SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kevzara 175 mg/ml solution for injection

2QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial 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.

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.

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.

<u>Gastrointestinal perforation and diverticulitis</u>
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).

<u>Malignancies</u>

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 (E432)
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 co-administered 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 Yellow Card Scheme at:
www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 Medicines and Healthcare products Regulatory Agency (MHRA) 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 (E432)
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

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 vial (type 1 glass) containing 1.14 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

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

Aventis Pharma Ltd
410 Thames Valley Park Drive
Reading
Berkshire
RG6 1PT
UK

Trading as:

Sanofi
410 Thames Valley Park Drive
Reading
Berkshire
RG6 1PT
UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 04425/0912

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/06/2025

10 DATE OF REVISION OF THE TEXT

16/03/2026