▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – KEVZARA (SARILUMAB) PRE-FILLED PEN AND PRE-FILLED SYRINGE

1 NAME OF THE MEDICINE

sarilumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each syringe and pre-filled injection-pen delivers 1.14 mL (200 mg or 150 mg) of sarilumab. For the full list of excipients, see Section 6.1- LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Kevzara solution for subcutaneous administration is supplied as a sterile, colourless to pale yellow, preservative-free liquid solution of approximately pH 6.0. It is supplied in a single-dose pre-filled syringe and single use pre-filled pen.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Kevzara in combination with non-biological Disease-Modifying Anti-Rheumatic Drugs (DMARDs) or as monotherapy is indicated for the treatment of moderate to severe active Rheumatoid Arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs.

4.2 DOSE AND METHOD OF ADMINISTRATION

GENERAL CONSIDERATIONS WHEN PRESCRIBING

- treatment should be initiated by physicians knowledgeable in the diagnosis and management of RA, including experience in initiating treatment with biological therapies
- Kevzara subcutaneous injection is not intended for intravenous administration.
- the first dose of Kevzara must be administered under the supervision of a qualified healthcare professional, in a healthcare facility with necessary medical equipment, treatments and protocols sufficient to initiate the management of acute hypersensitivity reactions including anaphylaxis. The patient must be closely monitored during the injection and afterwards for a hypersensitivity reaction.

- Kevzara is intended for use under the guidance and supervision of the patient's treating physician. Patients and/or caregivers who have been trained on the preparation and administration of Kevzara according to the Instructions for use, may self-inject Kevzara if their treating physician determines that it is appropriate and is satisfied that the patient can safely self-inject in the home environment with medical follow-up if required.
- Do not initiate treatment with Kevzara in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 150,000 per mm^3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).
- The concurrent use of Kevzara with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators has not been studied. Avoid using Kevzara with biological DMARDs.
- In the absence of compatibility studies, this medicinal product must not be mixed with any other medicinal product.
- Instruct patients to inform a healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions [see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE].
- Product is for single use in one patient only. Discard any residue.

DOSAGE

Kevzara may be used as monotherapy or in combination with methotrexate (MTX) or other non-biological DMARDs as a subcutaneous injection.

The recommended dose of Kevzara is 200 mg once every 2 weeks given as a subcutaneous injection.

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 elevated liver enzymes.

If a patient develops a serious infection, interrupt treatment with Kevzara until the infection is controlled.

Recommended dosage modifications in case of neutropenia, thrombocytopenia or liver enzyme elevations:

Low Absolute Neutrophil Count (ANC) [see Section 4.4-SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5- PHARMACOLOGICAL PROPERTIES]

Lab Value (cells/mm^3)	Recommendation
ANC greater than 1000	Maintain current dose of KEVZARA
ANC 500-1000 (0.5-1 x 109/l)	Interrupt treatment with KEVZARA until >1000. KEVZARA can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
ANC less than 500	Discontinue KEVZARA

Low Platelet Count [see Section 4.4-SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5 PHARMACOLOGICAL PROPERTIES]	
Lab Value (cells/mm^3)	Recommendation
50,000-100,000	Interrupt treatment with KEVZARA until >100,000. KEVZARA can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.
Less than 50,000	If confirmed by repeat testing, discontinue KEVZARA

Liver Enzyme Abnormalities [seeSection 4.4-SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 5-PHARMACOLOGICAL PROPERTIES]	
Lab Value	Recommendation
ALT > 1 to ≤ 3 x ULN	Consider dose modification of concomitant DMARDs as clinically appropriate.
ALT > 3 to ≤ 5 x ULN	Hold treatment with KEVZARA until < 3 x ULN. KEVZARA 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	Discontinue KEVZARA

TRACEABILITY

To ensure the traceability of any biological medicinal products, the trade-name and batch number of the administered product should be clearly recorded in the patient medical record.

INSTRUCTIONS FOR PATIENTS

Advise the patients to read the Consumer Medicine Information (CMI) and Instructions for Use.

General information and Instruction on Injection Technique:

Kevzara may be injected into the thigh, abdomen or upper arm and should not be injected into skin that is tender, broken, bruised or scarred. Injection sites should be rotated with each injection.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Kevzara solution for subcutaneous administration should be clear and colourless to pale yellow. Instruct patients not to use if the solution is cloudy, discoloured or contains particles, or if any part of the pre-filled syringe or pen appears to be damaged.

Instruct patients and caregivers to read the Instructions for Use before the patient starts using Kevzara, and each time the patient gets a refill as there may be new information they need to know.

Provide guidance to patients and caregivers on proper subcutaneous injection technique, including aseptic technique, and how to use the pre-filled syringe or pen correctly (see Instructions for Use package insert).

To ensure proper use, after removing the pre-filled syringe from the refrigerator, allow the pre-filled syringe to sit at room temperature for 30 minutes prior to subcutaneous injection. After removing pen

from the refrigerator, allow the pen to sit at room temperature for 60 minutes prior to subcutaneous injection. Do not warm Kevzara in any other way.

Instruct patients to inject the full amount in the syringe or pen (1.14 mL), which provides 200 mg or 150 mg of Kevzara, according to the directions provided in the IFU.

The syringe or pen should be used within 14 days after being taken out of the refrigerator. If the syringe or pen is left out of refrigeration for more than 14 days, it must be discarded.

A puncture-resistant container for disposal of syringes or pens should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper pre-filled syringe or pen disposal, and caution against reuse of these items.

Missed Dose

If a dose of Kevzara 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.

Infections

Inform patients that Kevzara may lower their resistance to infections. Instruct patients to contact their physician immediately when symptoms suggesting infection appear, to ensure rapid evaluation and appropriate treatment.

Gastrointestinal Perforation

Inform patients that some patients, particularly those also taking NSAIDS, steroids and/or methotrexate, have had tears (perforations) of the stomach or intestines. Instruct patients to contact their physician immediately when symptoms of severe, persistent abdominal pain appear to ensure rapid evaluation and appropriate treatment.

4.3 CONTRAINDICATIONS

Kevzara is contraindicated in:

- patients with known hypersensitivity to sarilumab or to any of the excipients [see Section 4.8- ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].
- in patients with an active serious infection.[see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE]

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious Infections

Do not administer KEVZARA in patients with an active infection. [see Section 4.3- CONTRAINDICATIONS]

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 KEVZARA for rheumatoid arthritis (RA). The most frequently observed serious infections with Kevzara included pneumonia and cellulitis [see Section 4.8- ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Among opportunistic infections, tuberculosis, candidiasis, and pneumocystis were reported with Kevzara.

Some patients presented with disseminated rather than localized disease and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids, which in addition to RA may predispose them to infections. While not reported in Kevzara clinical studies, other serious infections (e.g., histoplasmosis, cryptococcus, aspergillosis) have been reported in patients receiving other immunosuppressive agents for the treatment of RA.

Do not administer Kevzara in patients with an active infection, including localized infections. Consider the risks and benefits of treatment prior to initiating Kevzara in patients who have:

- chronic or recurrent infection
- a history of serious or opportunistic infections
- 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

Closely monitor patients for the development of signs and symptoms of infection during treatment with Kevzara as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants. [see Section 4.2- DOSE AND METHOD OF ADMINISTRATION, Section 4.8-ADVERSE EFFECTS (UNDESIRABLE EFFECTS) , and Instructions for Patients package insert]. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

If a serious or an opportunistic infection develops, interrupt Kevzara until active infection is controlled.

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

Tuberculosis

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating and during treatment with Kevzara. Patients with latent tuberculosis should be treated with standard anti-mycobacterial therapy before initiating Kevzara. Consider anti-tuberculosis therapy prior to initiation of KEVZARA 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. 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

KEVZARA is not recommended in patients with HIV, hepatitis B infection, hepatitis C infection, or symptomatic EBV infection. Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster were observed in clinical studies with Kevzara. No cases of Hepatitis B reactivation were observed in the clinical trial; however patients who were at risk for reactivation were excluded.

Laboratory Abnormalities and Monitoring

Neutrophils

Treatment with Kevzara was associated with a higher incidence of decrease in absolute neutrophil count (ANC) including neutropenia. Decrease in ANC was not associated with higher incidence of infections, including serious infections. [see Section 4.8-ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]

Initiating treatment with Kevzara is not recommended in patients with a low neutrophil count, i.e., ANC less than 2000 per mm^3. In patients who develop an ANC less than 500 per mm3, discontinue treatment with KEVZARA.

Monitor neutrophil count prior to initiating therapy, 4 to 8 weeks after start of therapy and every 3 months thereafter [see Section 5-PHARMACOLOGICAL PROPERTIES]. For recommended dose modifications based on ANC results see Section 4.2-DOSE AND METHOD OF ADMINISTRATION.

Based on the pharmacodynamics of the changes in ANC [see Section 5-PHARMACOLOGICAL PROPERTIES], use results obtained at the end of the dosing interval when considering dose modification.

Platelet Count

Treatment with Kevzara was associated with a reduction in platelet counts in clinical studies. Reduction in platelets was not associated with bleeding events [see Section 4.8-ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Initiating treatment with Kevzara is not recommended in patients with a platelet count below 150,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3, discontinue treatment with Kevzara.

Monitor platelets prior to initiating therapy, 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommended dose modifications based on platelet counts [see Section 4.2-DOSE AND METHOD OF ADMINISTRATION].

Liver Enzymes

Treatment with Kevzara 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-ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with Kevzara.

Initiating treatment with Kevzara is not recommended in patients with elevated transaminases, ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT greater than 5x ULN, discontinue treatment with Kevzara [see Section 4.2-DOSE AND METHOD OF ADMINISTRATION].

Monitor ALT and AST levels prior to initiating therapy, 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-DOSE AND METHOD OF ADMINISTRATION].

Lipid Abnormalities

Lipid levels may be reduced in patients with chronic inflammation. Treatment with Kevzara was associated with increases in lipid parameters such as LDL cholesterol, HDL cholesterol and/or triglycerides [see Section 4.8- ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Assess lipid parameters approximately 4 to 8 weeks following initiation of treatment with Kevzara, then at approximately 6 month intervals.

Manage patients according to clinical guidelines for the management of hyperlipidemia

Hypersensitivity Reactions

Hypersensitivity reactions have been reported in association with KEVZARA [see Section 4.8-ADVERSE EFFECTS (UNDESIRABLE EFFECTS)]. Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions.

Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

If anaphylaxis or other hypersensitivity reaction occurs, stop administration of KEVZARA immediately.

Do not administer KEVZARA to patients with known hypersensitivity to sarilumab [see Section 4.3-CONTRAINDICATIONS and Section 4.8-ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Gastrointestinal Perforation

Events of gastrointestinal perforation have been reported in clinical studies, primarily as complications of diverticulitis. Use Kevzara with caution in patients who may be at increased risk for gastrointestinal perforation. GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Promptly evaluate patients presenting with new onset abdominal symptoms [see Section 4.8-ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Malignancies

Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with Kevzara on the development of malignancies is not known but malignancies were reported in clinical studies. In the 52-week placebo-controlled population, malignancies occurred at the same rate in patients receiving either Kevzara + DMARD or placebo + DMARD (1.0 events per 100 patient-years). In the long-term safety population, the rate of malignancies was consistent with the rate observed in the placebo-controlled period [see Section 4.8-ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Cardiovascular risk

RA patients have an increased risk for cardiovascular disorders and should have risk factors (e.g. hypertension, hyperlipidaemia) managed as part of usual standard of care (see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE– Lipid Parameters). Elevations in LDL and HDL lipids have been observed, with no clinical consequences identified. No data are available concerning cardiovascular outcomes with long-term use of Kevzara.

Use with other Biological Therapies including TNF-antagonists

The concurrent use of Kevzara with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators has not been studied. Avoid using Kevzara with biological DMARDs.

Vaccination

Avoid concurrent use of live vaccines during treatment with Kevzara 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 Kevzara. The interval between live vaccinations and initiation of Kevzara therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents [see Section 4.5- INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

Use in hepatic impairment

The safety and efficacy of Kevzara have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology.[see Section 4.4-SPECIAL WARNINGS AND PRECAUTIONS FOR USE]

Treatment with Kevzara is not recommended in patients with active hepatic disease or hepatic impairment [see Section 4.8- ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Use in renal impairment

No dose adjustment is required in patients with mild to moderate renal impairment.[see Section 4.2-DOSE and METHOD OF ADMINSTRATION]

Kevzara has not been studied in patients with severe renal impairment [see Section 5.2-PHARMACOKINETIC PROPERTIES].

Use in the elderly

Of the total number of patients in clinical studies of Kevzara [see Section 5.1-PHARMACODYNAMIC PROPERTIES- CLINICAL TRIALS], 15.0% were 65 years of age and over, while 1.6% were 75 years and over. In clinical studies, no overall differences in safety and efficacy were observed between older and younger patients. The frequency of serious infection among Kevzara and placebo-treated patients 65 years of age and older was higher than those under

the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

No dosage adjustment is required in patients over 65 years of age.

Paediatric use

Safety and efficacy of Kevzara has not been established in children under 18 years of age.

Effects on laboratory tests

No data available. [see also Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE -Laboratory Abnormalities and Monitoring]

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Use with other drugs for the Treatment of Rheumatoid Arthritis

Sarilumab exposure was not affected when coadministered with methotrexate (MTX). Kevzara has not been investigated in combination with JAK inhibitors or biological DMARDs such as TNF antagonists [see Section 4.2-DOSE AND METHOD OF ADMINISTRATION].

Interactions with CYP450 Substrates

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 and therefore have the potential to alter the pharmacokinetics of concomitantly administered drugs that are substrates of these enzymes. Elevated interleukin-6 (IL-6) concentration 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 signaling by IL-6Rα antagonists such as sarilumab might reverse the inhibitory effect of IL-6 and restore CYP activity, leading to altered drug 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 Kevzara, in patients being treated with CYP substrate medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., theophylline) and adjust the individual dose of the medicinal product as needed. The effect of KEVZARA on CYP450 enzyme activity may persist for several weeks after stopping therapy.

Caution should be exercised when Kevzara is co-administered with CYP3A4 substrates (e.g. oral contraceptives or statins) as there may be a reduction in exposure which may reduce the activity of the CYP3A4 substrate. In 17 patients with RA, one week following a single 200-mg SC administration of sarilumab, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively [see Section 5.2-PHARMACOKINETIC PROPERTIES].

Live Vaccines

Avoid concurrent use of live vaccines during treatment with Kevzara [see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy (Category C)

Kevzara may be used in combination with non-biological Disease Modifying Anti-Rheumatic Drugs (DMARDs). Non-biological Disease Modifying Anti-Rheumatic Drugs (DMARDs) may be contraindicated in pregnant women. Adequate and well controlled studies with Kevzara have not been conducted in pregnant women. In general, monoclonal antibodies are transported across the placenta with the largest amount transferred during the third trimester.

Women of childbearing potential must use effective contraception during and up to 3 months after treatment.

In animal reproduction studies, intravenous administration of sarilumab to cynomolgus monkeys from early gestation to natural birth (approximately 21 weeks) at weekly doses up to 50 mg/kg/week (approximately 84 times the human exposure based on AUC after subcutaneous doses of 200 mg every two weeks) did not affect embryo-fetal development.

In an enhanced pre-/postnatal developmental toxicity study, pregnant cynomolgus monkeys were administered sarilumab once-weekly intravenously at doses of 5, 15, or 50 mg/kg/week (approximately 84 times the human exposure based on AUC after subcutaneous doses of 200 mg every two weeks) from early gestation to natural birth (approximately 21 weeks). Sarilumab did not cause any maternal or embryo-foetal effects in the study. Slight increases of stillbirth ratio and total pregnancy loss were observed with high systemic cumulative exposure in the 50 mg/kg/week high-dose group (≥84 times human exposure) compared to vehicle control and lower-dose groups. Whilst the relationship between this finding and Kevzara has not been established, it cannot be excluded that this finding is related to Kevzara treatment.

Sarilumab had no effect on the neonates evaluated up to one 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 one month.

The potential effect of sarilumab on the infants' immune system function is not known.

The incidence of malformations and pregnancy loss in human pregnancies has not been established for Kevzara. However, all pregnancies, regardless of drug exposure, have a background rate of approximately 2 to 4% for major malformations and 15 to 20% for pregnancy loss. Kevzara should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

There is no information regarding the presence of sarilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Because monoclonal antibodies could be excreted in small amounts in human milk, a decision should be made whether to discontinue nursing or to discontinue Kevzara, taking into account the importance of the drug to the mother.

Kevzara may be used in combination with non-biological Disease Modifying Anti-Rheumatic Drugs (DMARDs). Non-biological Disease Modifying Anti-Rheumatic Drugs (DMARDs) may be contraindicated in breast-feeding women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of ability to drive and operate machinery after administration of sarilumab have been performed. Kevzara has no or negligible influence on the ability to drive or operate machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse events

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems (Australia).

Clinical Trials Experience

The safety of Kevzara in combination with DMARDs was evaluated based on data from seven studies, of which two were placebo-controlled, consisting of 2887 patients (long-term safety population). Of these, 2170 patients received Kevzara for at least 24 weeks, 1546 for at least 48 weeks, 1020 for at least 96 weeks, and 624 for at least 144 weeks.

All patients in the safety data described had moderately to severely active rheumatoid arthritis.

The two placebo-controlled studies were pooled to evaluate the safety of Kevzara + DMARD in comparison to placebo + DMARDs for up to 24 weeks in one study and 52 weeks in the other. In total, 1982 patients were evaluated (661 patients on 200 mg 660 patients on 150 mg, and 661 patients on placebo). The use of Kevzara monotherapy was assessed in two studies with a total of 467 patients, of which 402 received Kevzara 200 mg and 65 patients received Kevzara 150 mg.

The most common serious adverse reactions were infections [see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

The most frequent adverse reactions (occurring in at least 3% of patients treated with Kevzara in combination with DMARDs) observed with Kevzara in the clinical studies were neutropenia, increased ALT, injection site erythema, upper respiratory infections, and urinary tract infections.

In the 52-week placebo-controlled population, premature discontinuation due to adverse reactions occurred in 12.6%, 10.9% and 4.7% of patients treated with Kevzara 200 mg, Kevzara 150 mg, and placebo, respectively.

The most common adverse reactions (>1%) that resulted in discontinuation of therapy with Kevzara were neutropenia and increased ALT, which also included protocol requirements for discontinuation.

Table 1 - Adverse Events Occurring in 2% or More of Patients Administered 150 mg or 200 mg KEVZARA + DMARD and Greater Than Those Observed in Patients on Placebo + DMARD during the TEAE period (0-12 weeks) - Placebo-controlled safety population

		Sarilumab	
Primary System Organ Class Preferred Term	**Placebo + DMARD (N=661)**	**150 mg q2w + DMARD (N=660)**	**200 mg q2w + DMARD (N=661)**
Any class	278 (42.1%)	326 (49.4%)	350 (53.0%)
Infections and infestations	103 (15.6%)	118 (17.9%)	134 (20.3%)
Upper respiratory tract infection	16 (2.4%)	19 (2.9%)	21 (3.2%)
Nasopharyngitis	15 (2.3%)	18 (2.7%)	16 (2.4%)
Urinary tract infection	13 (2.0%)	16 (2.4%)	16 (2.4%)
Blood and lymphatic system disorders	12 (1.8%)	40 (6.1%)	77 (11.6%)
Neutropenia	1 (0.2%)	38 (5.8%)	64 (9.7%)
Metabolism and nutrition disorders	10 (1.5%)	27 (4.1%)	20 (3.0%)
Hypertriglyceridaemia	3 (0.5%)	16 (2.4%)	5 (0.8%)
Nervous system disorders	29 (4.4%)	27 (4.1%)	25 (3.8%)
Headache	15 (2.3%)	16 (2.4%)	11 (1.7%)
Gastrointestinal disorders	45 (6.8%)	36 (5.5%)	54 (8.2%)
Diarrhoea	13 (2.0%)	9 (1.4%)	15 (2.3%)
Musculoskeletal and connective tissue disorders	51 (7.7%)	23 (3.5%)	32 (4.8%)
Rheumatoid arthritis	15 (2.3%)	2 (0.3%)	9 (1.4%)
General disorders and administration site conditions	21 (3.2%)	53 (8.0%)	59 (8.9%)
Injection site erythema	4 (0.6%)	22 (3.3%)	20 (3.0%)
Investigations	25 (3.8%)	50 (7.6%)	50 (7.6%)
Alanine aminotransferase increased	9 (1.4%)	25 (3.8%)	28 (4.2%)
Injury, poisoning and procedural complications	46 (7.0%)	29 (4.4%)	42 (6.4%)
Accidental overdose	21 (3.2%)	16 (2.4%)	21 (3.2%)

*Pre-rescue (0-12 week) placebo controlled population

Medically relevant adverse reactions occurring at an incidence less than 2% in patients with rheumatoid arthritis treated with KEVZARA in controlled studies were oral herpes, thrombocytopenia, leukopenia, injection site pruritus, bronchitis, influenza and hypercholesterolaemia.

Overall Infections

In the 52-week placebo-controlled population, the rate of infections in the 200 mg and 150 mg Kevzara + DMARD group was 84.5 and 81.0 events per 100 patient-years, respectively, compared to 75.1 events per 100 patient-years in the placebo + DMARD group. The most commonly reported infections (5% to 7% of patients) were upper respiratory tract infections, urinary tract infections, and nasopharyngitis.

In the 52-week placebo-controlled population, 0.8% of patients (5 patients) treated with KEVZARA 200 mg + DMARD, 0.6% (4 patients) treated with KEVZARA 150 mg + DMARD and 0.5% (3 patients) treated with placebo + DMARD had an event of herpes zoster. (see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE- viral reactivation)

The overall rate of infections with Kevzara + DMARD in the long-term safety population was consistent with rates in the controlled periods of the studies.

A higher incidence of overall and infection related adverse events was experienced by patients weighing more than 100 kg.

Serious Infections

In the 52-week placebo-controlled population, the rate of serious infections in the 200 mg and 150 mg Kevzara + DMARD group was 4.3 and 3.0 events per 100 patient-years, respectively, compared to 3.1 events per 100 patient-years in the placebo + DMARD group.

In the long-term safety population, the rates of infections and serious infection (sarilumab any dose) 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

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

Gastrointestinal Perforation

In the 52-week placebo-controlled population, one patient on KEVZARA therapy experienced a gastrointestinal (GI) perforation (0.11 events per 100 patient-years). In the Kevzara+ DMARD long-term safety population, the rate of GI perforations was 0.14 events per 100 patient-years.

In the long-term safety population, the overall rate of GI perforation was consistent with rates in the controlled periods of the studies. Reports of GI perforation were primarily reported as complications of diverticulitis including lower GI perforation and abscess. Most patients who developed GI perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs),

corticosteroids, or methotrexate. The contribution of these concomitant medications relative to KEVZARA in the development of GI perforations is not known. There were no reports of gastrointestinal perforation in the Kevzara monotherapy population [see Section 4.4-SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Hypersensitivity Reactions

In the 52-week placebo-controlled population, the proportion of patients who discontinued treatment due to hypersensitivity reactions was higher among those treated with Kevzara (0.9% in 200 mg, 0.5% in 150 mg) than placebo (0.2%). The rate of discontinuations due to hypersensitivity in the long-term safety population was consistent with the placebo-controlled period. In the placebo-controlled population, 0.2% of the patients treated with Kevzara
200 mg q2w + DMARD reported serious adverse events of hypersensitivity reactions, and none from Kevzara 150 mg q2w + DMARD group. No cases of anaphylaxis were observed in clinical studies.

Injection Site Reactions

In the 52-week placebo-controlled population, injection site reactions were reported in 9.5% of patients receiving Kevzara 200 mg, 8% receiving Kevzara 150 mg, and 1.4% receiving placebo. These injection site reactions (including erythema and pruritus) were mild in severity for the majority of patients. Two patients on Kevzara (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 is prior to patients being permitted to switch from placebo to Kevzara.

Neutrophils

In the 12-week placebo-controlled population, decreases in neutrophil counts below 1000 per mm^3 occurred in 6.4% and 3.6% of patients in the 200 mg and 150 mg Kevzara + DMARD group, respectively, compared to no patients in the placebo + DMARD group. Decreases in neutrophil counts below 500 per mm^3 occurred in 0.8% and 0.6% of patients in the 200 mg and 150 mg Kevzara + DMARD groups, respectively. In patients experiencing a decrease in absolute neutrophil count (ANC), modification of treatment regimen such as interruption of Kevzara or reduction in dose resulted in an increase or normalization of ANC [see Section 4.2-DOSE AND METHOD OF ADMINISTRATION]. Decrease in ANC was not associated with higher incidence of infections, including serious infections.

In clinical trials, a numerically higher incidence of neutrophil counts below 1000 per mm^3 was observed in patients with weight <60 kg, however decrease in ANC was not associated with higher incidence of infections, including serious infections.

In the long-term safety population, neutrophil counts below 1000 per mm^3 cumulatively occurred in 11.2% and 6.9% of patients receiving the 200 mg and 150 mg dose respectively. Observations on neutrophil counts in the Kevzara + DMARD long-term safety population and the Kevzara monotherapy population were consistent with those seen in the placebo-controlled population.

Platelet Count

In the 12-week placebo-controlled population, decreases in platelet counts below 100,000 per mm^3 occurred in 1.1% and 0.6% of patients on 200 mg and 150 mg Kevzara + DMARD, respectively, compared to no patients on placebo + DMARD, without associated bleeding events.

In the Kevzara + DMARD long-term safety population and the Kevzara monotherapy population, the observations on platelet counts were consistent with what was seen in the placebo-controlled population [see Section 4.4- SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Liver Enzymes

Liver enzyme abnormalities in the 12-week placebo-controlled population (Kevzara + DMARD or placebo + DMARD) are summarized in Table 2. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as interruption of Kevzara or reduction in dose, resulted in decrease or normalization of liver enzymes [see Section 4.2-DOSE AND METHOD OF ADMINISTRATION]. 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-SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Table 2 - Incidence of Liver Enzyme Abnormalities in controlled clinical studies

	Placebo + DMARD N = 661	**Kevzara 150 mg + DMARD N = 660**	**Kevzara 200 mg + DMARD N = 661**	**Kevzara Monotherapy Any Dose N = 467**
AST				
>3x 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%

ULN = Upper Limit of Normal

Lipids

Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of Kevzara + DMARD in the placebo-controlled population. Increases were observed at this time point with no additional increases observed thereafter. Changes in lipid parameters from baseline to Week 4 are summarized below:

- Mean LDL increased by 0.32mmol/ L in the KEVZARA 150 mg every two weeks + DMARD group and 0.41 mmol/L in the KEVZARA 200 mg every two weeks + DMARD group.

- Mean triglycerides increased by 0.21mmol/L in the KEVZARA 150 mg every two weeks + DMARD group and 0.31 mmol/l in the KEVZARA 200 mg every two weeks + DMARD group.
- Mean HDL increased by 0.08 mmol/L in both the KEVZARA 150 mg every two weeks + DMARD and KEVZARA 200 mg every two weeks + DMARD groups.

In the Kevzara + DMARD long-term safety population and the Kevzara monotherapy population, the observations in lipid parameters were consistent with what was observed in the placebo-controlled clinical studies.

Immunogenicity

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

In the 52-week placebo-controlled population, 4.0% of patients treated with Kevzara 200 mg + DMARD, 5.6% of patients treated with Kevzara 150 mg + DMARD and 2.0% of patients treated with placebo + DMARD, exhibited an anti-drug antibody (ADA) response in the ADA assay. Positive responses in the neutralizing antibody (NAb) assay were detected in 1.0% of patients on Kevzara 200 mg, 1.6% of patients on Kevzara 150 mg and 0.2% of patients on placebo.

In the Kevzara monotherapy population, observations were consistent with the Kevzara + DMARD population.

ADA formation may affect pharmacokinetics of Kevzara. No correlation was observed between ADA development and either loss of efficacy or adverse events.

The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Kevzara with the incidence of antibodies to other products may be misleading.

Malignancies

In the 52-week placebo-controlled population, 9 malignancies (exposure-adjusted event rate of 1.0 event per 100 patient-years) were diagnosed in patients receiving Kevzara + DMARD compared to 4 malignancies in patients in the control group (placebo + DMARD (exposure-adjusted event rate of 1.0 event per 100 patient-years).

In the Kevzara + DMARD long-term safety population and the Kevzara monotherapy population, the rates of malignancies were consistent with the rate observed in the placebo-controlled population.

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. For further information on the management of overdose, contact the Poison Information Centre on 131126.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Kevzara is a human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6Rα and mIL-6Rα), and has been shown to inhibit IL-6-mediated signaling through these receptors. Sarilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

Sarilumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6Rα and mIL-6Rα), and inhibits IL-6-mediated signaling. 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 and play an important role in both the pathologic inflammation and joint destruction that are hallmarks of rheumatoid arthritis (RA).

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. The reduction of inflammation that occurs with IL-6 receptor blockade is associated with laboratory changes such as decrease in absolute neutrophil count (ANC) and elevation in lipids.

Pharmacodynamic Effects

Following single-dose subcutaneous administration of sarilumab 200mg and 150mg 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, absolute neutrophil counts decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline. Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in haemoglobin and serum albumin.

Clinical trials

The efficacy and safety of Kevzara were assessed in three randomized, double-blind, controlled multicenter studies (MOBILITY and TARGET were placebo-controlled studies and MONARCH was an active comparator controlled study) in patients older than18 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.

Table 3 provides key baseline activity measures in subjects that participated in the 2 pivotal trials.

Table 3 - Disease characteristics at baseline - Phase 3, placebo-controlled studies [MOBILITY (EFC11072 Part B, Cohort 2) and TARGET (EFC10832)]

	MOBILITY			TARGET		
	Placebo (N=398)	Sarilumab 150 mg q2w (N=400)	Sarilumab 200 mg q2w (N=399)	Placebo (N=181)	Sarilumab 150 mg q2w (N=181)	Sarilumab 200 mg q2w (N=184)
Years of RA Mean (SD)	9.05 (8.07)	9.51 (8.45)	8.57 (7.02)	12.04 (9.99)	11.55 (8.55)	12.68 (9.63)
Age (years) Mean (SD)	50.9 (11.2)	50.1 (11.9)	50.8 (11.8)	51.9 (12.4)	54.0 (11.7)	52.9 (12.9)
female	80.7 %	79.8%	84.5%	85.1%	78.5%	82.1%
Weight (kg) Mean (SD)	74.15 (17.27)	74.05 (18.54)	74.68 (19.72)	79.41 (21.3)	78.59 (22.04)	76.68 (21.25)
BMI (kg/m^2) Mean (SD)	28.126 (5.84)	28.04 (6.57)	28.57 (6.67)	30.24 (7.78)	29.14 (6.92)	29.21 (6.75)
Functional class						
I	11.8%	13.3%	10.5%	7.2%	11.0%	10.3%
II	68.8%	63.5%	69.4%	60.8%	55.2%	57.1%
III	19.3%	23.3 %	20.1%	32.0%	33.7%	32.6%
IV	0	0	0	0	0	0
RF positive	84.4%	87.1%	82.6%	78.9%	74.6%	72.9%
Anti-CCP positive	85.4%	90.2%	84.9%	83.3%	75.0%	76.1%
TJC (0-68) Mean (SD)	26.80 (13.75)	27.21 (14.15)	26.50 (14.46)	29.42 (14.54)	27.66 (15.57)	29.55 (15.54)
SJC (0-66) Mean (SD)	16.68 (9.30)	16.60 (8.96)	16.77 (9.68)	20.21 (11.34)	19.60 (11.23)	19.97 (11.94)
CRP (mg/L) Mean (SD)	20.46 (23.01)	22.57 (23.10)	22.23 (23.78)	26.02 (25.20)	23.60 (23.44)	30.77 (28.35)
HAQ-DI (0-3) Mean (SD)	1.61 (0.66)	1.63 (0.63)	1.69 (0.64)	1.80 (0.64)	1.72 (0.62)	1.82 (0.62)
DAS28-CRP Mean (SD)	5.93 (0.87)	5.95 (0.91)	5.97 (0.87)	6.23 (0.86)	6.09 (0.90)	6.29 (0.98)
CDAI (0-76) Mean (SD)	40.60 (11.95)	40.45 (12.51)	40.40 (12.33)	44.17 (12.27)	42.53 (12.89)	44.11 (13.93)
mTSS (0-448) Mean (SD)	47.74 (63.78)	54.64 (64.95)	44.99 (56.31)	NA	NA	NA

CCP= cyclic citrullinated peptide; CDAI=Clinical disease Activity Index; CRP=C-reactive protein; DAS=Disease activity Score; HAQ-DI=Health assessment Questionnaire - Disability Index; mTSS=modified Total Sharp Score; NA=not available; RF=rheumatoid factor NA=not available; SD=standard deviation; SJC=Swollen Joint Count; TJC=Tender Joint Count.

RF (Rheumatoid Factor) positive: ≥15 IU/mL; Anti-Cyclic Citrullinated Peptide (CCP) positive: ≥17 IU/mL

Placebo-controlled Studies

The MOBILITY study evaluated 1197 patients with moderately to severely active rheumatoid arthritis who had inadequate clinical response to methotrexate (MTX). Patients received subcutaneous Kevzara 200 mg, Kevzara 150 mg, or placebo every 2 weeks with concomitant MTX. After Week 16, patients with an inadequate response could have been rescued with KEVZARA 200 mg every two weeks. 67.7% of patients who received the 200 mg dose and 67.5% of patients who received the 150 mg dose completed the double-blind period, compared to 49.2% in the placebo group. The primary endpoints were the proportion of Kevzara 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. The key secondary endpoint was a major clinical response (defined as ACR70 response maintained for 24 weeks).

The TARGET study evaluated 546 patients with moderately to severely active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF-α antagonists. Patients received subcutaneous Kevzara 200 mg, Kevzara 150 mg, or placebo every 2 weeks with a concomitant non-biological DMARDs. After Week 12, patients with an inadequate response could have been rescued with KEVZARA 200 mg every two weeks. 72.3% of patients who received the 200 mg dose and 69.1% % of patients who received the 150 mg dose completed the double-blind period, compared to 55.8 % in the placebo group. The primary endpoints were the proportion of Kevzara 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 KEVZARA+MTX/DMARD-treated patients achieving ACR20, 50 and 70 responses in Studies 1 and 2 are shown in Table 4. In both studies, patients treated with either 200 mg or 150 mg of KEVZARA +MTX/DMARD every two weeks had higher ACR20, ACR50, and ACR70 response rates versus placebo-treated patients at Week 24.

Table 4 - Clinical Response at Weeks 12, 24 and 52 in Placebo-Controlled MOBILITY and TARGET studies in adults with moderate to severely active RA *

	Percentage of Patients					
	MOBILITY MTX Inadequate Responders			TARGET TNF Inhibitor Inadequate Responders		
	Placebo + MTX N=398	KEVZARA 150 mg + MTX N=400	KEVZARA 200 mg + MTX N=399	Placebo + DMARD(s) † N=181	KEVZARA 150 mg + DMARD(s) † N=181	KEVZARA 200 mg + DMARD(s) † N=184
ACR20						
Week 12	34.7%	54.0%	64.9%	37.6%	54.1%	62.5%
Difference from placebo, (95% CI) ‡		19.4% (12.6%, 26.1%)	30.2% (23.6%, 36.8%)		16.6% (6.7%, 26.5%)	25.3% (15.7%, 34.8%)
Week 24 §	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
Difference from placebo, (95% CI) ‡		24.6% (18.0%, 31.3%)	33.0% (26.5%, 39.5%)		22.1% (12.6%, 31.6%)	27.4% (17.7%, 37.0%)

Week 52	31.7%	53.5%	58.6%			
Difference from placebo, (95% CI) ‡		21.9% (15.2%, 28.5%)	27.0% (20.5%, 33.6%)	NA¶	NA¶	NA¶
ACR50						
Week 12	12.3%	26.5%	36.3%	13.3%	30.4%	33.2%
Difference from placebo, (95% CI) ‡		14.2% (8.9%, 19.6%)	24.1% (18.4%, 29.8%)		17.1% (9.2%, 25.1%)	20.1% (12.0%, 28.3%)
Week 24	16.6%	37.0%	45.6%	18.2%	37.0%	40.8%
Difference from placebo, (95% CI) ‡		20.4% (14.5%, 26.3%)	29.1% (23.0%, 35.1%)		18.8% (10.2%, 27.4%)	22.8% (14.0%, 31.6%)
Week 52	18.1%	40.0%	42.9%			
Difference from placebo, (95% CI) ‡		21.9% (15.8%, 28.0%)	24.8% (18.7%, 30.9%)	NA¶	NA¶	NA¶
ACR70						
Week 12	4.0%	11.0%	17.5%	2.2%	13.8%	14.7%
Difference from placebo, (95% CI) ‡		7.0% (3.4%, 10.6%)	13.5% (9.4%, 17.7%)		11.6% (6.2%, 17.0%)	12.5% (7.1%, 17.9%)
Week 24	7.3%	19.8%	24.8%	7.2%	19.9%	16.3%
Difference from placebo, (95% CI) ‡		12.5% (7.8%, 17.1%)	17.5% (12.6%, 22.5%)		12.7% (6.1%, 19.3%)	9.2% (2.8%, 15.7%)
Week 52	9.0%	24.8%	26.8%			
Difference from placebo, (95% CI) ‡		15.7% (10.6%, 20.8%)	17.8% (12.6%, 23.0%)	NA¶	NA¶	NA¶
Major clinical response#						
Responders	3.0%	12.8%	14.8%	NA¶	NA¶	NA¶
Difference from placebo, (95% CI) ‡		9.7% (6.1%, 13.4%)	11.8% (7.9%, 15.6%)			
DAS28-CRP < 2.6Þ						
Week 12						
Percentage of patients	4.8%	18.0%	23.1%	3.9%	17.1%	17.9%
Difference from placebo (95% CI) ‡		13.3% (9.0%, 17.5%)	18.3% (13.7%, 23.0%)		13.3% (7.3%, 19.3%)	14.1% (8.0%, 20.3%)
Week 24						
Percentage of patients	10.1%	27.8%	34.1%	7.2%	24.9%	28.8%
Difference from placebo (95% CI) ‡		17.7% (12.5%, 23.0%)	24.0% (18.5%, 29.5%)		17.7% (10.5%, 24.9%)	21.7% (14.3%, 29.1%)

[*] Patients who were rescued or discontinued were considered non-responders for the analyses included in this table. In Study 1, at week 52, 196, 270, and 270 patients remained on placebo, KEVZARA 150 mg, and KEVZARA 200 mg respectively.
[†] DMARDs in Study 2 included MTX, sulfasalazine, leflunomide, and/or hydroxychloroquine
[‡] Weighted estimate of the rate difference; CI=confidence interval
[§] Primary end point
[¶] NA=Not Applicable as Study 2 was a 24-week study
[#] Major clinical response = ACR70 for at least 24 consecutive weeks during the 52-week period.
[Þ] Patients with DAS28-CRP < 2.6 may have active joints

In the MOBILITY study higher ACR20 response rates were observed within 2 weeks compared to placebo and were maintained over the 52-week study (Figure 1and Figure 2)

Figure 1 - Percent of ACR20 Response by Visit for MOBILITY

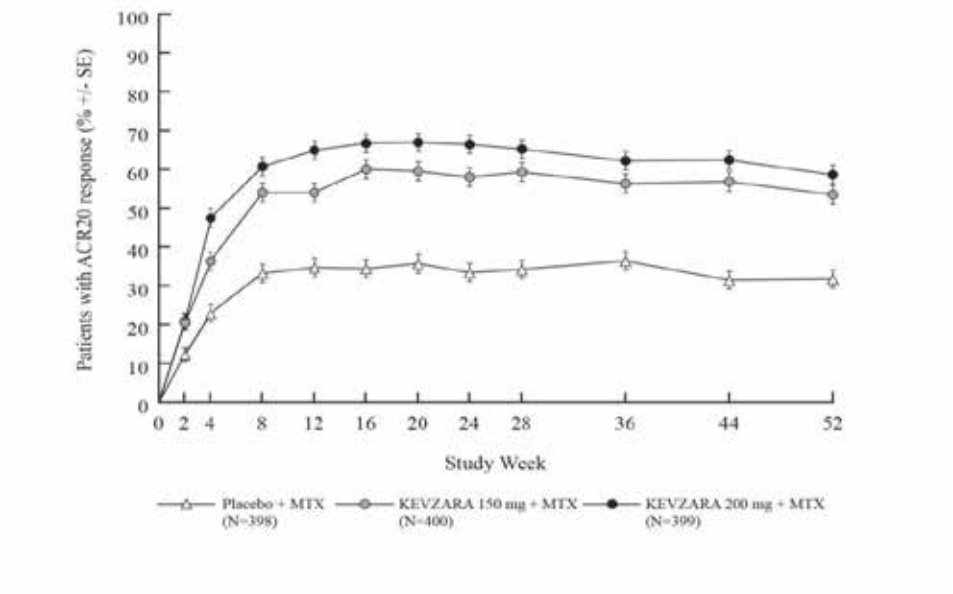
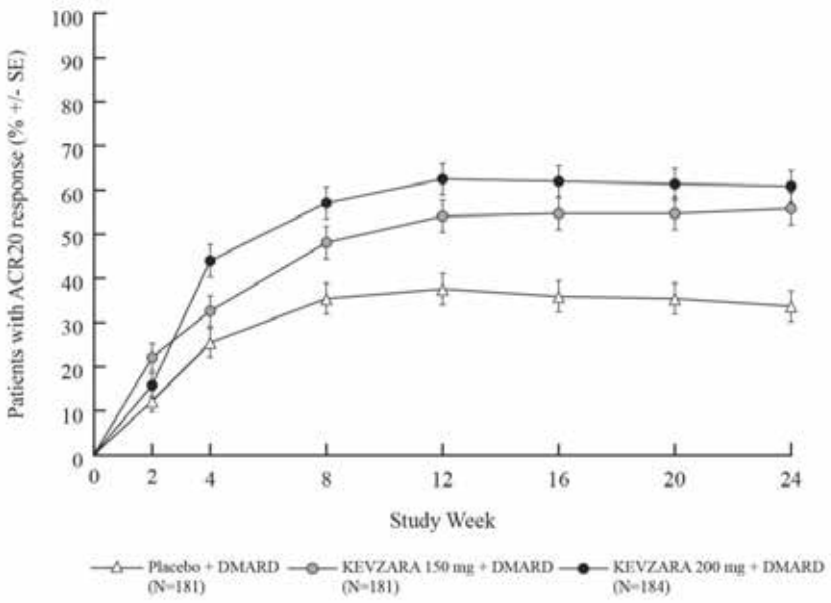


Figure 2 - Percent of ACR20 Response by Visit for TARGET



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

Table 5 - Mean change from baseline in components of ACR score at Week 12 (prior to rescue) in adults with moderate to severe active RA

	MOBILITY			TARGET		
Component means (range/units)	Placebo + MTX (N=398)	KEVZARA 150 mg + MTX (N=400)	KEVZARA 200 mg + MTX (N=399)	Placebo + DMARD (N=181)	KEVZARA 150 mg + DMARD (N=181)	KEVZARA 200 mg + DMARD (N=184)
Tender Joints (0-68)						
Baseline	26.80	27.21	26.50	29.42	27.66	29.55
Week 12	16.25	12.88	11.78	19.18	13.38	13.10
Change from baseline	-10.51	-14.42	-14.94	-9.79	-14.11	-15.92
Swollen Joints (0-66)						
Baseline	16.68	16.60	16.77	20.21	19.60	19.97
Week 12	9.66	7.50	6.79	12.50	8.82	8.28
Change from baseline	-7.02	-9.03	-10.12	-7.25	-10.77	-10.89
Pain VAS* (0-100 mm)						
Baseline	63.71	65.48	66.71	71.57	71.02	74.86
Week 12	49.25	41.47	36.93	54.77	43.45	41.66
Change from baseline	-14.45	-23.73	-29.77	-16.12	-27.95	-32.77
Physician global VAS* (0-100 mm)						
Baseline	62.86	63.43	63.59	68.39	68.10	67.76
Week 12	39.25	31.32	28.47	43.73	33.65	30.18
Change from baseline	-23.63	-31.85	-34.84	-24.60	-34.92	-36.92
Patient global VAS* (0-100 mm)						
Baseline	63.70	64.43	66.49	68.77	67.71	70.89
Week 12	49.37	41.52	38.05	53.67	41.99	41.74
Change from baseline	-13.92	-22.88	-28.39	-15.05	-26.05	-28.83
HAQ-DI (0-3)						
Baseline	1.61	1.63	1.69	1.80	1.72	1.82
Week 12	1.34	1.15	1.13	1.49	1.23	1.33
Change from baseline	-0.27	-0.47	-0.57	-0.29	-0.50	-0.49
CRP (mg/L)						
Baseline	20.46	22.57	22.23	26.02	23.60	30.77
Week 12	19.61	9.24	3.30	21.72	9.21	4.58

	MOBILITY			TARGET		
Change from baseline	-0.58	-13.59	-18.31	-3.39	-14.24	-25.91

* VAS=visual analog scale

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 Kevzara + MTX were superior to placebo + MTX in the change from baseline in mTSS at 24 and 52 weeks (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 Kevzara + MTX was associated with significantly less radiographic progression of structural damage as compared with placebo. At Week 52, 55.6% of patients receiving Kevzara 200 mg and 47.8% of patients receiving Kevzara 150 mg had no progression of structural damage (as defined by a change in the Total Sharp Score of zero or less) compared with 38.7% of patients receiving placebo.

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

Table 6 - Mean Radiographic Change from Baseline at Weeks 24 and Week 52 in MOBILITY

	MOBILITY MTX Inadequate Responders		
	Placebo + MTX (N = 398)	'TM' 150 mg q2w* + MTX (N = 400)	'TM' 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†††

	MOBILITY MTX Inadequate Responders		
	Placebo + MTX (N = 398)	'TM' 150 mg q2w* + MTX (N = 400)	'TM' 200 mg q2w* + MTX (N = 399)
* q2w=every two weeks † p-value <0.01 †† p-value <0.001 ††† p-value <0.0001 ‡ Primary end point			

Physical Function Response

Sarilumab has been shown to improve physical function. In both the MOBILITY and TARGET studies, physical function and disability were assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI). Patients receiving Kevzara 200 mg and 150 mg + MTX/DMARD 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 (mean change of-0.58, -0.54 and -0.30 for Kevzara 200 mg + MTX, Kevzara 150 mg + MTX and placebo + MTX, every two weeks, respectively). TARGET demonstrated significant improvement in HAQ-DI scores at Week 12 compared to placebo (mean change of -0.49, -0.50 and -0.29 for Kevzara 200 mg + DMARD, Kevzara 150 mg + DMARD and placebo + DMARD, 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 Kevzara 200 mg + MTX, Kevzara 150 mg + MTX, and placebo + MTX treatment groups, respectively).

Patients treated with Kevzara + 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 Studies 1 and 2. Patients receiving KEVZARA 200 mg every two weeks + MTX/DMARD demonstrated greater improvement from baseline compared to placebo + MTX/DMARD in the physical component summary (PCS) at Week 24, but there was no evidence of a difference between the treatment groups in the mental component summary (MCS) at Week 24. Patients receiving KEVZARA 200 mg + MTX/DMARD 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.

Active Comparator-controlled Study

MONARCH was a 24 –week randomized double-blind, double-dummy study that compared Kevzara 200 mg monotherapy with adalimumab 40 mg monotherapy administered subcutaneously every two weeks in 369 patients with moderate to severe RA who were inappropriate for treatment with MTX including those who were intolerant of or inadequate responders to MTX.

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

Table 7 - Efficacy results for MONARCH

	Adalimumab 40 mg q2w* (N=185)	**Kevzara 200 mg q2w (N=184)**
DAS28-ESR (primary endpoint) (LSM (SE) 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 (LSM (SE) 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
LSM (SE) = least square mean (standard error)

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The pharmacokinetics of sarilumab were characterized in 2186 patients with RA treated with sarilumab which included 751 patients treated with 150 mg and 891 patients treated with 200 mg SC doses every two weeks for up to 52 weeks. The median t_{max} was observed in 2 to 4 days.

At steady state, exposure over the dosing interval measured by area under curve (AUC) increased 2-fold with an increase in dose from 150 to 200 mg every two weeks. Steady state was reached in 14 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 (± SD) steady-state AUC, C_{min} and C_{max} of sarilumab were 210 ± 115 mg.day/L, 6.95± 7.60mg/L, and 20.4± 8.27 mg/L, respectively.

For the 200mg 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± 13.5mg/L, and 35.4± 13.9-mg/L, respectively.

In a usability study sarilumab exposure after 200 mg Q2W was slightly higher (Cmax + 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.

Metabolism

The metabolic pathway of sarilumab has not been characterized. 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.

Excretion

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 a terminal concentration-dependent half-life of 2 to 4 days.

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 area under the curve (AUC) increased approximately 2-fold with a 1.33-fold increase in dose from 150 to 200 mg every two weeks.

Pharmacokinetics in Specific Populations

Population pharmacokinetic analyses in adult patients with RA showed that age, gender and race did not meaningfully influence the pharmacokinetics of sarilumab. Decrease in body weight resulted in an increase in sarilumab exposure, while an increase in body weight resulted in a decrease in sarilumab exposure. No dose adjustments are recommended for any of these demographics.

Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of sarilumab was conducted.

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 dosage adjustment is required in patients with mild to moderate renal impairment. Patients with severe renal impairment were not studied.

CYP450 Substrates

Simvastatin is a CYP3A4 substrate. In 17 patients with RA, one week following a single 200-mg SC administration of sarilumab, exposure of simvastatin and simvastatin acid decreased by 45% and 36%, respectively [see Section 4.5-INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS]

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The mutagenic potential of sarilumab has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

Carcinogenicity

No long-term animal studies have been performed to establish the carcinogenic potential of sarilumab.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each pre-filled syringe and pre-filled injection pen contains:

8.94 mg arginine hydrochloride, 3.71 mg histidine, 2.28 mg polysorbate 20, 57 mg sucrose, and water for Injections, USP.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Refrigerate at 2◦C to 8◦C. Do not freeze.

The pre-filled syringe or pen should not be exposed to heat or direct sunlight. Protect from light by storage in the original carton until time of use.

6.5 NATURE AND CONTENTS OF CONTAINER

All presentations 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 is available as:

Single use pre-filled syringe delivering 150mg per 1.14 mL of Kevzara (131.6 mg/mL) in packs of 2.

Single use pre-filled injection syringe delivering 200mg per 1.14 mL of Kevzara (175 mg/mL) in packs of 2.

Single use pre-filled pen delivering 150mg per 1.14 mL of Kevzara (131.6 mg/mL) in packs of 2.

Single use pre-filled pen delivering 200mg per 1.14 mL of Kevzara (175 mg/mL) in packs of 2.

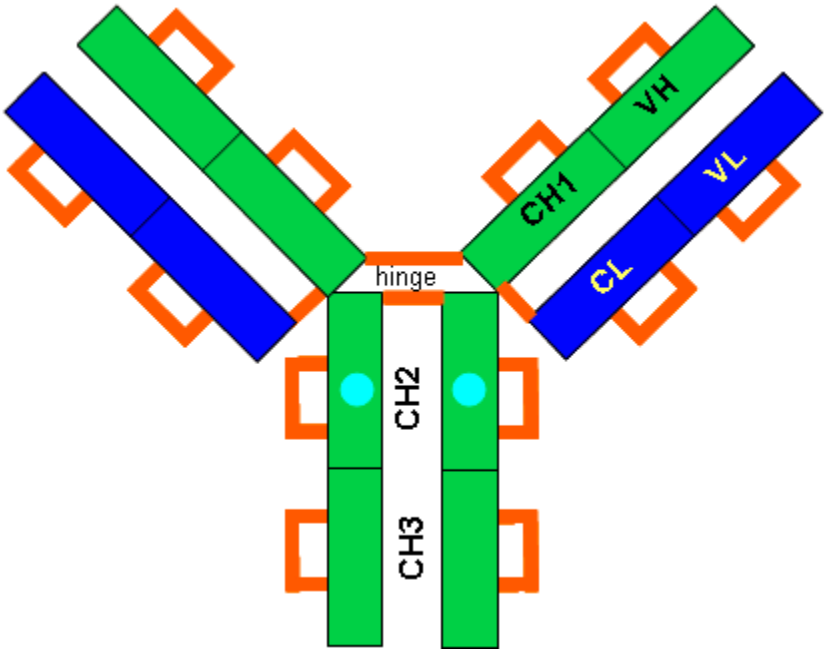
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Sarilumab is a covalent heterotetramer consisting of two disulfide linked human heavy chains, each covalently linked through disulfide bonds to a human kappa light chain. The sarilumab heavy chain has an IgG1 isotype constant region with a single N-linked glycosylation site, located within the constant region in the Fc portion of the molecule. The variable domains of the heavy and light chains combine to form the IL-6Rα binding site within the antibody.

structure



CAS number

1189541-98-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd

12-24 Talavera Road

Macquarie Park. NSW 2113

9 DATE OF FIRST APPROVAL

14 September 2018

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
