara have access to the patient card.

The patient card shall contain the following key messages:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Kevzara.
- That Kevzara treatment may increase the risks of serious infections, neutropenia and intestinal perforation.
- Educate patients and/or parents/caregivers on signs or symptoms that could represent serious infections or gastrointestinal perforations to seek for medical attention immediately.
- Contact details of the prescriber for Kevzara.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 150 mg solution for injection in pre-filled syringe
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20 E 432, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled syringe
2 pre-filled syringes

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, KEVZARA should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1196/009 1 pre-filled syringe
EU/1/17/1196/001 2 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 150 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 150 mg solution for injection in pre-filled syringe
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 6 (3 packs of 2) pre-filled syringes.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton 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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/002 6 pre-filled syringes (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 150 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON without Blue Box – 2 PRE-FILLED SYRINGES (MULTIPACK PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 150 mg solution for injection in pre-filled syringe
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled syringes. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/002 6 pre-filled syringes (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 150 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

KEVZARA 150 mg injection
sarilumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.14 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 200 mg solution for injection in pre-filled syringe
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20 E432, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled syringe
2 pre-filled syringes

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1196/010 1 pre-filled syringe
EU/1/17/1196/003 2 pre-filled syringes

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 200 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 200 mg solution for injection in pre-filled syringe
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 6 (3 packs of 2) pre-filled syringes.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton 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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/004 6 pre-filled syringes (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 200 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON without Blue Box – 2 PRE-FILLED SYRINGES (MULTIPACK PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 200 mg solution for injection in pre-filled syringe
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled syringe contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
2 pre-filled syringes. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/004 6 pre-filled syringes (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 200 mg syringe

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

KEVZARA 200 mg injection
sarilumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.14 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 150 mg solution for injection in pre-filled pen
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20 E 432, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled pen
2 pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1196/011 1 pre-filled pen
EU/1/17/1196/005 2 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 150 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 150 mg solution for injection in pre-filled pen
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 6 (3 packs of 2) pre-filled pens.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton 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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/006 6 pre-filled pens (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 150 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON without Blue Box – 2 PRE-FILLED PENS (MULTIPACK PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 150 mg solution for injection in pre-filled pen
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 150 mg sarilumab in 1.14 ml solution (131.6 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
2 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/006 6 pre-filled pens (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 150 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

KEVZARA 150 mg injection
sarilumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.14 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 200 mg solution for injection in pre-filled pen
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20 E 432, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
1 pre-filled pen
2 pre-filled pens

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1196/012 1 pre-filled pen
EU/1/17/1196/007 2 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 200 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 200 mg solution for injection in pre-filled pen
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
Multipack: 6 (3 packs of 2) pre-filled pens.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton 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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/008 6 pre-filled pens (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 200 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON without Blue Box – 2 PRE-FILLED PENS (MULTIPACK PRESENTATION)

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 200 mg solution for injection in pre-filled pen
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each pre-filled pen contains 200 mg sarilumab in 1.14 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

solution for injection
2 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only
Read the package leaflet before use.
Open here

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 carton in order to protect from light.

Date of removal from the refrigerator: .../.../...
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/008 6 pre-filled pens (3 packs of 2)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

kevzara 200 mg pen

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

KEVZARA 200 mg injection
sarilumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.14 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – VIAL PRESENTATION

1. NAME OF THE MEDICINAL PRODUCT

KEVZARA 175 mg/ml solution for injection
sarilumab

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 270 mg sarilumab in 1.54 ml solution (175 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: histidine, arginine, polysorbate 20 E 432, sucrose, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

270 mg/1.54 mlsolution for injection
2 vials

5. METHOD AND ROUTE OF ADMINISTRATION

Subcutaneous use
For single use only.
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 carton in order to protect from light.
Once removed from the refrigerator, Kevzara should be administered within 14 days and should not be stored above 25 ºC.

Date of removal from the refrigerator: .../.../...

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

Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

12. MARKETING AUTHORISATION NUMBER

EU/1/17/1196/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

KEVZARA 175 mg/ml injection
sarilumab

2. METHOD OF ADMINISTRATION

SC

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

270 mg/1.54 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kevzara 150 mg solution for injection in pre-filled syringe
Kevzara 200 mg solution for injection in pre-filled syringe
sarilumab

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, pharmacist, or nurse.
- 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, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a patient card, which contains important safety information that you need before and during treatment with Kevzara.

What is in this leaflet

1. What Kevzara is and what it is used for

What Kevzara is
Kevzara contains the active substance sarilumab. It is a type of protein called a monoclonal antibody.

What Kevzara is used for
Kevzara is used to treat adults with moderately to severely active rheumatoid arthritis (RA) if previous therapy did not work well enough or was not tolerated. Kevzara can be used alone or together with a medicine called methotrexate.
It may help you by:
- slowing down damage to joints
- improving your ability to perform daily activities.

Kevzara is used to treat adults with polymyalgia rheumatica after corticosteroids have been used and did not work well or if you experience a relapse while decreasing the dose of corticosteroids (taper). Kevzara can be used alone or together with a medicine called corticosteroid.

How Kevzara works
- Kevzara attaches to another protein called interleukin-6 (IL-6) receptor and blocks its action.
- IL-6 plays a major role in the symptoms of RA such as pain, swollen joints, morning stiffness, and fatigue.

2. What you need to know before you use Kevzara

Do not use Kevzara:
- if you are allergic to sarilumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an active severe infection.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse if:
- you have any infection or you get a lot of infections. Kevzara can lower your body's ability to fight infection: this means it can make you more likely to get infections or make your infection worse.
- You have tuberculosis (TB), symptoms of TB (persistent cough, weight loss, listlessness, mild fever), or have been in close contact with someone with TB. Before you are given Kevzara, your doctor will check you for TB.
- You have had viral hepatitis or other liver disease. Before you use Kevzara, your doctor will do a blood test to check your liver function.
- You have had diverticulitis (a condition of the lower bowel) or ulcers in your stomach or intestines, or develop symptoms such as fever and stomach (abdominal) pain that does not go away.
- You have ever had any type of cancer.
- You have recently had any vaccination or are going to have a vaccination.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using Kevzara.

You will have blood tests before you are given Kevzara. You will also have the tests during your treatment. This is to check for low blood cell count, liver problems, or changes in your cholesterol levels.

Every time youget a new pack of Kevzara, it is important you note down the name of the medicine, the date of the administration and the batch number (which is on the packaging after “Lot”) and keep this information in a safe place.

Children and adolescents
The Kevzara pre-filled syringe has not been studied in children 2 years of age and older with pJIA and is not intended for use in children.
Kevzara is not recommended in children under 2 years of age. Kevzara must not be given to children with pJIA weighing less than 10 kg.

Other medicines and Kevzara
Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines. This is because Kevzara can affect the way some other medicines work. Also some other medicines can affect the way Kevzara works.

In particular, do not use Kevzara and tell your doctor or pharmacist if you are using:
- a group of medicines called “Janus kinase (JAK) inhibitors” (used for diseases like rheumatoid arthritis and cancer)
- other biological medicines used in the treatment of RA

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist.

Kevzara can affect the way some medicines work: this means the dose of other medicines may need changing. If you are using any of the following medicines, tell your doctor or pharmacist before using Kevzara:
- statins, used to reduce cholesterol level
- oral contraceptives
- theophylline, used to treat asthma
- warfarin, used to prevent blood clots.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist.

Pregnancy and breast-feeding
Talk to your doctor before using Kevzara if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

- Do not take Kevzara if you are pregnant unless your doctor specifically recommends it.
- The effects of Kevzara on an unborn baby are not known.
- You and your doctor should decide if you should use Kevzara if you are breast-feeding.

Driving and using machines
The use of Kevzara is not expected to affect your ability to drive or use machines. However, if you are feeling tired or unwell after you use Kevzara, you should not drive or use machines.

KEVZARA contains polysorbate 20
This medicine contains 2.28 mg of polysorbate 20 in each 1.14 ml of solution for injection which is equivalent to 2 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Kevzara

Treatment should be started by a doctor experienced in the diagnosis and treatment of RA or polymyalgia rheumatica. Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adult patients
The recommended dose is one 200 mg injection every two weeks.
- Your doctor may adjust the dose of your medicine based on results of blood tests.

Kevzara is given as an injection under the skin (called "subcutaneous" injection).

Learning how to use the pre-filled syringe
- Your doctor, pharmacist, or nurse will show you how to inject Kevzara. Following these instructions, Kevzara can be self-injected or administered by a care-giver after proper training.
- Carefully follow the "Instructions for Use" provided in the carton.
- Use the pre-filled syringe exactly as described in the "Instructions for Use".

If you use more Kevzara than you should
If you have used more Kevzara than you should, talk to your doctor, pharmacist or nurse.

If you miss a dose of Kevzara
If it has been 3 days or less since the missed dose:
- inject your missed dose as soon as you can.
- then inject your next dose at your regular time.

If it has been 4 days or more, inject the next dose at your regular time. Do not inject a double dose to make up for a forgotten injection.
If you are unsure when to inject your next dose: ask your doctor, pharmacist or nurse for instructions.

If you stop using Kevzara
Do not stop using Kevzara without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

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

<u>Serious side effect</u>

Tell your doctor straight away if you think you have an **infection** (which may affect up to 1 in every 10 people). The symptoms may include fever, sweats, or chills.

Other side effects
Tell your doctor, pharmacist, or nurse if you notice any of the following side effects:

Adults
Very common (may affect more than 1 in 10 people)
- Low white blood cell counts shown by blood tests

Common (may affect up to 1 in 10 people)
- infections in your sinuses or throat, blocked or runny nose and sore throat (upper respiratory tract infection)
- urinary tract infection
- cold sores (oral herpes)
- low platelet counts shown by blood tests
- high cholesterol, high triglycerides shown by blood tests
- abnormal liver function tests
- injection-site reactions (including redness and itching).
- inflammation of the deep skin tissue
- infection of the lungs

Uncommon (may affect up to 1 in 100 people)
- diverticulitis (a disease affecting the gut often with stomach (abdominal) pain, nausea and vomiting, fever, and constipation, or less commonly diarrhoea)

Rare (may affect up to 1 in 1 000 people)
- perforation in stomach or intestines (a hole that develops in the wall of the gut)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. 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 Kevzara

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.
- Once taken out of the refrigerator, do not store Kevzara above 25 ºC.
- Write down the date of removal from the refrigerator in the space provided on the outer carton.
- Use the syringe within 14 days after taking it out of the refrigerator or the insulated bag.
- Keep the syringe in the original carton in order to protect from light.

Do not use this medicine if the solution in the syringe is cloudy, discoloured or contains particles, or if any part of the pre-filled syringe looks damaged.

After use, put the syringe into a puncture-resistant container. Always keep the container out of the sight and reach of children. Ask your doctor, pharmacist, or nurse how to throw away the container.

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 Kevzara contains
- The active substance is sarilumab. Each pre-filled syringe contains 150 mg or 200 mg sarilumab in 1.14 ml solution.
- The other ingredients are arginine, histidine, polysorbate 20 (E 432), sucrose, and water for injections.

What Kevzara looks like and contents of the pack
Kevzara is a clear, colourless to pale yellow solution for injection that comes in a pre-filled syringe.

Each pre-filled syringe contains 1.14 ml of solution delivering one single dose. Kevzara is available in packs containing 1 or 2 pre-filled syringes and in multipacks comprising 3 cartons, each containing 2 pre-filled syringes.

Not all pack sizes may be marketed.

Kevzara is available as 150 mg or 200 mg pre-filled syringes.

Marketing Authorisation Holder
Sanofi Winthrop Industrie
82 avenue Raspail
94250 Gentilly
France

Manufacturer
Sanofi Winthrop Industrie
1051 Boulevard Industriel
76580 Le Trait,
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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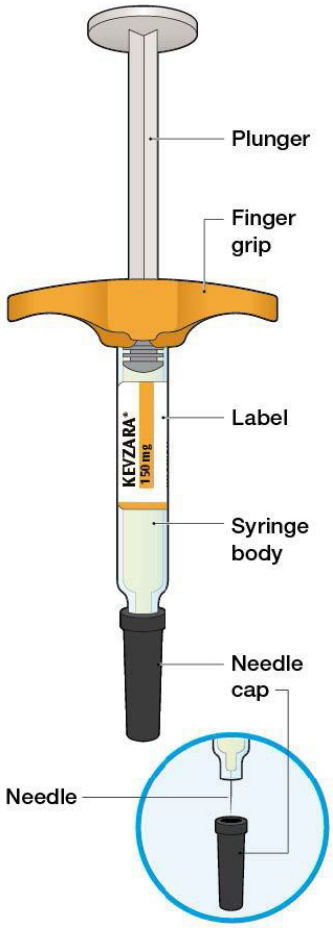
This leaflet was last revised in .

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

Kevzara 150 mg solution for injection in pre-filled syringe
sarilumab

Instructions for use

The parts of the Kevzara pre-filled syringe are shown in this picture.



Important information

This device is a single-dose pre-filled syringe (called "syringe" in these instructions). It contains 150 mg of Kevzara for injection under the skin (subcutaneous injection) once every two weeks.

Ask your healthcare professional to show you the right way to use the syringe before your first injection.

Do

- ✓ Read all of the instructions carefully before using a syringe.
- ✓ Check that you have the correct medicine and the correct dose.
- ✓ Keep unused syringes in the original carton and store in the refrigerator between 2ºC and 8ºC.
- ✓ Keep the carton in an insulated bag with an ice pack when travelling.
- ✓ Let the syringe warm up to room temperature for at least 30 minutes before using.
- ✓ Use the syringe within 14 days after taking it out of the refrigerator or insulated bag.
- ✓ Keep the syringe out of the sight and reach of children.

Do not

✗ Do not use the syringe if it has been damaged or the needle cap is missing or not attached.

✗ Do not remove the needle cap until just before you are ready to inject.

- Do not touch the needle.
- Do not try to put the cap back on the syringe.
- Do not re-use the syringe.
- Do not freeze or heat the syringe.
- Once removed from the refrigerator, do not store the syringe above 25ºC.
- Do not expose the syringe to direct sunlight.
- Do not inject through your clothes.

If you have any further questions, ask your doctor, pharmacist or nurse.

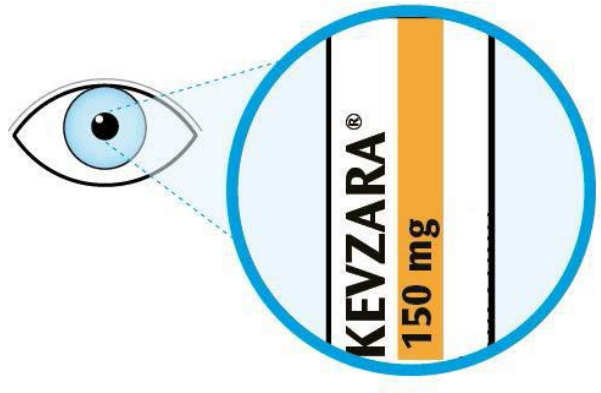
Step A: Get ready for an injection

1. Prepare all the equipment you will need on a clean, flat working surface.

- You will need an alcohol wipe, a cotton ball or gauze, and a puncture-resistant container.
- Take one syringe out of the packaging by holding the middle of the syringe body. Keep the remaining syringe in the carton in the refrigerator.

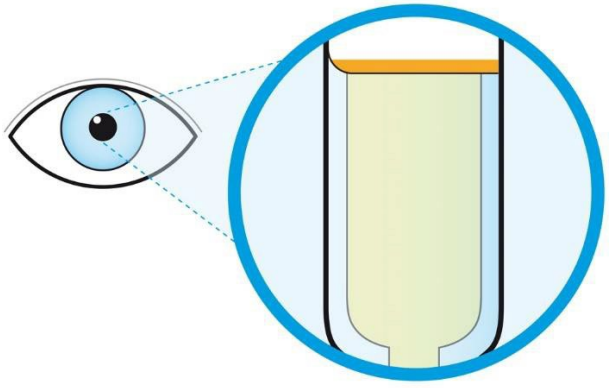
2. Look at the label.

- Check that you have the correct medicine and the correct dose.
- Check the expiry date (EXP).
- **Do not** use the syringe if the date has passed.



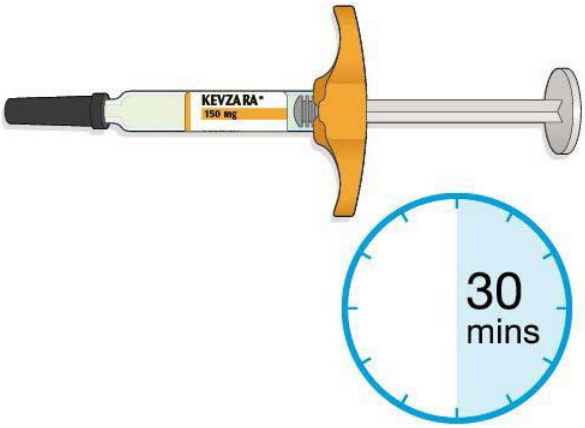
3. Look at the medicine.

- Check that the liquid is clear and colourless to pale yellow.
- You may see an air bubble, this is normal.
- **Do not** inject if the liquid is cloudy, discoloured or contains particles.



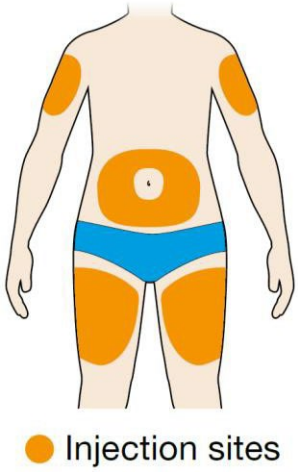
4. Lay the syringe on a flat surface and allow it to warm up to room temperature (<25°C) **for at least 30 minutes.**

- Using the syringe at room temperature may make the injection more comfortable.
- **Do not** use the syringe if it has been out of the refrigerator for more than 14 days.
- **Do not** heat the syringe; let it warm up on its own.
- **Do not** expose the syringe to direct sunlight.



5. Select the injection site.

- You can inject into your thigh or belly (abdomen) except for the 5 cm around your belly button (navel). If somebody else gives you the injection, you can also use the outer area of the upper arm.
- Change injection site each time you inject.
- **Do not** inject into skin that is tender, damaged or has bruises or scars.



6. Prepare the injection site.

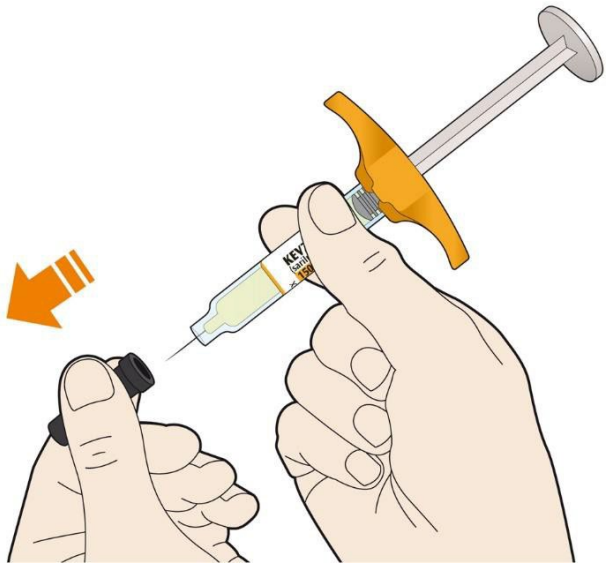
- Wash your hands.
- Clean skin with an alcohol wipe.
- **Do not** touch the injection site again before the injection.

Step B: Perform the injection – Perform Step B only after completing Step A "Get ready for an injection"

1. Pull off the needle cap.

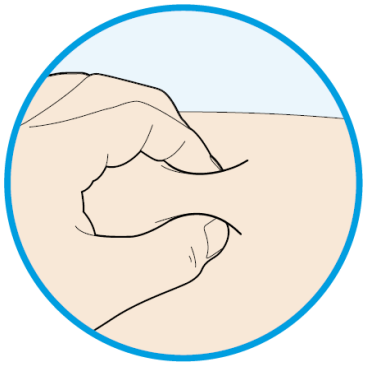
- Hold the syringe in the middle of the syringe body with the needle pointing away from you.
- Keep your hand away from the plunger.
- **Do not** get rid of any air bubbles in the syringe.

- **Do not** pull off the needle cap until you are ready to inject.
- **Do not** put the needle cap back on.

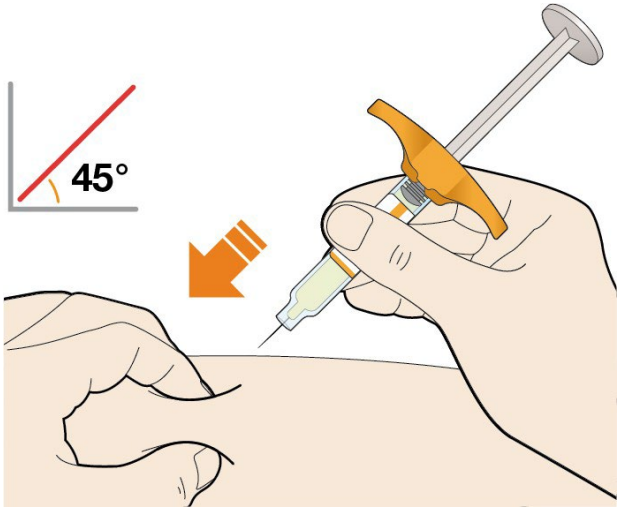


2. Pinch the skin.

- Use your thumb and first (index) finger to pinch a fold of skin at the injection site.

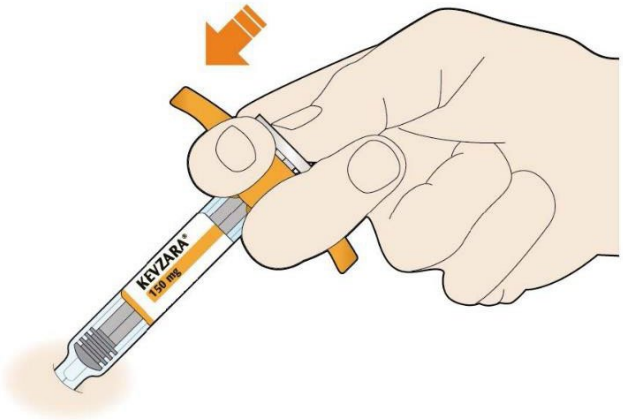


3. Insert the needle into the fold of skin at roughly a 45º angle.



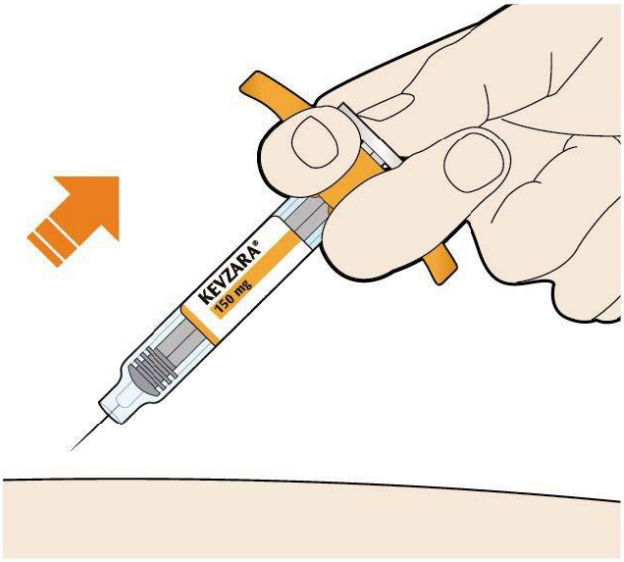
4. Push the plunger down.

- Slowly push the plunger down as far as it will go until the syringe is empty.



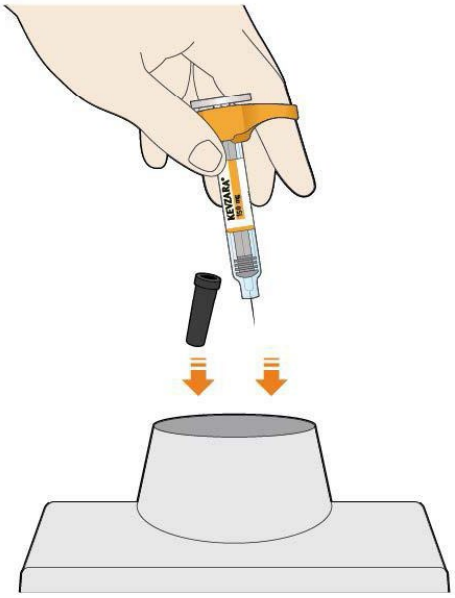
5. Before you remove the needle, check that the syringe is empty.

- Pull the needle out at the same angle it was injected.
- If you see any blood, press a cotton ball or gauze on the site.
- **Do not** rub your skin after the injection.



6. Put your used syringe and the cap into a puncture-resistant container right away after use.

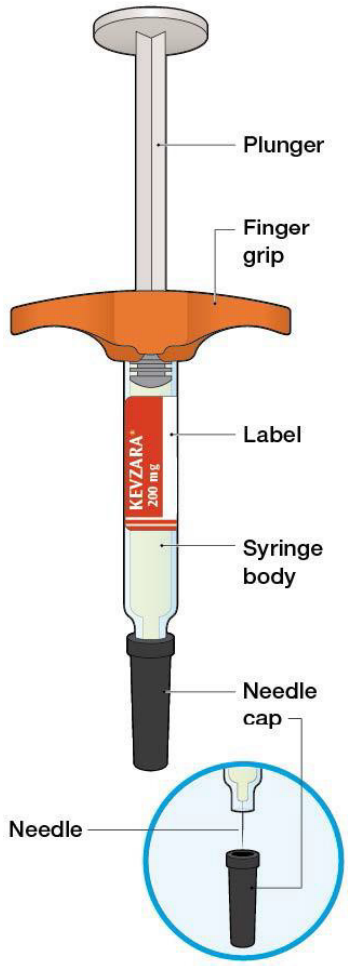
- Always keep the container out of the sight and reach of children.
- **Do not** put the needle cap back on.
- **Do not** throw the used syringe in household waste.
- **Do not** dispose of your used puncture-resistant container in your household waste unless your local guidelines permit this. Ask your doctor, pharmacist or nurse how to throw away the container.


KEVZARA

Kevzara 200 mg solution for injection in pre-filled syringe
sarilumab

Instructions for use

The parts of the Kevzara pre-filled syringe are shown in this picture.



Important information

This device is a single-dose pre-filled syringe (called "syringe" in these instructions). It contains 200 mg of Kevzara for injection under the skin (subcutaneous injection) once every two weeks.

Ask your healthcare professional to show you the right way to use the syringe before your first injection.

Do

- ✓ Read all of the instructions carefully before using a syringe.
- ✓ Check that you have the correct medicine and the correct dose.
- ✓ Keep unused syringes in the original carton and store in the refrigerator between 2ºC and 8ºC.
- ✓ Keep the carton in an insulated bag with an ice pack when travelling.
- ✓ Let the syringe warm up to room temperature for at least 30 minutes before using.
- ✓ Use the syringe within 14 days after taking it out of the refrigerator or insulated bag.
- ✓ Keep the syringe out of the sight and reach of children.

Do not

✗ Do not use the syringe if it has been damaged or the needle cap is missing or not attached.

✗ Do not remove the needle cap until just before you are ready to inject.

- Do not touch the needle.
- Do not try to put the cap back on the syringe.
- Do not re-use the syringe.
- Do not freeze or heat the syringe.
- Once removed from the refrigerator, do not store the syringe above 25ºC.
- Do not expose the syringe to direct sunlight.
- Do not inject through your clothes.

If you have any further questions, ask your doctor, pharmacist or nurse.

Step A: Get ready for an injection

1. Prepare all the equipment you will need on a clean, flat working surface.

- You will need an alcohol wipe, a cotton ball or gauze, and a puncture-resistant container.
- Take one syringe out of the packaging by holding the middle of the syringe body. Keep the remaining syringe in the carton in the refrigerator.

2. Look at the label.

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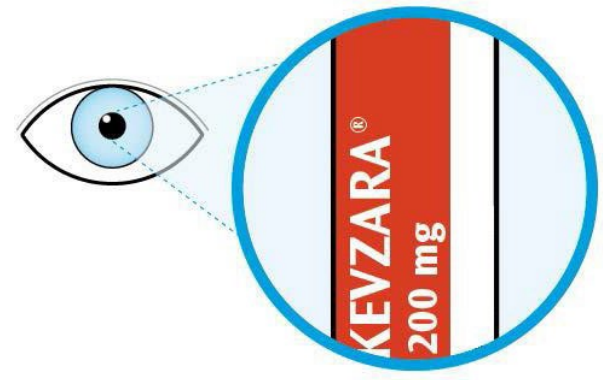
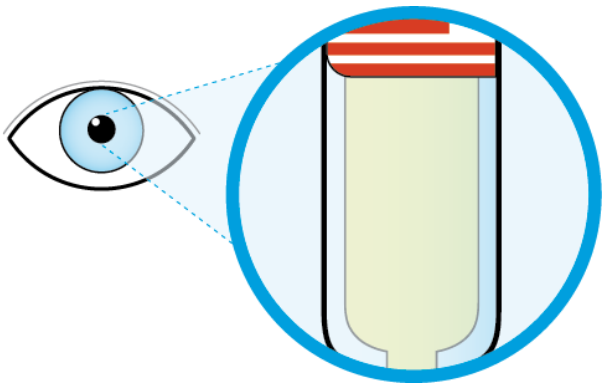


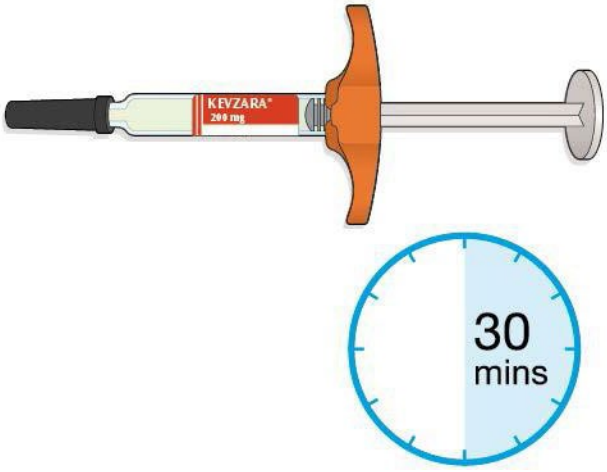
3. Look at the medicine.

- Check that the liquid is clear and colourless to pale yellow.
- You may see an air bubble, this is normal.
- **Do not** inject if the liquid is cloudy, discoloured or contains particles.



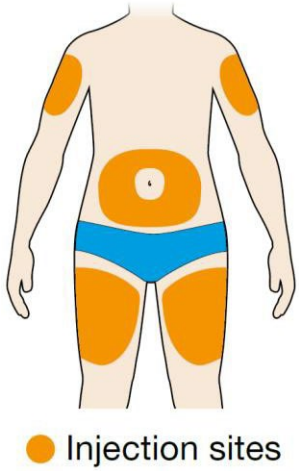
4. Lay the syringe on a flat surface and allow it to warm up to room temperature (<25°C) **for at least 30 minutes.**

- Using the syringe at room temperature may make the injection more comfortable.
- **Do not** use the syringe if it has been out of the refrigerator for more than 14 days.
- **Do not** heat the syringe; let it warm up on its own.
- **Do not** expose the syringe to direct sunlight.



5. Select the injection site.

- You can inject into your thigh or belly (abdomen) except for the 5 cm around your belly button (navel). If somebody else gives you the injection, you can also use the outer area of the upper arm.
- Change injection site each time you inject.
- **Do not** inject into skin that is tender, damaged or has bruises or scars.



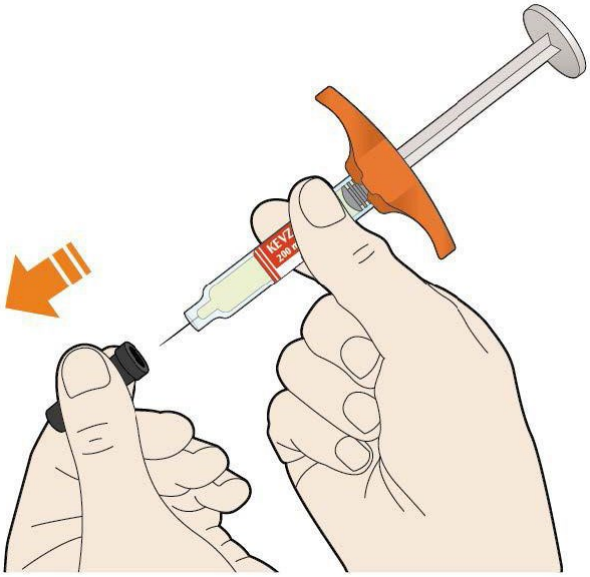
6. Prepare the injection site.

- Wash your hands.
- Clean skin with an alcohol wipe.
- **Do not** touch the injection site again before the injection.

Step B: Perform the injection – Perform Step B only after completing Step A "Get ready for an injection"

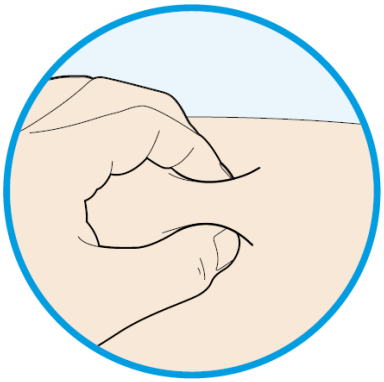
1. Pull off the needle cap.

- Hold the syringe in the middle of the syringe body with the needle pointing away from you.
- Keep your hand away from the plunger.
- **Do not** get rid of any air bubbles in the syringe.
- **Do not** pull off the needle cap until you are ready to inject.
- **Do not** put the needle cap back on.

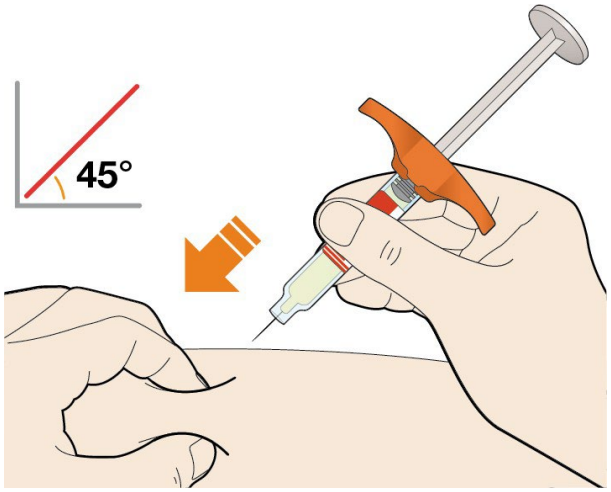


2. Pinch the skin.

- Use your thumb and first (index) finger to pinch a fold of skin at the injection site.

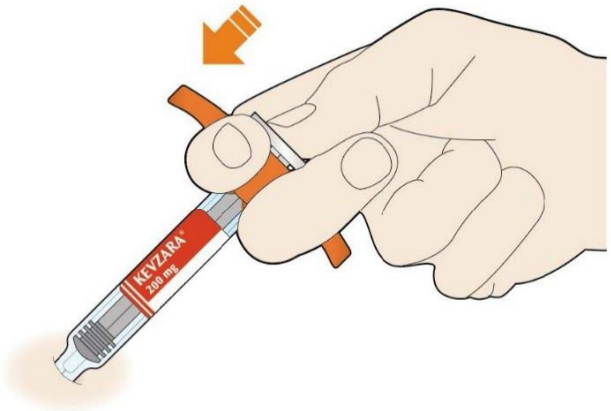


3. Insert the needle into the fold of skin at roughly a 45º angle.



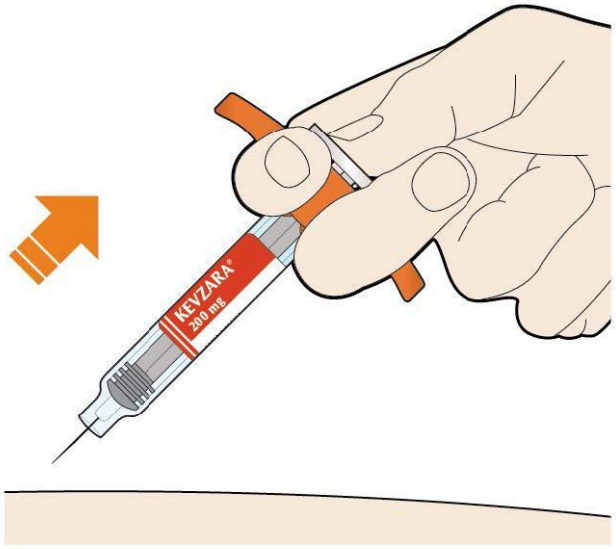
4. Push the plunger down.

- Slowly push the plunger down as far as it will go until the syringe is empty.



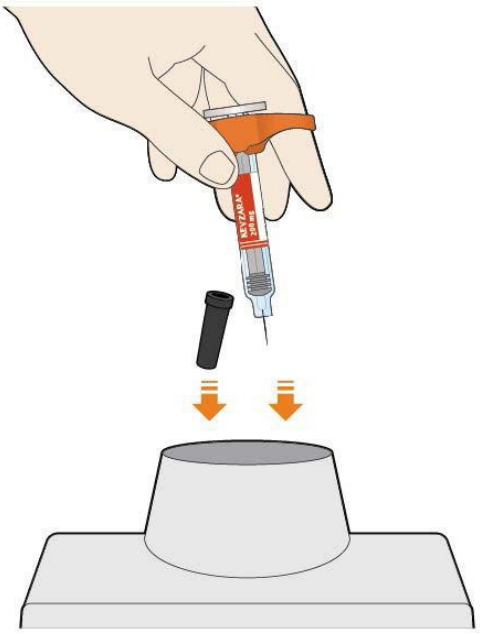
5. Before you remove the needle, check that the syringe is empty.

- Pull the needle out at the same angle it was injected.
- If you see any blood, press a cotton ball or gauze on the site.
- **Do not** rub your skin after the injection.



6. Put your used syringe and the cap into a puncture-resistant container right away after use.

- Always keep the container out of the sight and reach of children.
- **Do not** put the needle cap back on.
- **Do not** throw the used syringe in household waste.
- **Do not** dispose of your used puncture-resistant container in your household waste unless your local guidelines permit this. Ask your doctor, pharmacist or nurse how to throw away the container.



Package leaflet: Information for the patient

Kevzara 150 mg solution for injection in pre-filled pen
Kevzara 200 mg solution for injection in pre-filled pen
sarilumab

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, pharmacist, or nurse.
- 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, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a patient card, which contains important safety information that you need before and during treatment with Kevzara.

What is in this leaflet

1. What Kevzara is and what it is used for

What Kevzara is
Kevzara contains the active substance sarilumab. It is a type of protein - called a "monoclonal antibody".

What Kevzara is used for
Kevzara is used to treat adults with moderately to severely active rheumatoid arthritis (RA) if previous therapy did not work well enough or was not tolerated. Kevzara can be used alone or together with a medicine called MTX.
It may help you by:
- slowing down damage to joints
- improving your ability to perform daily activities.

Kevzara is used to treat adults with polymyalgia rheumatica after corticosteroids have been used and did not work well or if you experience a relapse while decreasing the dose of corticosteroids (taper). Kevzara can be used alone or together with a medicine called corticosteroid.

How Kevzara works
- Kevzara attaches to another protein called interleukin-6 (IL-6) receptor and blocks its action.
- IL-6 plays a major role in the symptoms of RA such as pain, swollen joints, morning stiffness, and fatigue.

2. What you need to know before you use Kevzara

Do not use Kevzara:
- if you are allergic to sarilumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an active severe infection.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse if:
- you have any infection or, you get a lot of infections. Kevzara can lower your body's ability to fight infection and this means it can make you more likely to get infections or make your infection worse.
- you have tuberculosis (TB), symptoms of TB (persistent cough, weight loss, listlessness, mild fever), or have been in close contact with someone with TB. Before you are given Kevzara, your doctor will check you for TB.
- you have had viral hepatitis or other liver disease. Before you use Kevzara, your doctor will do a blood test to check your liver function.
- you have had diverticulitis (a condition of the lower bowel) or ulcers in your stomach or intestines, or develop symptoms such as fever and stomach (abdominal) pain that does not go away.
- you have ever had any type of cancer.
- you have recently had any vaccination or are going to have a vaccination.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before using Kevzara.

You will have blood tests before you are given Kevzara. You will also have the tests during your treatment. This is to check if you have a low blood cell count, liver problems, or changes in your cholesterol levels.

Every time you get a new pack of Kevzara, it is important you note down the name of the medicine, the date of the administration and the batch number (which is on the packaging after "Lot") and keep this information in a safe place.

Children and adolescents
The Kevzara pre-filled pen has not been studied in children 2 years of age and older with pJIA and is not intended for use in children.
Kevzara is not recommended in children under 2 years of age. Kevzara must not be given to children with pJIA weighing less than 10 kg.

Other medicines and Kevzara
Tell your doctor or pharmacist if you are using, have recently used, or might use any other medicines. This is because Kevzara can affect the way some other medicines work. Also some other medicines can affect the way Kevzara works.

In particular, do not use Kevzara and tell your doctor or pharmacist if you are using:
- a group of medicines called "Janus kinase (JAK) inhibitors" (used for disease like rheumatoid arthritis and cancer)
- other biological medicines used in the treatment of RA.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist.

Kevzara can affect the way some medicines work: this means the dose of other medicines may need changing. If you are using any of the following medicines, tell your doctor or pharmacist before using Kevzara:
- statins, used to reduce cholesterol level
- oral contraceptives
- theophylline, used to treat asthma
- warfarin, used to prevent blood clots

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist.

Pregnancy and breast-feeding
Talk to your doctor before using Kevzara if you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby.
- Do not take Kevzara if you are pregnant – unless your doctor specifically recommends it.
- The effects of Kevzara on an unborn baby are not known.
- You and your doctor should decide if you should use Kevzara if you are breast-feeding.

Driving and using machines
The use of Kevzara is not expected to affect your ability to drive or use machines. However, if you are feeling tired or unwell after you use Kevzara, you should not drive or use machines.

KEVZARA contains polysorbate 20
This medicine contains 2.28 mg of polysorbate 20 in each 1.14 mL of solution for injection which is equivalent to 2 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Kevzara

Treatment should be started by a doctor experienced in the diagnosis and treatment of RAor polymyalgia rheumatica. Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adult patients
The recommended dose is one 200 mg injection every two weeks.
- Your doctor may adjust the dose of your medicine based on results of blood tests.

Kevzara is given as an injection under the skin (called "subcutaneous" injection).

Learning how to use the pre-filled pen
- Your doctor, pharmacist, or nurse will show you how to inject Kevzara. Following these instructions Kevzara can be self-injected or administered by a care-giver after proper training.
- Carefully follow the "Instructions for Use" provided in the carton.
- Use the pre-filled pen exactly as described in the "Instructions for Use".

If you use more Kevzara than you should
If you have used more Kevzara than you should, talk to your doctor, pharmacist or nurse.

If you miss a dose of Kevzara
If it has been 3 days or less since the missed dose:
- inject your missed dose as soon as you can.
- then inject your next dose at your regular time.

If it has been 4 days or more, inject the next dose at your regular time. Do not inject a double dose to make up for a forgotten injection.
If you are unsure when to inject your next dose: ask your doctor, pharmacist or nurse for instructions.

If you stop using Kevzara
Do not stop using Kevzara without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

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

Serious side effect
Tell your doctor straight away if you think you have an **infection** (which may affect up to 1 in every 10 people). The symptoms may include fever, sweats, or chills.

Other side effects
Tell your doctor, pharmacist, or nurse if you notice any of the following side effects:

Adults
Very common (may affect more than 1 in 10 people):
- Low white blood cell counts shown by blood tests

Common (may affect up to 1 in 10 people):
- infections in your sinuses or throat, blocked or runny nose and sore throat ("upper respiratory tract infection")
- urinary tract infection
- cold sores ("oral herpes")
- low platelet counts shown by blood tests
- high cholesterol, high triglycerides shown by blood tests
- abnormal liver function tests
- injection site reactions (including redness and itching)
- inflammation of the deep skin tissue
- infection of the lungs

Uncommon (may affect up to 1 in 100 people):
- diverticulitis (a disease affecting the gut often with stomach (abdominal) pain, nausea and vomiting, fever, and constipation, or less commonly diarrhoea)

Rare (may affect up to 1 in 1 000 people):
- perforation in stomach or intestines (a hole that develops in the wall of the gut)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. 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 Kevzara

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.
- Once taken out the refrigerator, do not store Kevzara above 25ºC.
- Write down the date of removal from the refrigerator in the space provided on the outer carton.
- Use the pen within 14 days after taking it out of the refrigerator or the insulated bag.
- Keep the pen in the original carton in order to protect from light.

Do not use this medicine if the solution in the pen is cloudy, discoloured or contains particles, or if any part of the pre-filled pen looks damaged.

After use, put the pen into a puncture-resistant container. Always keep the container out of the sight and reach of children. Ask your doctor, pharmacist, or nurse how to throw away the container.

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 Kevzara contains
- The active substance is sarilumab. Each pre-filled pen contains 150 mg or 200 mg sarilumab in 1.14 ml solution
- The other ingredients are arginine, histidine, polysorbate 20 (E 432) , sucrose, and water for injections.

What Kevzara looks like and contents of the pack
Kevzara is a clear, colourless to pale yellow solution for injection that comes in a pre-filled pen.

Each pre-filled pen contains 1.14 ml of solution delivering one single dose. Kevzara is available in packs containing 1 or 2 pens and in multipacks comprising 3 cartons, each containing 2 pens.

Not all pack sizes may be marketed.

Kevzara is available as 150 mg or 200 mg pre-filled pens.

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France

Manufacturer
Sanofi-Aventis Deutschland GmbH
Brüningstraße 50
Industriepark Höchst
65926 Frankfurt am Main
Germany

Genzyme Ireland Ltd
IDA Industrial Park
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Waterford,
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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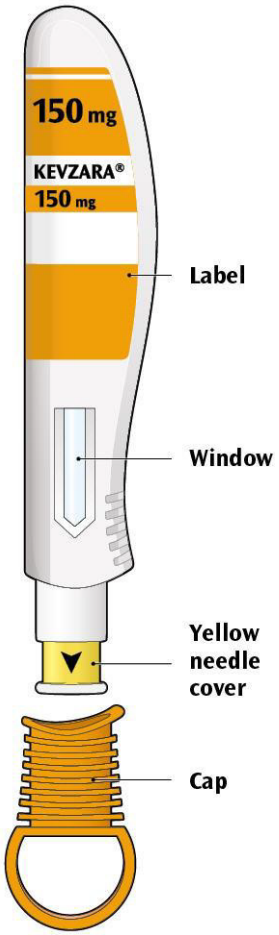
This leaflet was last revised in

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

Kevzara 150 mg solution for injection in pre-filled pen
sarilumab

Instructions for use

The parts of the Kevzara pre-filled pen are shown in this picture.



Important information

This device is a single-dose pre-filled pen (called "pen" in these instructions). It contains 150 mg of Kevzara for injection under the skin (subcutaneous injection) once every two weeks.

Ask your healthcare professional to show you the right way to use the pen before your first injection.

Do

✓ Read all of the instructions carefully before using a pen.
✓ Check that you have the correct medicine and the correct dose.
✓ Keep unused pens in the original carton and store in the refrigerator between 2ºC and 8ºC.
✓ Keep the carton in an insulated bag with an ice pack when travelling.
✓ Let the pen warm up to room temperature for at least 60 minutes before using.
✓ Use the pen within 14 days after taking it out of the refrigerator or insulated bag.
✓ Keep the pen out of the sight and reach of children.

Do not

✗ Do not use a pen if it has been damaged or the cap is missing or not attached.
✗ Do not remove the cap until just before you are ready to inject.

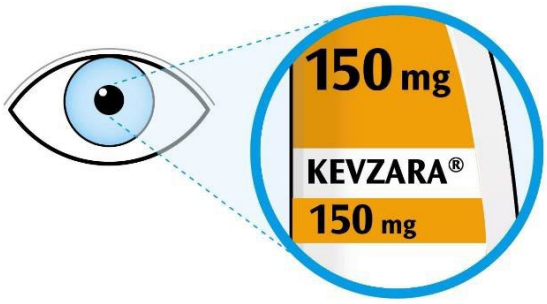
- Do not press or touch the yellow needle cover with your fingers.
- Do not try to put the cap back on a pen.
- Do not re-use the pen.
- Do not freeze or heat the pen.
- Once removed from the refrigerator, do not store the pen above 25ºC.
- Do not expose the pen to direct sunlight.
- Do not inject through your clothes.

If you have any further questions, ask your doctor, pharmacist or nurse.

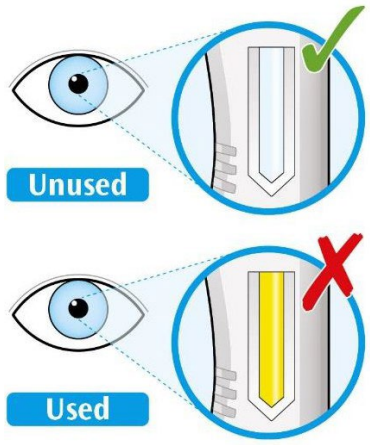
Step A: Get ready for an injection

1. Prepare all the equipment you will need on a clean, flat working surface.
- You will need an alcohol wipe, a cotton ball or gauze, and a puncture-resistant container.
- Take one pen out of the packaging by holding the middle of the pen body. Keep the remaining pen in the carton in the refrigerator.

2. Look at the label.
- Check that you have the correct medicine and the correct dose.
- Check the expiry date (EXP), this is shown on the side of the pens.
- **Do not** use the pen if the date has passed.



3. Look at the window.
- Check that the liquid is clear and colourless to pale yellow.
- You may see an air bubble, this is normal.
- **Do not** inject if the liquid is cloudy, discoloured or contains particles.
- **Do not** use if the window is solid yellow.

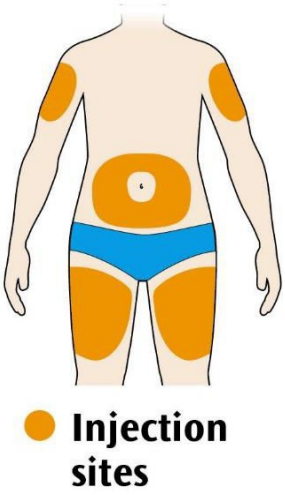


4. Lay the pen on a flat surface and allow it to warm up to room temperature (<25°C) for at least 60 minutes.

- Using the pen at room temperature may make the injection more comfortable.
- **Do not** use the pen if it has been out of the refrigerator for more than 14 days.
- **Do not** heat the pen; let it warm up on its own.
- **Do not** expose the pen to direct sunlight.

5. Select the injection site.

- You can inject into your thigh or belly (abdomen) except for the 5 cm around your belly button (navel). If somebody else gives you the injection, you can also use the outer area of the upper arm.
- Change injection site each time you inject.
- **Do not** inject into skin that is tender, damaged or has bruises or scars.



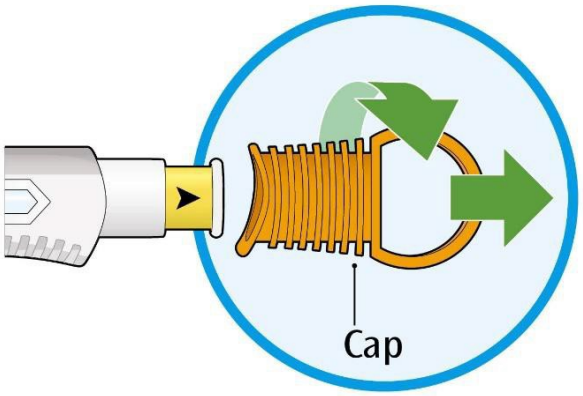
6. Prepare the injection site.

- Wash your hands.
- Clean skin with an alcohol wipe.
- **Do not** touch the injection site again before the injection.

Step B: Perform the injection – Perform Step B only after completing Step A "Get ready for an injection"

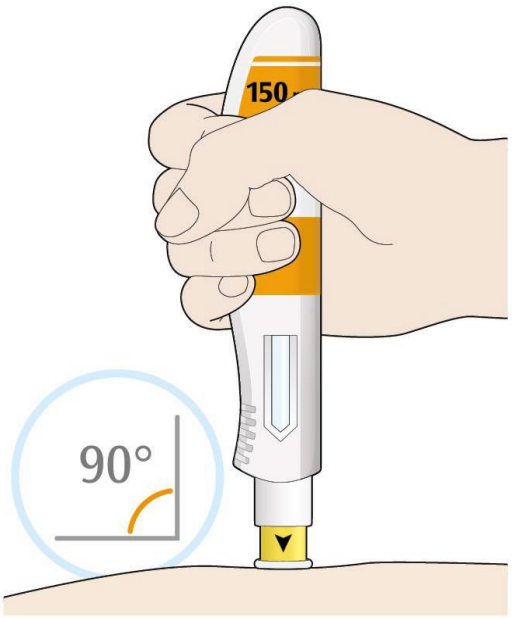
1. Twist or pull off the orange cap.

- **Do not** remove the cap until you are ready to inject.
- **Do not** press or touch the yellow needle cover with your fingers.
- **Do not** put the cap back on.



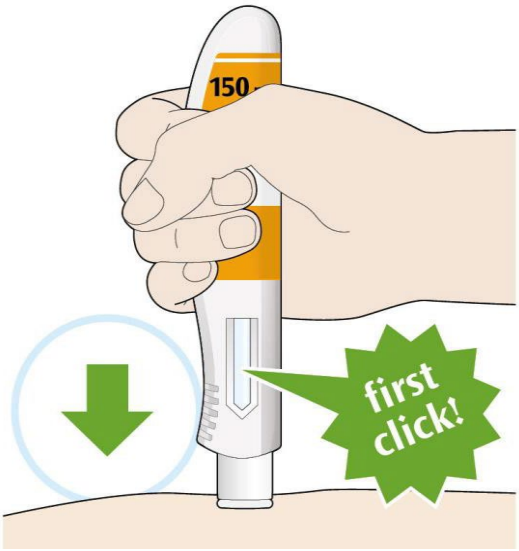
2. Put the yellow needle cover on your skin at roughly a 90° angle.

- Make sure you can see the window.



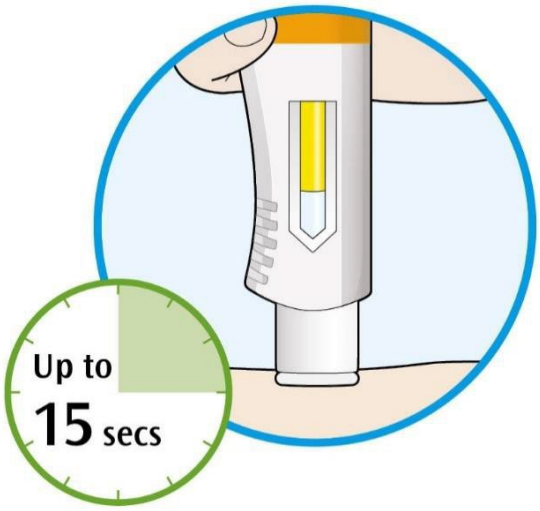
3. Press down and hold the pen firmly against your skin.

- There will be a “click” when the injection starts.



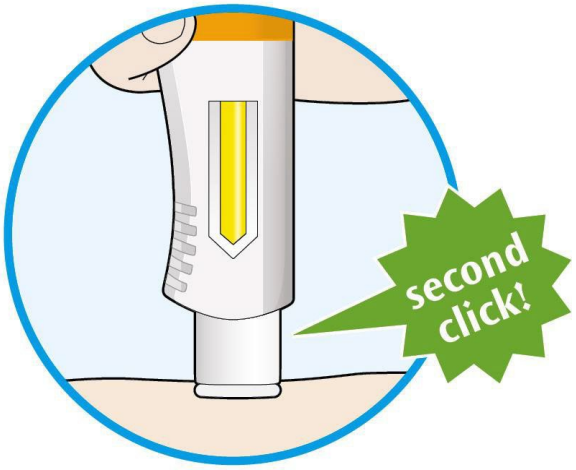
4. Keep holding the pen firmly against your skin.

- The window will start to turn yellow.
- The injection can take up to 15 seconds.



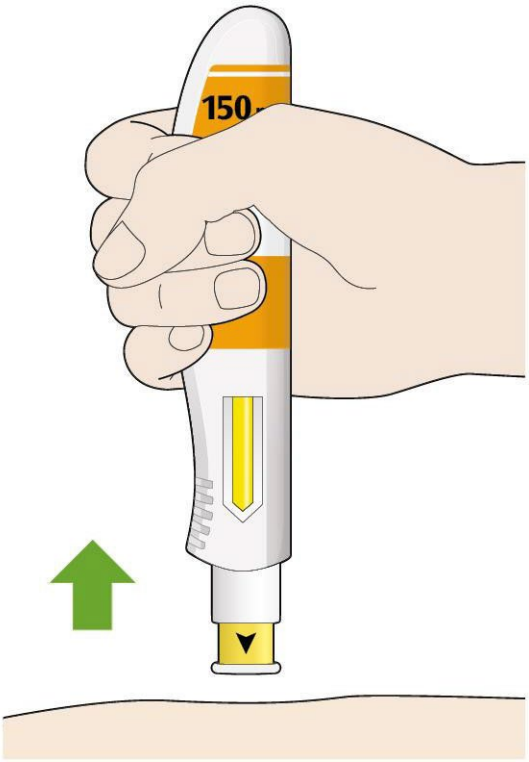
5. There will be a second click. Check to see if the entire window has turned yellow before you remove the pen.

- If you do not hear the second click, you should still check to see if the window has turned fully yellow.
- If the window does not turn fully yellow, **do not** give yourself a second dose without speaking to your healthcare provider.



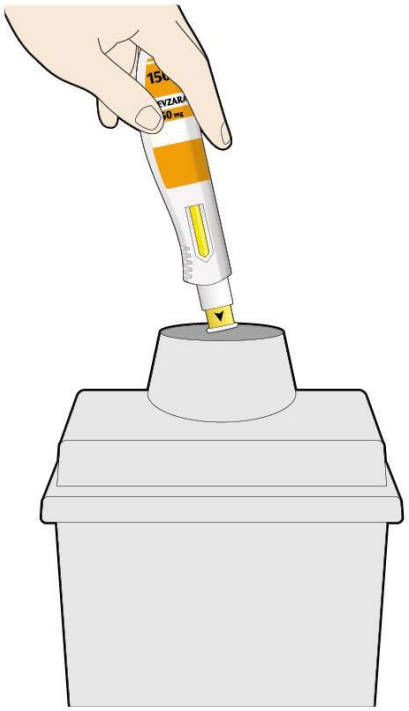
6. Pull the pen away from your skin.

- If you see any blood, press a cotton ball or gauze on the site.
- **Do not** rub your skin after the injection.



7. Put your used pen and the cap into a puncture-resistant container right away after use.

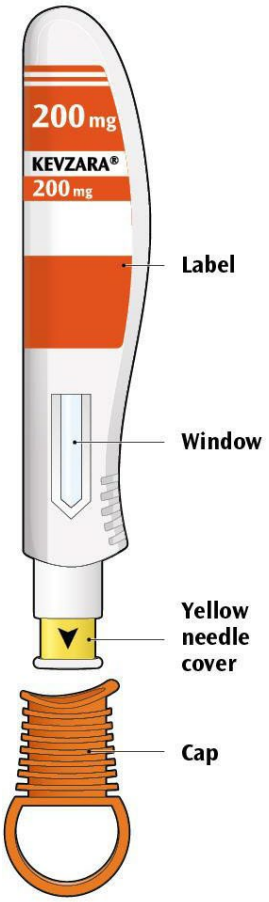
- Always keep the container out of the sight and reach of children.
- **Do not** put the cap back on.
- **Do not** throw the used pens in household waste.
- **Do not** dispose of your used puncture-resistant container in your household waste unless your local guidelines permit this. Ask your doctor, pharmacist or nurse how to throw away the container.



Kevzara 200 mg solution for injection in pre-filled pen
sarilumab

Instructions for use

The parts of the Kevzara pre-filled pen are shown in this picture.



Important information

This device is a single-dose pre-filled pen (called "pen" in these instructions). It contains 200 mg of Kevzara for injection under the skin (subcutaneous injection) once every two weeks.

Ask your healthcare professional to show you the right way to use the pen before your first injection.

Do

✓ Read all of the instructions carefully before using a pen.
✓ Check that you have the correct medicine and the correct dose.
✓ Keep unused pens in the original carton and store in the refrigerator between 2ºC and 8ºC.
✓ Keep the carton in an insulated bag with an ice pack when travelling.
✓ Let the pen warm up to room temperature for at least 60 minutes before using.
✓ Use the pen within 14 days after taking it out of the refrigerator or insulated bag.
✓ Keep the pen out of the sight and reach of children.

Do not

✗ Do not use a pen if it has been damaged or the cap is missing or not attached.
✗ Do not remove the cap until just before you are ready to inject.

- Do not press or touch the yellow needle cover with your fingers.
- Do not try to put the cap back on a pen.
- Do not re-use the pen.
- Do not freeze or heat the pen.
- Once removed from the refrigerator, do not store the pen above 25ºC.
- Do not expose the pen to direct sunlight.
- Do not inject through your clothes.

If you have any further questions, ask your doctor, pharmacist or nurse.

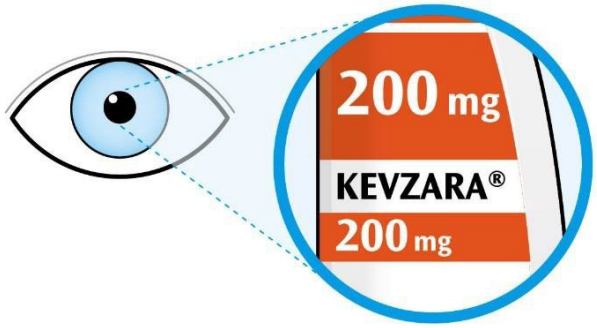
Step A: Get ready for an injection

1. Prepare all the equipment you will need on a clean, flat working surface.

- You will need an alcohol wipe, a cotton ball or gauze, and a puncture-resistant container.
- Take one pen out of the packaging by holding the middle of the pen body. Keep the remaining pen in the carton in the refrigerator.

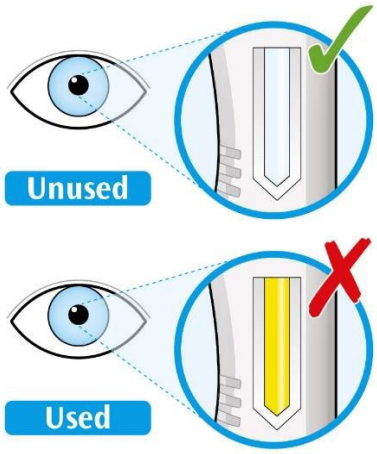
2. Look at the label.

- Check that you have the correct medicine and the correct dose.
- Check the expiry date (EXP), this is shown on the side of the pens.
- **Do not** use the pen if the date has passed.



3. Look at the window.

- Check that the liquid is clear and colourless to pale yellow.
- You may see an air bubble, this is normal.
- **Do not** inject if the liquid is cloudy, discoloured or contains particles.
- **Do not** use if the window is solid yellow.

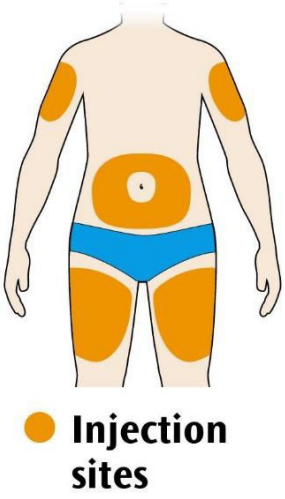


4. Lay the pen on a flat surface and allow it to warm up to room temperature (<25°C) for at least 60 minutes.

- Using the pen at room temperature may make the injection more comfortable.
- **Do not** use the pen if it has been out of the refrigerator for more than 14 days.
- **Do not** heat the pen; let it warm up on its own.
- **Do not** expose the pen to direct sunlight.

5. Select the injection site.

- You can inject into your thigh or belly (abdomen) except for the 5 cm around your belly button (navel). If somebody else gives you the injection, you can also use the outer area of the upper arm.
- Change injection site each time you inject.
- **Do not** inject into skin that is tender, damaged or has bruises or scars.



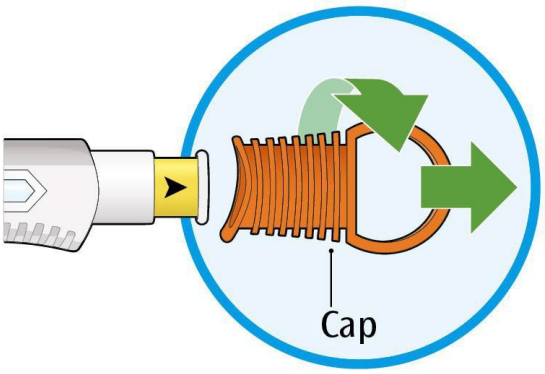
6. Prepare the injection site.

- Wash your hands.
- Clean skin with an alcohol wipe.
- **Do not** touch the injection site again before the injection.

Step B: Perform the injection – Perform Step B only after completing Step A "Get ready for an injection"

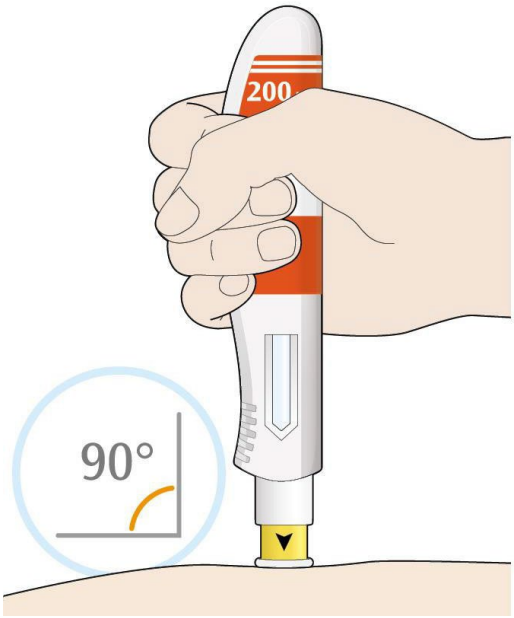
1. Twist or pull off the orange cap.

- **Do not** remove the cap until you are ready to inject.
- **Do not** press or touch the yellow needle cover with your fingers.
- **Do not** put the cap back on.



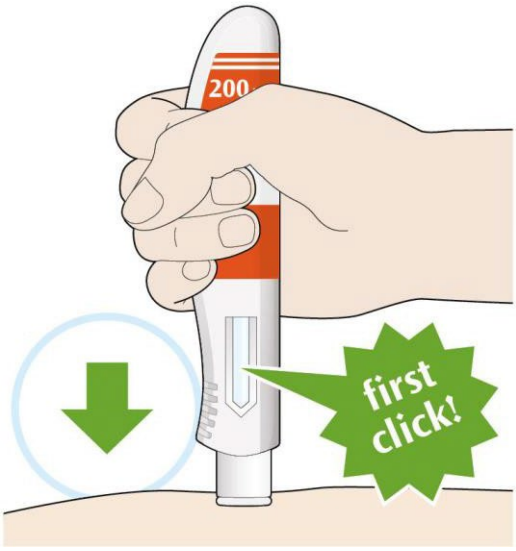
2. Put the yellow needle cover on your skin at roughly a 90° angle.

- Make sure you can see the window.



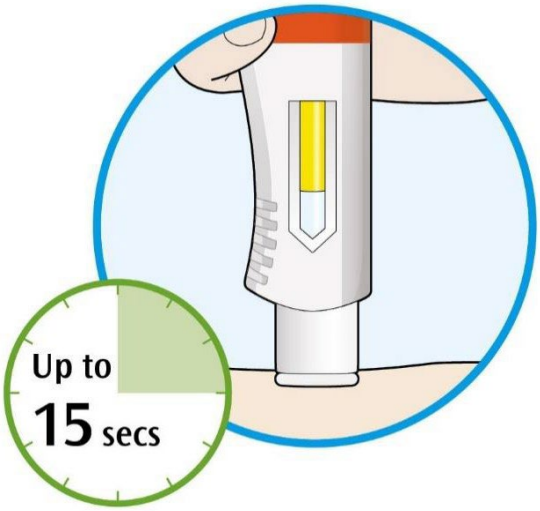
3. Press down and hold the pen firmly against your skin.

- There will be a “click” when the injection starts.



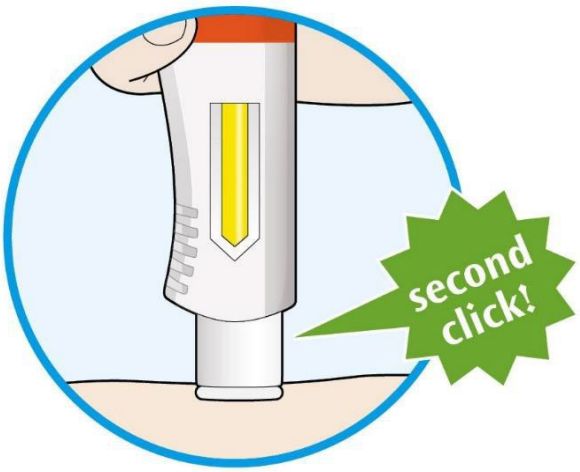
4. Keep holding the pen firmly against your skin.

- The window will start to turn yellow.
- The injection can take up to 15 seconds.



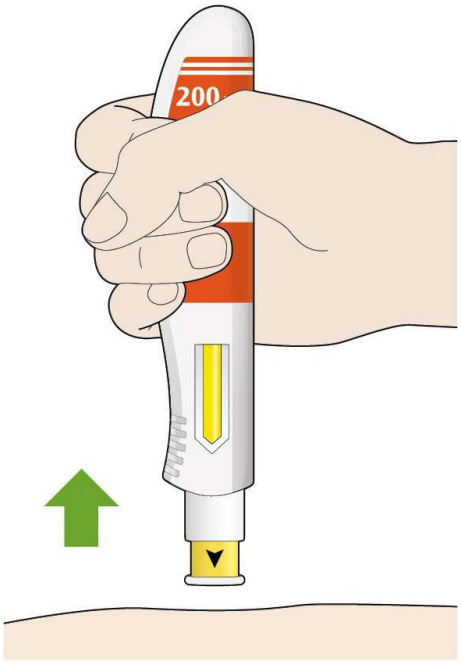
5. There will be a second click. Check to see if the entire window has turned yellow before you remove the pen.

- If you do not hear the second click, you should still check to see if the window has turned fully yellow.
- If the window does not turn fully yellow, **do not** give yourself a second dose without speaking to your healthcare provider.



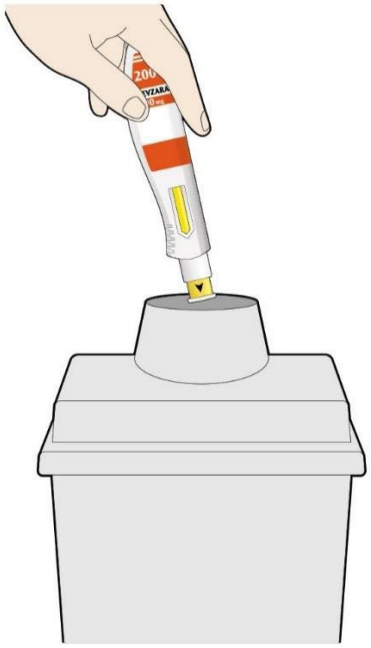
6. Pull the pen away from your skin.

- If you see any blood, press a cotton ball or gauze on the site.
- **Do not** rub your skin after the injection.



7. Put your used pen and the cap into a puncture-resistant container right away after use.

- Always keep the container out of the sight and reach of children.
- **Do not** put the cap back on.
- **Do not** throw the used pens in household waste.
- **Do not** dispose of your used puncture-resistant container in your household waste unless your local guidelines permit this. Ask your doctor, pharmacist or nurse how to throw away the container.



Package leaflet: Information for the patient

Kevzara 175 mg/ml solution for injection
sarilumab

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, pharmacist, or nurse.
- 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, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, you will be given a patient card, which contains important safety information that you need before and during treatment with Kevzara.

What is in this leaflet

1. What Kevzara is and what it is used for

What Kevzara is
Kevzara contains the active substance sarilumab. It is a type of protein - called a "monoclonal antibody".

What Kevzara is used for
Kevzara is used to treat children aged 2 years of age and older who have active polyarticular juvenile idiopathic arthritis (pJIA) if previous therapy did not work well. Kevzara can be used alone or together with a medicine called methotrexate.

How Kevzara works
- Kevzara attaches to another protein called interleukin-6 (IL-6) receptor and blocks its action.
- IL-6 plays a major role in the symptoms of RA such as pain, swollen joints, morning stiffness, and fatigue.

2. What you need to know before you use Kevzara

Do not use Kevzara:
- if you/your child are/is allergic to sarilumab or any of the other ingredients of this medicine (listed in section 6).
- if you/your child have/has an active severe infection.

Warnings and precautions
Talk to your doctor, pharmacist, or nurse if:
- you/your child have/has any infection or, you get a lot of infections. Kevzara can lower your body's ability to fight infection and this means it can make you more likely to get infections or make your infection worse.

- you/your child have/has tuberculosis (TB), symptoms of TB (persistent cough, weight loss, listlessness, mild fever), or have been in close contact with someone with TB. Before you are given Kevzara, your doctor will check you for TB.
- you/your child have/has had viral hepatitis or other liver disease. Before you use Kevzara, your doctor will do a blood test to check your liver function.
- you/your child have/has had diverticulitis (a condition of the lower bowel) or ulcers in your stomach or intestines, or develop symptoms such as fever and stomach (abdominal) pain that does not go away.
- you/your child have/has ever had any type of cancer.
- you/your child have/has recently had any vaccination or are going to have a vaccination.

If any of the above apply to you/your child (or you are not sure), talk to your doctor, pharmacist or nurse before using Kevzara.

You/your child will have blood tests before you are given Kevzara. You/your child will also have the tests during your treatment. This is to check if you have a low blood cell count, liver problems, or changes in your cholesterol levels.

Every time you/your child get a new pack of Kevzara, it is important you note down the name of the medicine, the date of the administration and the batch number (which is on the packaging after "Lot") and keep this information in a safe place.

Children and adolescents
Kevzara is not recommended in children under 2 years of age.
Kevzara must not be given to children with pJIA weighing less than 10 kg.

Other medicines and Kevzara
Tell your doctor or pharmacist if you (or your child if they are the patient) are using, have recently used, or might use any other medicines.
This is because Kevzara can affect the way some other medicines work. Also some other medicines can affect the way Kevzara works.

In particular, do not use Kevzara and tell your doctor or pharmacist if you are using:
- a group of medicines called "Janus kinase (JAK) inhibitors" (used for disease like rheumatoid arthritis and cancer)
- other biological medicines used in the treatment of pJIA

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist.

Kevzara can affect the way some medicines work: this means the dose of other medicines may need changing. If you are using any of the following medicines, tell your doctor or pharmacist before using Kevzara:
- statins, used to reduce cholesterol level
- oral contraceptives
- theophylline, used to treat asthma
- warfarin, used to prevent blood clots

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist.

Pregnancy and breast-feeding
Talk to your doctor before using Kevzara if you are pregnant or breast feeding, think you may be pregnant or are planning to have a baby.
- Do not take Kevzara if you are pregnant – unless your doctor specifically recommends it.
- The effects of Kevzara on an unborn baby are not known.
- You and your doctor should decide if you should use Kevzara if you are breast-feeding.

Driving and using machines

The use of Kevzara is not expected to affect your ability to drive or use machines. However, if you/ your child are feeling tired or unwell after you use Kevzara, you/your child should not drive/ride a bicycle or use machines.

KEVZARA contains polysorbate 20
This medicine contains 2.28 mg of polysorbate 20 in each 1.14 ml of solution for injection which is equivalent to 2 mg/ml. Polysorbates may cause allergic reactions. Tell your doctor if you or your child have any known allergies.

3. How to use Kevzara

Treatment should be started by a doctor experienced in the diagnosis and treatment of pJIA.

Children with pJIA (aged 2 and over)
The usual dose of Kevzara depends on your weight.
- If you weigh 10 to less than 30 kg: the dose is 4 mg for every kilogram of body weight
- If you weigh 30 kg or more: the dose is 3 mg for every kilogram of body weight

The dose is calculated based on your body weight at each administration.

Kevzara is given as an injection under the skin (called "subcutaneous" injection).

How Kevzara vial will be given
- Kevzara will be given to you as an injection under the skin (called "subcutaneous injection") by a healthcare professional.
- The dose you will be given will depend on your body weight.

If you use more Kevzara than you should
If you have used more Kevzara than you should, talk to your doctor, pharmacist or nurse.

If you miss a dose of Kevzara
If it has been 3 days or less since the missed dose:
- inject your missed dose as soon as you can.
- then inject your next dose at your regular time.

If it has been 4 days or more, inject the next dose at your regular time. Do not inject a double dose to make up for a forgotten injection.
If you are unsure when to inject your next dose: ask your doctor, pharmacist or nurse for instructions.

If you stop using Kevzara
Do not stop using Kevzara without talking to your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

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

Serious side effect
Tell your doctor straight away if you think you have an **infection** (which may affect up to 1 in every 10 people). The symptoms may include fever, sweats, or chills.

Other side effects
Tell your doctor, pharmacist, or nurse if you notice any of the following side effects:

Children
Very common (may affect more than 1 in 10 people)
- infections in your sinuses or throat, blocked or runny nose and sore throat (upper respiratory tract infection, nasopharyngitis)
- low white blood cell counts shown by blood tests (neutropenia)
- injection-site reactions (including redness and itching).

Common (may affect up to 1 in 10 people)
- abnormal liver function tests (increased alanine aminotransferase)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist, or nurse. 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 Kevzara

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.
- Once taken out the refrigerator, do not store Kevzara above 25 ºC.
- Write down the date of removal from the refrigerator in the space provided on the outer carton.
- Use the vial within 14 days after taking it out of the refrigerator.
- Keep the vial in the original carton in order to protect from light.

Do not use this medicine if the solution in the vial is cloudy, discoloured or contains particles, or if any part of the vial looks damaged.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional is responsible for disposing of any unused product correctly. These measures will help protect the environment.

6. Contents of the pack and other information

What Kevzara contains
- The active substance is sarilumab. Each vial contains 270 mg sarilumab in 1.54 ml solution
- The other ingredients are arginine, histidine, polysorbate 20 (E 432), sucrose, and water for injections.

What Kevzara looks like and contents of the pack
Kevzara is a clear, colourless to pale yellow solution for injection that comes in a vial.

Each vial contains 1.54 ml of solution. Kevzara is available in a pack containing 2 vials.

Not all pack sizes may be marketed.

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