

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

<sup>Pr</sup>**KEVZARA**<sup>TM</sup>

sarilumab

solution for subcutaneous injection  
150 mg/1.14 mL or 200 mg/1.14 mL solution in a single-dose pre-filled syringe

interleukin-6 (IL-6) receptor antagonist

**KEVZARA (sarilumab) should be prescribed and supervised by physicians who are experienced in the use of biologics in the management of patients with moderate to severe rheumatoid arthritis and who have fully familiarized themselves with the efficacy and safety profile of KEVZARA.**

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Pr**KEVZARA**<sup>TM</sup>

sarilumab

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients</b>
Subcutaneous injection	Injection: single-dose pre-filled syringe •200 mg/1.14 mL •150 mg/1.14 mL	Arginine, histidine, polysorbate 20, sucrose and water for injection. <i>For a complete listing see Dosage Forms, Composition and Packaging section</i>

**DESCRIPTION**

KEVZARA<sup>TM</sup> (sarilumab) is a fully human IgG1 monoclonal antibody that binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R $\alpha$  and mIL-6R $\alpha$ ), and has been shown to inhibit IL-6-mediated signaling through these receptors.

**INDICATIONS AND CLINICAL USE**

KEVZARA (sarilumab) is indicated in the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more biologic or non-biologic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) (See PART II: CLINICAL TRIALS).

**Geriatrics (> 65 years of age):**

No overall differences in efficacy were observed between older and younger patients.

**Pediatrics (<18 years of age):**

Efficacy of KEVZARA has not been studied in children less than 18 years of age.

## CONTRAINDICATIONS

KEVZARA is contraindicated in patients with known hypersensitivity to sarilumab or to any of the excipients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING Section.

## WARNINGS AND PRECAUTIONS

### SERIOUS WARNINGS AND PRECAUTIONS

Patients treated with KEVZARA are at increased risk for developing serious infections that may lead to hospitalization or death (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS Sections). Opportunistic infections have also been reported in patients receiving KEVZARA. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Do not administer KEVZARA to patients with an active infection.

Patients should be tested for tuberculosis before treatment with KEVZARA. Treatment for latent tuberculosis infection should be initiated prior to KEVZARA use (see WARNINGS AND PRECAUTIONS Section).

Patients should be closely monitored for signs and symptoms of infection during treatment with KEVZARA. If a serious infection develops, interrupt KEVZARA until the infection is controlled.

The risks and benefits of treatment with KEVZARA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

### Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents for rheumatoid arthritis (RA). The most frequently observed serious infections with KEVZARA included pneumonia and cellulitis (see ADVERSE REACTIONS Section). 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 traveled to areas of endemic tuberculosis or endemic mycoses.

Closely monitor patients for the development of signs and symptoms of infection during treatment with KEVZARA (see ADVERSE REACTIONS and DOSAGE AND ADMINISTRATION Sections).

Hold treatment with KEVZARA if a patient develops a serious infection or an opportunistic infection.

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 treatment with KEVZARA. Patients with latent tuberculosis should be treated with standard antimycobacterial 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***

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

### ***Monitoring and Laboratory Tests***

#### ***Neutrophils***

Treatment with KEVZARA was associated with a higher incidence of decrease in absolute neutrophil count (ANC). Decrease in ANC was not associated with higher incidence of infections, including serious infections.

- Initiating treatment with KEVZARA is not recommended in patients with a low neutrophil count, i.e., ANC less than  $2 \times 10^9/L$ . In patients who develop an ANC less than  $0.5 \times 10^9/L$ , discontinue treatment with KEVZARA.
- Monitor neutrophil count 4 to 8 weeks after start of therapy and approximately every 3 months thereafter (see ACTION AND CLINICAL PHARMACOLOGY Section). For recommended dose modifications based on ANC results see DOSAGE AND ADMINISTRATION Section.
- Based on the pharmacodynamics of the changes in ANC (see ACTION AND CLINICAL PHARMACOLOGY Section), 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 ADVERSE REACTIONS Section).

- Initiating treatment with KEVZARA is not recommended in patients with a platelet count below  $150 \times 10^9/L$ . In patients who develop a platelet count less than  $50 \times 10^9/L$ , discontinue treatment with KEVZARA.
- Monitor platelets 4 to 8 weeks after start of therapy and approximately every 3 months thereafter. For recommended dose modifications based on platelet counts see DOSAGE AND ADMINISTRATION Section.

#### 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 ADVERSE REACTIONS Section). Increased frequency and magnitude of these elevations were observed when potentially hepatotoxic medications (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  $1.5 \times ULN$ . In patients who develop elevated ALT greater than  $5 \times ULN$ , discontinue treatment with KEVZARA (see DOSAGE AND ADMINISTRATION Section).
- Monitor ALT and AST levels 4 to 8 weeks after start of therapy and approximately every 3 months thereafter. When clinically indicated, consider other liver function tests such as bilirubin. For recommended dose modifications based on transaminases see DOSAGE AND ADMINISTRATION Section.

#### 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 ADVERSE REACTIONS Section).

- 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.

### **Gastrointestinal**

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis. Use KEVZARA with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms (see ADVERSE REACTIONS Section).

### **Hepatic**

Treatment with KEVZARA is not recommended in patients with active hepatic disease or hepatic impairment (see *Special Populations*, and ADVERSE REACTIONS Section).

### **Immunosuppression**

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 (see ADVERSE REACTIONS Section).

### **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 DRUG INTERACTIONS Section).

### ***Special Populations***

#### **Pregnant Women:**

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

KEVZARA is generally used in combination with disease-modifying antirheumatic drugs (DMARDs). Product monographs for certain DMARDs, such as methotrexate, recommend discontinuation when a patient becomes pregnant, therefore KEVZARA should also be discontinued (see the Special Populations section of the product monograph of concomitant medication).

#### ***Risk Summary***

No studies have been conducted with KEVZARA in pregnant women and relevant data from clinical use are very limited. A total of 9 pregnancies were reported during the clinical trials with the following outcomes: 4 miscarried in the first trimester (ie, spontaneous abortion, missed abortion, blighted ovum); 2 of these subjects had a prior history of spontaneous or unspecified abortions; 4 delivered a healthy infant; and one (who had been on concomitant MTX) delivered a full-term infant diagnosed at birth with pneumonia. The infant recovered after a course of parenteral antibiotics, although no organism was identified.

Monoclonal antibodies are transported across the placenta with the largest amount transferred during the third trimester. Studies in cynomolgus monkeys demonstrated that sarilumab crosses the placental barrier. The potential effect of sarilumab on the infant's immune system function is not known. Humoral immune response (IgG) to antigen challenge was suppressed in adult cynomolgus monkeys receiving  $\geq 5$  mg/kg sarilumab weekly by intravenous administration, suggesting the potential for KEVZARA to impact maternal and infant immune response.

No embryotoxicity or developmental effects were observed in a combined embryo-fetal and pre-postnatal development study exposing pregnant cynomolgus monkeys to sarilumab by intravenous administration from early gestation through parturition up to dose levels of 50 mg/kg weekly. Maternal exposure levels (AUC) were approximately 84 times higher than would be expected clinically.

Fertility was not affected in CD-1 mice receiving a murine surrogate against IL-6R $\alpha$  by subcutaneous injection up to dose levels of 100 mg/kg twice weekly. In females, compound-related microscopic findings were observed in the uterus. At least one implantation site with degeneration was observed microscopically in the uterus of 1/24, 2/24 and 6/24 mice receiving 0, 25 and 100 mg/kg respectively.

The clinical relevance of these findings is not known (See Part II: Toxicology).

The incidence of malformations and pregnancy loss in human pregnancies has not been established for KEVZARA.

KEVZARA should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### *Pregnancy Exposure Registry*

There is a registry that monitors pregnancy outcomes in women exposed to KEVZARA during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972

#### **Nursing Women:**

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 medication to the mother.

#### **Pediatrics (< 18 years of age):**

Safety and efficacy of KEVZARA have not been established in children less than 18 years of age.

#### **Geriatrics (>65 years of age):**

Of the total number of patients in clinical studies of KEVZARA (see CLINICAL TRIALS), 15.0% were 65 years of age and over, while 1.6% were 75 years and over. In clinical trials, 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.

### **Hepatic Impairment**

The safety and efficacy of KEVZARA have not been studied in patients with hepatic impairment, including patients with positive Hepatitis B virus (HBV) and Hepatitis C virus (HCV) serology (see WARNINGS AND PRECAUTIONS Section).

### **Renal Impairment**

No dose adjustment is required in patients with mild to moderate renal impairment. KEVZARA has not been studied in patients with severe renal impairment (see ACTION AND CLINICAL PHARMACOLOGY Section).

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

#### **Clinical Trial Adverse Drug Reactions**

*Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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

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.

The 52-week placebo-controlled population includes patients from one Phase 2 study of 12 week duration and two Phase 3 efficacy studies (one of 24 week duration and the other of 52 week duration). In this population, 661 patients, 660 patients, and 661 patients received KEVZARA 200 mg, KEVZARA 150 mg, or placebo once every two weeks, respectively, in combination with DMARDs.

The 12-week placebo-controlled population includes patients from the two Phase 3 efficacy studies from weeks 0 to 12 and was used to assess common adverse events and laboratory

abnormalities prior to patients being permitted to switch from placebo to KEVZARA. In this population, 582 patients, 579 patients, and 579 patients received KEVZARA 200 mg, KEVZARA 150 mg, or placebo once every two weeks, respectively, in combination with DMARDs.

The most common serious adverse reactions were infections (see WARNINGS AND PRECAUTIONS Section).

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, and upper respiratory 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.

The use of KEVZARA as monotherapy was assessed in 132 patients, of which 67 received KEVZARA 200 mg and 65 patients received KEVZARA 150 mg without concomitant DMARDs. The safety profile was generally consistent with that in the population receiving concomitant DMARDs.

### 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.

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.

### 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 overall rate of serious infections was consistent with rates in the controlled periods of the studies. The most frequently observed serious infections included pneumonia and cellulitis. Cases of opportunistic infection have been reported (see WARNINGS AND PRECAUTIONS Section).

### 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 long-term safety population, the overall rate of GI perforation was consistent with that seen in the placebo-controlled clinical 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 relative contribution of these concomitant medications versus KEVZARA in the development of GI perforations is not known (see WARNINGS AND PRECAUTIONS Section).

### 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 that seen in the placebo-controlled clinical studies.

No cases of anaphylaxis were observed in the placebo-controlled trials or in the long-term safety population.

### Injection Site Reactions

In the 12-week placebo-controlled population, injection site reactions were reported in 6.0% of patients receiving KEVZARA 200 mg, 4.7% receiving KEVZARA 150 mg, and 0.9% receiving placebo. These injection site reactions (including erythema and pruritus) were mild in severity for the majority of patients and necessitated medication discontinuation in 2 (0.2%) patients receiving KEVZARA.

### Laboratory Abnormalities

#### *Neutrophils*

In the 12-week placebo-controlled population, decreases in neutrophil counts below 1000/ $\mu$ L occurred in 5.9% and 4.0% 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 / $\mu$ L occurred in 0.7% of patients in both 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 DOSAGE AND ADMINISTRATION Section). Decrease in ANC was not associated with higher incidence of infections, including serious infections.

In the long-term safety population, the observations on neutrophil counts were consistent with those seen in the placebo-controlled clinical studies (see WARNINGS AND PRECAUTIONS Section).

*Platelet count*

In the 12-week placebo-controlled population, decreases in platelet counts below  $100 \times 10^9/L$  occurred in 1.2% and 0.7% of patients on 200 mg and 150 mg KEVZARA + DMARD, respectively, compared to no patients on placebo + DMARD, without associated bleeding events.

In the long-term safety population, the observations on platelet counts were consistent with those seen in the placebo-controlled clinical studies (see WARNINGS AND PRECAUTIONS Section).

*Liver Enzymes*

Liver enzyme abnormalities in the 12-week placebo-controlled population (KEVZARA + DMARD or placebo + DMARD) are summarized in Table 1. In the monotherapy population the incidence of transaminase elevation in the KEVZARA group was lower than that in the DMARD treatment group. 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 DOSAGE AND ADMINISTRATION Section). 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 WARNINGS AND PRECAUTIONS Section).

**Table 1 : Incidence of Liver Enzyme Abnormalities in the Phase 3 Placebo-Controlled Efficacy Population through Week 12**

	<b>Placebo + DMARDs N=579</b>	<b>KEVZARA 150 mg + DMARDs N=579</b>	<b>KEVZARA 200 mg + DMARDs N=582</b>
<b>AST</b>			
>ULN – 3x ULN	13.3%	25.1%	28%
>3x ULN – 5x ULN	0%	1.4%	1.0%
>5x ULN	0%	0.7%	0.2%
<b>ALT</b>			
>ULN – 3x ULN	23.1%	36.2%	41.6%
>3x ULN – 5x ULN	0.7%	2.9%	2.8%
>5x ULN	0%	1.2%	0.7%

ULN = Upper Limit of Normal

### *Lipids*

Lipid parameters (LDL, HDL, and triglycerides) were first assessed at 4 weeks following initiation of KEVZARA + DMARDs in the placebo-controlled population. At Week 4 the mean LDL increased by 0.36 mmol/L; mean triglycerides increased by 0.26 mmol/L; and mean HDL increased by 0.08 mmol/L. After Week 4 no additional increases were observed. There were no meaningful differences between doses.

In the long-term safety population, the observations in lipid parameters were consistent with those observed in the placebo-controlled clinical trials.

### *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. Neutralizing antibodies (NAb) 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 patients treated with KEVZARA monotherapy, 9.2% of patients exhibited an ADA response with 6.9% of patients also exhibiting NAbs. Prior to administration of KEVZARA, 2.3% of patients exhibited an ADA response.

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, 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 that in the placebo-controlled clinical studies (see WARNINGS AND PRECAUTIONS Section).

*Other Adverse Reactions*

**Table 2: Adverse Reactions Occurring in 1% or More of Patients Administered Placebo + DMARD, 150 mg KEVZARA + DMARD, or 200 mg KEVZARA + DMARD**

Primary System Organ Class Preferred Term	Placebo + DMARD (N=579)	KEVZARA	
		150 mg q2w + DMARD (N=579)	200 mg q2w + DMARD (N=582)
Any class	242 (41.8%)	287 (49.6%)	306 (52.6%)
Infections and infestations	92 (15.9%)	106 (18.3%)	120 (20.6%)
Upper respiratory tract infection	13 (2.2%)	17 (2.9%)	18 (3.1%)
Urinary tract infection	11 (1.9%)	15 (2.6%)	15 (2.6%)
Nasopharyngitis	12 (2.1%)	16 (2.8%)	14 (2.4%)
Sinusitis	5 (0.9%)	6 (1.0%)	11 (1.9%)
Bronchitis	7 (1.2%)	4 (0.7%)	10 (1.7%)
Oral herpes	0	4 (0.7%)	10 (1.7%)
Pharyngitis	9 (1.6%)	6 (1.0%)	9 (1.5%)
Influenza	9 (1.6%)	5 (0.9%)	8 (1.4%)
Gastroenteritis	6 (1.0%)	5 (0.9%)	6 (1.0%)
Blood and lymphatic system disorders	12 (2.1%)	38 (6.6%)	67 (11.5%)
Neutropenia	1 (0.2%)	36 (6.2%)	55 (9.5%)
Leukopenia	0	4 (0.7%)	11 (1.9%)
Thrombocytopenia	0	3 (0.5%)	6 (1.0%)
Anaemia	7 (1.2%)	0	1 (0.2%)
Metabolism and nutrition disorders	8 (1.4%)	26 (4.5%)	20 (3.4%)
Hypercholesterolaemia	0	6 (1.0%)	5 (0.9%)
Hypertriglyceridaemia	3 (0.5%)	15 (2.6%)	5 (0.9%)
Psychiatric disorders	6 (1.0%)	9 (1.6%)	11 (1.9%)
Insomnia	6 (1.0%)	4 (0.7%)	3 (0.5%)
Nervous system disorders	27 (4.7%)	24 (4.1%)	23 (4.0%)
Headache	13 (2.2%)	13 (2.2%)	10 (1.7%)
Dizziness	6 (1.0%)	2 (0.3%)	6 (1.0%)
Vascular disorders	15 (2.6%)	8 (1.4%)	13 (2.2%)
Hypertension	7 (1.2%)	4 (0.7%)	11 (1.9%)
Gastrointestinal disorders	39 (6.7%)	31 (5.4%)	49 (8.4%)
Diarrhoea	13 (2.2%)	7 (1.2%)	13 (2.2%)
Nausea	10 (1.7%)	7 (1.2%)	5 (0.9%)

Primary System Organ Class Preferred Term	Placebo + DMARD (N=579)	KEVZARA	
		150 mg q2w + DMARD (N=579)	200 mg q2w + DMARD (N=582)
Musculoskeletal and connective tissue disorders	44 (7.6%)	22 (3.8%)	30 (5.2%)
Rheumatoid arthritis	14 (2.4%)	2 (0.3%)	9 (1.5%)
General disorders and administration site conditions	16 (2.8%)	43 (7.4%)	50 (8.6%)
Injection site erythema	4 (0.7%)	20 (3.5%)	19 (3.3%)
Injection site pruritus	1 (0.2%)	11 (1.9%)	9 (1.5%)
Investigations	23 (4.0%)	46 (7.9%)	47 (8.1%)
Alanine aminotransferase increased	9 (1.6%)	22 (3.8%)	26 (4.5%)
Aspartate aminotransferase increased	2 (0.3%)	2 (0.3%)	7 (1.2%)
Transaminases increased	2 (0.3%)	8 (1.4%)	5 (0.9%)
Injury, poisoning and procedural complications	37 (6.4%)	24 (4.1%)	32 (5.5%)
Accidental overdose	14 (2.4%)	13 (2.2%)	17 (2.9%)
Fall	7 (1.2%)	3 (0.5%)	3 (0.5%)

## **DRUG INTERACTIONS**

### **Use with Other Medications for Treatment of Rheumatoid Arthritis**

Sarilumab exposure was not affected when coadministered with methotrexate (MTX), KEVZARA has not been investigated in combination with Janus kinase (JAK) inhibitors or biological DMARDs such as Tumor Necrosis Factor (TNF) antagonists (see DOSAGE AND ADMINISTRATION Section).

### **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 medication that are substrates of these enzymes. Elevated interleukin-6 (IL-6) concentration may down-regulate CYP activity in patients with RA and hence increase drug levels compared to subjects without RA. Blockade of IL-6 signaling by IL-6R $\alpha$  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.

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 (see ACTION AND CLINICAL PHARMACOLOGY Section).

### **Live Vaccines**

Avoid concurrent use of live vaccines during treatment with KEVZARA (see WARNINGS AND PRECAUTIONS Section).

### ***Drug-Drug Interactions***

#### **Cytochrome P450 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.



## DOSAGE AND ADMINISTRATION

Continuing therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

### Dosing Considerations

KEVZARA should be used in combination with methotrexate (MTX) or other traditional DMARDs.

KEVZARA may be given as monotherapy in cases of intolerance or contraindication to methotrexate or DMARDs.

### Recommended Dose and Dosage Adjustment

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 (see WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS Section).

If a patient develops a serious infection, hold treatment with KEVZARA until the infection is controlled.

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

<b>Low Absolute Neutrophil Count (ANC) (see WARNINGS AND PRECAUTIONS, and ACTION AND CLINICAL PHARMACOLOGY Section).</b>	
<b>Lab Value (cells/L)</b>	<b>Recommendation</b>
<b>ANC greater than <math>1 \times 10^9/L</math></b>	<b>Maintain current dose of KEVZARA</b>
<b>ANC <math>0.5-1 \times 10^9/L</math></b>	<b>Hold treatment with KEVZARA until <math>&gt;1 \times 10^9/L</math>. KEVZARA can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.</b>
<b>ANC less than <math>0.5 \times 10^9/L</math></b>	<b>Discontinue KEVZARA</b>

<b>Low Platelet Count</b> (see WARNINGS AND PRECAUTIONS Section).	
<b>Lab Value (cells/<math>\mu</math>L)</b>	<b>Recommendation</b>
<b>50-100 x 10<sup>3</sup>/<math>\mu</math>L</b>	<b>Hold treatment with KEVZARA until &gt;100 x 10<sup>3</sup>/<math>\mu</math>L. KEVZARA can then be resumed at 150 mg every 2 weeks and increased to 200 mg every 2 weeks as clinically appropriate.</b>
<b>Less than 50 x 10<sup>3</sup>/<math>\mu</math>L</b>	<b>If confirmed by repeat testing, discontinue KEVZARA</b>

<b>Liver Enzyme Abnormalities</b> (see WARNINGS AND PRECAUTIONS Section).	
<b>Lab Value</b>	<b>Recommendation</b>
<b>ALT &gt; 1 to <math>\leq</math> 3 x ULN</b>	<b>Consider dose modification of concomitant DMARDs as clinically appropriate.</b>
<b>ALT &gt; 3 to <math>\leq</math> 5 x ULN</b>	<b>Hold treatment with KEVZARA until &lt; 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.</b>
<b>ALT &gt; 5 x ULN</b>	<b>Discontinue KEVZARA</b>

### ***Renal impairment***

No dose adjustment is required in patients with mild to moderate renal impairment. KEVZARA has not been studied in patients with severe renal impairment.

### **Missed Dose**

Patients who miss a dose of KEVZARA and for whom it has been 3 days or less since the missed dose should be advised to take their dose as soon as they can. The next dose should be taken at the regularly scheduled time. If it has been 4 days or more, or if the patient is unsure when to take their next dose of KEVZARA, they should be advised to call their healthcare provider for instructions.

### **Administration**

#### **General Considerations for Administration**

Do not initiate treatment with KEVZARA in patients with an absolute neutrophil count (ANC) below  $2 \times 10^9/L$ , platelet count below  $150 \times 10^3/\mu L$ , 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.

#### **Preparation and Administration Instructions**

KEVZARA subcutaneous injection is not intended for intravenous administration.

KEVZARA is intended for use under the guidance of a healthcare professional. A patient may self-inject KEVZARA or the patient's caregiver may administer KEVZARA. Provide proper training to patients and/or caregivers on the preparation and administration of KEVZARA prior to use according to the Instructions for Use (IFU).

To ensure proper use, allow the pre-filled syringe to sit at room temperature for 30 minutes prior to subcutaneous injection. Do not warm KEVZARA in any other way.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEVZARA solution for subcutaneous administration should be clear and colorless to pale yellow. Do not use if the solution is cloudy, discolored or contains particles, or if any part of the pre-filled syringe appears to be damaged.

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

Rotate injection sites with each injection. Do not inject into skin that is tender, damaged, or has bruises or scars.

## **OVERDOSAGE**

During the clinical development program, 2 patients were administered 400 mg of sarilumab within a 24-hour period. Neither patient experienced any adverse event or laboratory abnormalities (i.e., ANC, LFTs, and lipids were within normal range) as a consequence.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Sarilumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R $\alpha$  and mIL-6R $\alpha$ ), and inhibits IL-6-mediated signaling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as migration and activation of T-cells, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. Local production of IL-6 by synovial and endothelial cells in joints affected in chronic inflammatory disease, such as rheumatoid arthritis (RA), may play an important role in development of the inflammatory processes.

### **Pharmacodynamics**

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 rheumatoid arthritis, absolute neutrophil counts decreased to the nadir between 3 to 4 days and thereafter recovered towards baseline (see WARNINGS AND PRECAUTIONS

Section). Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in hemoglobin and serum albumin.

## **Pharmacokinetics**

### **Absorption:**

The pharmacokinetics of sarilumab were characterized by population pharmacokinetic analysis in 1770 patients with RA treated with sarilumab which included 631 patients treated with 150 mg and 682 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 ( $\pm$  SD) steady-state AUC,  $C_{\min}$  and  $C_{\max}$  of sarilumab were  $202 \pm 120$  mg·day/L,  $6.35 \pm 7.54$  mg/L, and  $20.0 \pm 9.20$  mg/L, respectively.

For the 200-mg every two weeks dose regimen, the estimated mean ( $\pm$  SD) steady-state AUC,  $C_{\min}$  and  $C_{\max}$  of sarilumab were  $395 \pm 207$  mg·day/L,  $16.5 \pm 14.1$  mg/L, and  $35.6 \pm 15.2$  mg/L, respectively.

### **Distribution:**

In patients with RA, the apparent volume of distribution at steady state was 7.3 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.

### **Elimination:**

Sarilumab is eliminated by parallel linear and non-linear pathways, depending on concentrations: 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 28 and 43 days, respectively. Monoclonal antibodies are not eliminated via renal or hepatic pathways.

Population pharmacokinetic analyses in patients with RA revealed that there was a trend toward

higher apparent clearance of sarilumab in the presence of anti-sarilumab antibodies. No dose adjustment is recommended.

### ***Special Populations and Conditions***

Population pharmacokinetic analyses in adult patients with rheumatoid arthritis showed that age, gender and race did not meaningfully influence the pharmacokinetics of sarilumab. Although bodyweight influenced pharmacokinetics of sarilumab, no dose adjustments are recommended for any of these demographics.

### **Hepatic Insufficiency:**

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

### **Renal Insufficiency:**

No formal study of the effect of renal impairment on the pharmacokinetics of sarilumab was conducted. Based on population pharmacokinetic analysis of data in patients with RA, 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.

## **STORAGE AND STABILITY**

Do not use KEVZARA beyond the expiration date printed on the container. Refrigerate at 2°C to 8°C (36°F to 46°F). Do not freeze.

Protect from light by storage in the original carton until time of use.

## **SPECIAL HANDLING INSTRUCTIONS**

KEVZARA is supplied in a single-dose pre-filled syringe. After removing the pre-filled syringe from the refrigerator it should be allowed to reach room temperature by waiting for 30 minutes before injecting KEVZARA.

The syringe should not be exposed to heat or direct sunlight.

Use the syringe within 14 days after removing from the refrigerator. If the syringe is left out of refrigeration for more than 14 days, it must be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If visibly opaque particles, discoloration or other foreign particles are observed, the solution should not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

In the absence of compatibility studies, KEVZARA must not be mixed with other medicinal products.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

KEVZARA solution for subcutaneous administration is supplied as a sterile, colorless to pale yellow, preservative-free liquid solution of approximately pH 6.0., Each pre-filled syringe delivers 1.14 mL (200 mg or 150 mg) of KEVZARA in a solution containing arginine (45 mM), histidine (21 mM), polysorbate 20 (0.2% w/v), sucrose (5% w/v) and water for injection.

The components of the prefilled syringe are latex free (including the needle cap).

Package: Two pre-filled syringes of 150 or 200 mg per carton.

## **PART II: SCIENTIFIC INFORMATION**

### **PHARMACEUTICAL INFORMATION**

#### **Product Characteristics**

Sarilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

KEVZARA 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-6R $\alpha$  binding site within the antibody.

KEVZARA has a molecular weight of approximately 144 kDa.

## CLINICAL TRIALS

### Study demographics and trial design

The efficacy and safety of KEVZARA were assessed in two randomized, double-blind, placebo-controlled multicenter studies (MOBILITY and TARGET) in patients older than 18 years with moderately to severely active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline.

One study, MOBILITY Part B, evaluated 1197 patients with moderately to severely active rheumatoid arthritis who had inadequate clinical response to methotrexate (MTX). Part B was a 52-week study, intended to confirm the efficacy and safety of the 2 dose regimens (150 mg q2w and 200 mg q2w) selected from the 12-week, dose-ranging part of the study (Part A). Only results from Part B, the confirmatory phase are described. Patients received subcutaneous KEVZARA 200 mg, KEVZARA 150 mg, or placebo every 2 weeks with concomitant MTX. All patients continued to receive MTX throughout the study. Starting at Week 16, patients with a lack of efficacy, defined as less than 20% improvement compared to baseline in swollen joints count (SJC) or tender joints count (TJC) for 2 consecutive visits, or any other clear lack of efficacy based on Investigator judgment could discontinue the randomized treatment and receive open-label KEVZARA at 200mg. The maximum duration of the study per patient was up to 52 weeks for treatment.

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).

Patient age ranged from 18 to 75 years, with a mean of 51 years. The majority of patients were female (82%). At baseline, the mean number of tender and swollen joints at baseline was 27 and 17 respectively.

Another study, TARGET, was a 24-week randomized, double-blind, placebo-controlled parallel group study which evaluated 546 patients with moderately to severely active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF- $\alpha$  antagonists. Patients received subcutaneous KEVZARA 200 mg, KEVZARA 150 mg, or placebo every 2 weeks with a concomitant traditional DMARD. The primary objective was to assess the clinical benefit of KEVZARA compared to placebo in moderate to severe active RA patients with an inadequate efficacy response (after at least 3 consecutive months of treatment) and/or intolerance of 1 or more TNF  $\alpha$  antagonists, when administered with background non-biologic DMARD treatment. The study was stratified by geographic region and the number of prior TNF  $\alpha$  antagonists used. Patients enrolling in the study were requested to continue treatment with at least one of the permitted background therapies that included MTX, sulfasalazine, leflunomide, and hydroxychloroquine. The overall study treatment duration was 24 weeks. After 12 weeks of blinded dosing, all patients in the study who had not shown a clinically meaningful improvement in their disease (defined as less than a 20% improvement from baseline in either SJC or TJC for



two joint assessments that were at least 4 weeks apart) were offered the opportunity to receive open-label treatment with KEVZARA in an ongoing long-term safety study.

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.

Patient age ranged from 19 to 88 years, with a mean of 53 years. The majority of patients were female (82%). At baseline, the mean number of tender and swollen joints at baseline was 29 and 20 respectively.

**Table 3 - Summary of trial design and patient demographics**

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age ± SD (Range)	Gender
MOBILITY, Part B <sup>a</sup>	Phase 3, MTX-IR, R, DB, PC, rescue <sup>b</sup> at 16 weeks MTX as concomitant therapy	Placebo, SAR 150 mg, SAR 200 mg. Subcutaneous. 52 weeks	SAR 150 mg q2w (400) SAR 200 mg q2w (399) Placebo (398) N = 1197	50.8 years ± 11.7 (18-75)	81.7% female, 18.3% male
TARGET	Phase 3, TNF-IR <sup>c</sup> , R, DB, PC, rescue <sup>d</sup> at 12 weeks DMARDs <sup>e</sup> as concomitant therapy	Placebo, SAR 150 mg, SAR 200 mg. Subcutaneous. 24 weeks	SAR 150 mg q2w (181) SAR 200 mg q2w (184) Placebo (181) N=546	52.9 years ± 12.4 (19-88)	81.9% female, 18.1% male

DB=double-blind; DMARD=disease-modifying antirheumatic drug; MTX=methotrexate; MTX-IR=inadequate response to methotrexate; PC=placebo-controlled; qw=once weekly; q2w=every two weeks; R=randomized; SAR=KEVZARA; TNF=tumor necrosis factor

- MOBILITY, was conducted as a seamless Phase 2/3 study. Part B was the Phase 3 study.
- Patients with an inadequate response were rescued with open-label sarilumab 200 mg q2w.
- Patients with a history of IR to or intolerant of TNF-antagonists were also allowed to enroll.
- Patients with an inadequate response were allowed to be rescued with open-label sarilumab 200 mg q2w.
- Concomitant DMARDs: MTX, sulfasalazine, leflunomide, or hydroxychloroquine.

## Study results

### Clinical Response

The percentages of KEVZARA+MTX/DMARD-treated patients achieving ACR20, ACR50, and ACR70 responses in MOBILITY Part B and TARGET 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 response rates versus placebo-treated patients at Week 24.

**Table 4 - Clinical Response at Weeks 12, 24 and 52 in Placebo-Controlled Studies  
MOBILITY Part B and TARGET**

	Percentage of Patients					
	MOBILITY Part B <sup>b,c</sup>			TARGET <sup>b,c,d</sup>		
	MTX Inadequate Responders			TNF Inhibitor Inadequate Responders		
	Placebo + MTX N = 398	KEVZARA 150 mg + MTX N = 400	KEVZARA 200 mg + MTX N = 399	Placebo + DMARD <sup>a</sup> N = 181	KEVZARA 150 mg + DMARD <sup>a</sup> N = 181	KEVZARA 200 mg + DMARD <sup>a</sup> N = 184
<b>ACR20</b>						
<b>Week 12</b>	34.7%	54.0%	64.9%	37.6%	54.1%	62.5%
Difference from placebo, (97.5% CI)		19.4% (11.7%, 27.0%)	30.2% (22.7%, 37.8%)		16.6% (5.3%, 27.9%)	25.3% (14.3%, 36.2%)
<b>Week 24<sup>e</sup></b>	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
Difference from placebo, (97.5% CI)		24.6% (17.0%, 32.2%)	33.0% (25.5%, 40.5%)		22.1% (11.2%, 33.0%)	27.4% (16.4%, 38.4%)
P-value vs placebo		<0.0001	<0.0001		<0.0001	<0.0001
<b>Week 52</b>	31.7%	53.5%	58.6%	NA <sup>f</sup>	NA <sup>f</sup>	NA <sup>f</sup>
Difference from placebo, (97.5% CI)		21.9% (14.3%, 29.4%)	27.0% (19.5%, 34.6%)			
<b>ACR50</b>						
<b>Week 12</b>	12.3%	26.5%	36.3%	13.3%	30.4%	33.2%
Difference from placebo, (97.5% CI)		14.2% (8.1%, 20.3%)	24.1% (17.6%, 30.6%)		17.1% (8.0%, 26.2%)	20.1% (10.9%, 29.4%)
<b>Week 24</b>	16.6%	37.0%	45.6%	18.2%	37.0%	40.8%
Difference from placebo, (97.5% CI)		20.4% (13.7%, 27.2%)	29.1% (22.1%, 36.0%)		18.8% (9.0%, 28.6%)	22.8% (12.8%, 32.8%)
P-value vs placebo		<0.0001	<0.0001		<0.0001	<0.0001
<b>Week 52</b>	18.1%	40.0%	42.9%	NA <sup>f</sup>	NA <sup>f</sup>	NA <sup>f</sup>
Difference from placebo, (97.5% CI)		21.9% (15.0%, 28.8%)	24.8% (17.8%, 31.8%)			
<b>ACR70</b>						
<b>Week 12</b>	4.0%	11.0%	17.5%	2.2%	13.8%	14.7%
Difference from placebo, (97.5% CI)		7.0% (2.8%, 11.1%)	13.5% (8.8%, 18.3%)		11.6% (5.5%, 17.7%)	12.5% (6.3%, 18.7%)

Percentage of Patients						
	MOBILITY Part B <sup>b,c</sup>			TARGET <sup>b, c, d</sup>		
	MTX Inadequate Responders			TNF Inhibitor Inadequate Responders		
	Placebo + MTX N = 398	KEVZARA 150 mg + MTX N = 400	KEVZARA 200 mg + MTX N = 399	Placebo + DMARD <sup>a</sup> N = 181	KEVZARA 150 mg + DMARD <sup>a</sup> N = 181	KEVZARA 200 mg + DMARD <sup>a</sup> N = 184
<b>Week 24</b>	7.3%	19.8%	24.8%	7.2%	19.9%	16.3%
Difference from placebo, (97.5% CI)		12.5% (7.2%, 17.8%)	17.5% (11.9%, 23.2%)		12.7% (5.1%, 20.3%)	9.2% (1.9%, 16.6%)
P-value vs placebo		<0.0001	<0.0001		0.0002	0.0050
<b>Week 52</b>	9.0%	24.8%	26.8%			
Difference from placebo, (97.5% CI)		15.7% (9.9%, 21.5%)	17.8% (11.9%, 23.7%)	NA <sup>f</sup>	NA <sup>f</sup>	NA <sup>f</sup>
<b>Major clinical response<sup>g</sup></b>						
Responders	3.0%	12.8%	14.8%	NA <sup>f</sup>	NA <sup>f</sup>	NA <sup>f</sup>
Difference from placebo, (97.5% CI)		9.7% (5.5%, 13.9%)	11.8% (7.4%, 16.2%)			
P-value vs placebo		<0.0001	<0.0001			
<b>DAS28-CRP &lt; 2.6</b>						
<b>Week 24</b>						
Responders	10.1%	27.8%	34.1%	7.2%	24.9%	28.8%
Difference from placebo (97.5% CI)		17.7% (11.7%, 23.7%)	24.0% (17.8%, 30.3%)		17.7% (9.5%, 25.9%)	21.7% (13.2%, 30.2%)
P-value vs placebo		<0.0001	<0.0001		<0.0001	<0.0001

<sup>a</sup> DMARDs in TARGET included MTX, sulfasalazine, leflunomide and hydroxychloroquine

<sup>b</sup> Mantel-Haenszel test, stratified by geographic region and prior use of biologic DMARD (Mobility-B) or number of prior anti-TNF drugs (TARGET). Each dose group was compared to placebo at the 2.5% significance level, and a hierarchical testing procedure was used to control the Type I error rate for the multiple endpoints.

<sup>c</sup> Patients that received rescue treatment or discontinued double blind treatment for other reasons were considered non-responders. In MOBILITY-B the number (%) of patients considered non-responders at or before Week 24 was 144 (36.2%), 86 (21.5%) and 78 (19.5%) in the placebo, 150mg and 200mg groups respectively.

In TARGET the number (%) of patients considered non-responders at or before Week 24 was 79 (43.6%), 54(29.8%) and 47(25.5%) in the placebo, 150mg and 200mg groups respectively.

<sup>d</sup> In TARGET the number of patients receiving methotrexate as part of the background treatment was 158 (87.3%), 154 (85.1%), 156 (84.8%) in the placebo, 150mg and 200mg groups respectively.

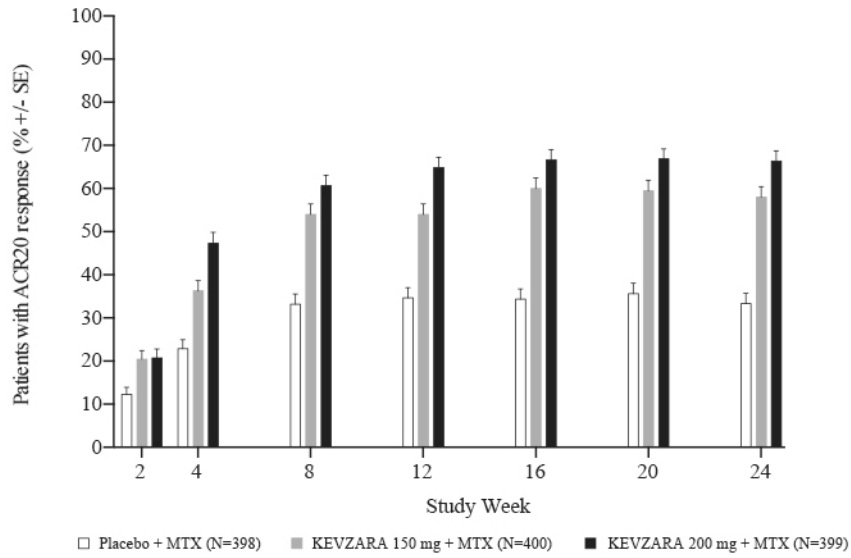
<sup>e</sup> Primary end point

<sup>f</sup> NA=Not Applicable as TARGET was a 24-week study

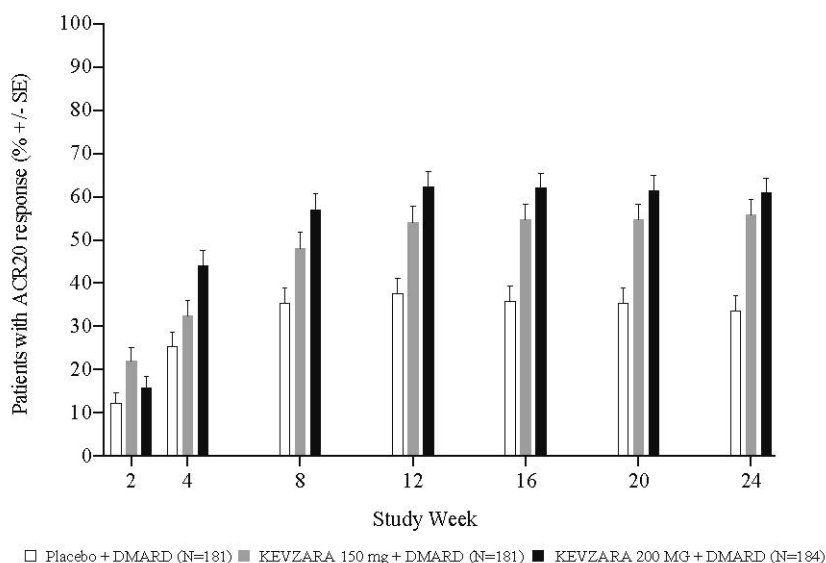
<sup>g</sup> Major clinical response is defined as the event of achieving and maintaining ACR70 for at least 24 consecutive weeks during the 52-week period.

ACR20 response rates by visit for MOBILITY Part B and TARGET are shown in Figure 1 and Figure 2 respectively.

**Figure 1: Percent of ACR20 Response by Visit for MOBILITY Part B**



**Figure 2: Percent of ACR20 Response by Visit for TARGET**



The results of the components of the ACR response criteria at Week 16 for MOBILITY Part B and Week 12 for TARGET are shown in Table 5.

**Table 5 - Mean change from baseline in components of ACR score at Week 16 for MOBILITY and Week 12 for TARGET**

Component means (range/units)	MOBILITY Part B			TARGET		
	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)
<b>Tender Joints (0-68)</b>						
Baseline	26.80	27.21	26.50	29.42	27.66	29.55
Week 12				19.18	13.38	13.10
Week 16	16.46	11.73	10.17			
Change from baseline	-10.29	-15.64	-16.44	-9.79	-14.11	-15.92
<b>Swollen Joints (0-66)</b>						
Baseline	16.68	16.60	16.77	20.21	19.60	19.97
Week 12				12.50	8.82	8.28
Week 16	10.15	6.73	6.14			

Component means (range/units)	MOBILITY Part B			TARGET		
	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)
Change from baseline	-6.48	-9.81	-10.74	-7.25	-10.77	-10.89
<b>Pain VAS*</b> <b>(0-100 mm)</b>						
Baseline	63.71	65.48	66.71	71.57	71.02	74.86
Week 12				54.77	43.45	41.66
Week 16	49.17	38.62	34.97			
Change from baseline	-14.41	-27.01	-31.43	-16.12	-27.95	-32.77
<b>Physician global VAS*</b> <b>(0-100 mm)</b>						
Baseline	62.86	63.43	63.59	68.39	68.10	67.76
Week 12				43.73	33.65	30.18
Week 16	39.99	28.09	24.99			
Change from baseline	-22.87	-35.13	-38.14	-24.60	-34.92	-36.92
<b>Patient global VAS*</b> <b>(0-100 mm)</b>						
Baseline	63.70	64.43	66.49	68.77	67.71	70.89
Week 12				53.67	41.99	41.74
Week 16	48.42	38.09	35.44			
Change from baseline	-14.82	-26.26	-31.00	-15.05	-26.05	-28.83
<b>HAQ-DI (0-3)</b>						
Baseline	1.61	1.63	1.69	1.80	1.72	1.82
Week 12				1.49	1.23	1.33
Week 16	1.31	1.08	1.11			
Change from baseline	-0.30	-0.54	-0.58	-0.29	-0.50	-0.49

Component means (range/units)	MOBILITY Part B			TARGET		
	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)
<b>CRP (mg/L)</b>						
Baseline	20.46	22.57	22.23	26.02	23.60	30.77
Week 12				21.72	9.21	4.58
Week 16	20.06	7.24	2.95			
Change from baseline	-0.18	-15.72	-19.01	-3.39	-14.24	-25.91

\* VAS=visual analog scale

### Radiographic Response

In MOBILITY Part B, 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 52 weeks (see Table 6).

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.

**Table 6 - Mean Radiographic Change from Baseline at Weeks 24 and Week 52 in MOBILITY Part B<sup>a, b</sup>**

	MOBILITY Part B		
	Placebo + MTX (N=398)	KEVZARA 150 mg q2w + MTX (N=400)	KEVZARA 200 mg q2w + MTX (N=399)
<b>Modified Total Sharp Score (mTSS)</b>			
<b>Week 24</b>			
Mean change	1.10	0.39	0.11
LS mean difference, 97.5% CI		-0.708 (-1.192,-0.225)	-0.986 (-1.468,-0.505)
<b>Week 52<sup>c</sup></b>			
Mean change	2.03 -	0.58	0.16
LS mean difference, 97.5% CI		-1.458 (-2.108,-0.809)	-1.877 (-2.526,-1.228)
p-value vs placebo		<0.0001	<0.0001
<b>Erosion score (0-280)</b>			
<b>Week 24</b>			
Mean change	0.61	0.19	-0.002
LS mean difference, 97.5% CI		-0.411 (-0.673,-0.150)	-0.608 (-0.869,-0.346)
<b>Week 52</b>			
Mean change	1.05	0.27	-0.04
LS mean difference, 97.5% CI		-0.777 (-1.146,-0.408)	-1.085 (-1.454,-0.716)
<b>Joint space narrowing score</b>			
<b>Week 24</b>			
Mean change	0.50	0.20	0.12
LS mean difference, 97.5% CI		-0.293 (-0.606,0.020)	-0.378 (-0.690,-0.066)
<b>Week 52</b>			
Mean change	0.99	0.31	0.20
LS mean difference, 97.5% CI		-0.678 (-1.052,-0.304)	-0.793 (-1.166,-0.419)

<sup>a</sup>Includes data after rescue or discontinuation of double-blind medication for 138 (34.7%), 59 (14.8%) and 52 (13.0%) patients in the placebo, 150mg and 200mg treatment groups respectively.

<sup>b</sup>Analyzed using a repeated measure model including baseline mTSS and stratification by geographic region and prior use of biologic DMARDs. Each dose group was compared to placebo at the 2.5% significance level.

<sup>c</sup> Primary end point

CI=confidence interval; LS=least squares; MTX=methotrexate

### Physical Function Response

In MOBILITY Part B and TARGET, 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 Part B and TARGET, respectively.

**Table 7 - Change from baseline in the HAQ-DI score at Week 16 for MOBILITY Part B and Week 12 for TARGET**

	MOBILITY Part B			TARGET <sup>b</sup>		
	Placebo + MTX N = 398	KEVZARA 150 mg + MTX N = 400	KEVZARA 200 mg + MTX N = 399	Placebo + DMARD <sup>a</sup> N = 181	KEVZARA 150 mg + DMARD <sup>a</sup> N = 181	KEVZARA 200 mg + DMARD <sup>a</sup> N = 184
<b>HAQ-DI Week 12</b>						
LS mean				-0.28	-0.47	-0.47
Difference from placebo, (97.5% CI) <sup>c</sup>					-0.197 (-0.331,-0.062)	-0.192 (-0.326,-0.057)
P-value vs placebo					0.0010	0.0014
% of patients with clinically meaningful improvement <sup>d</sup>				35.9%	47%	51.1%
<b>HAQ-DI Week 16</b>						
Change mean	-0.31	-0.52	-0.53			
Difference from placebo, (97.5% CI) <sup>c</sup>		-0.210 (-0.299,-0.121)	-0.222 (-0.312,-0.133)			
P-value vs placebo		<0.0001	<0.0001			
% of patients with clinically meaningful improvement <sup>d</sup>	42.5%	53.8%	57.4%			

<sup>a</sup> DMARDs in TARGET included MTX, sulfasalazine, leflunomide and hydroxychloroquine

<sup>b</sup> In TARGET the number of patients receiving methotrexate as part of the background treatment was 158 (87.3%), 154 (85.1%), 156 (84.8%) in the placebo, 150mg and 200mg groups respectively.

<sup>c</sup> Analyzed using a repeated measure model including baseline HAQ-DI and stratification by geographic region and prior use of biologic DMARD (Mobility-B) or number of prior anti-TNF drugs (TARGET). Missing data were imputed based on the observed response in the placebo group. Each dose group was compared to placebo at the 2.5% significance level.

<sup>d</sup> Change from baseline greater than 0.3 units.

### *Other Studies*

In an open-label uncontrolled study, the efficacy of KEVZARA as monotherapy was consistent with that observed with combination therapy.

## **DETAILED PHARMACOLOGY**

Sarilumab potently binds to human IL-6R $\alpha$  to block IL-6-induced receptor signaling. In addition to blockade of the cis-signaling pathway, sarilumab also blocks trans-signaling induced by IL-6/sIL-6R $\alpha$  complexes in cells that express gp130 but not membrane-bound IL-6R $\alpha$ .

## **TOXICOLOGY**

Cynomolgus monkeys were administered sarilumab intravenously up to dose levels of 50 mg/kg/weekly for 26 weeks and subcutaneously up to 100 mg/kg/ weekly for 13 weeks. -

Humoral immune response (IgG) to antigen challenge by keyhole limpet hemocyanin (KLH) was suppressed in adult cynomolgus monkeys receiving  $\geq 5$ mg/kg weekly sarilumab by intravenous administration. Other sarilumab related findings included neutropenia decrease in neutrophil counts and reductions in serum C - reactive protein (CRP) and fibrinogen. The effects observed were consistent with the pharmacological inhibition of IL-6 signaling and were generally reversible. No other sarilumab related events were noted up to dose levels of 50 mg/kg weekly for 26 weeks, corresponding to plasma exposure (AUC) approximately 80 times higher than would be expected clinically.

### **Carcinogenesis and Mutagenesis**

No long-term animal studies have been performed to establish the carcinogenicity potential of sarilumab. Mutagenicity studies have not been conducted with sarilumab.

## REFERENCES

1. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;7:R796–806.
2. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23 Suppl 39:S100–8.
3. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
4. Bruce B and Fried JF. The Stanford Health Assessment Questionnaire: Dimensions and Practical Applications. *Health Qual Life Outcomes*. 2003; 1: 20.
5. Canadian Thoracic Society (CTS) of the Canadian Lung Association (CLA) and the Public Health Agency of Canada (PHAC). Canadian Tuberculosis Standards. 7<sup>th</sup> edition. 2013
6. Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. *Rheumatology (Oxford)*. 2010;49:15-24.
7. Felson DT, Anderson JJ, Boers M, Bombardier C, Chernoff M, Fried B, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729–40.
8. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.
9. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.
10. Huizinga TW, Fleischmann RM, Jasson M, Radin AR, van Adelsberg J, Fiore S, et al. Sarilumab, a fully human monoclonal antibody against IL-6Ra in patients with rheumatoid arthritis and an inadequate response to methotrexate: efficacy and safety results from the randomised SARIL-RA-MOBILITY Part A trial. *Ann Rheum Dis* 2014;73:1626–34.
11. Kim HL, Lee MY, Park SY, Park SK, Byun JH, Kwon S, et al. Comparative effectiveness of cycling of tumor necrosis factor-alpha (TNF-alpha) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-alpha inhibitor using a Bayesian approach. *Arch Pharm Res*. 2014 May;37(5):662-70.
12. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, Pollono EN, Cueto JP, Gonzales-Crespo MR, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. *JAMA* 2012;308:898–908.

13. Mark C. Genovese, Roy Fleischmann, Alan J. Kivitz, Maria Rell-Bakalarska, Renata Martincova, Stefano Fiore, Patricia Rohane, Hubert van Hoogstraten, Anju Garg, Chunpeng Fan, Janet van Adelsberg, Steven P. Weinstein, Neil M. H. Graham, Neil Stahl, George D. Yancopoulos, Tom W. J. Huizinga, and Desiree van der Heijde, Sarilumab Plus Methotrexate in Patients With Active Rheumatoid Arthritis and Inadequate Response to Methotrexate Results of a Phase III Study, *ARTHRITIS & RHEUMATOLOGY* Vol. 67, No. 6, June 2015, pp 1424–1437
14. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44–8.
15. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guidelines for the treatment of rheumatoid Arthritis. *Arthritis Rheumatol.* 2015
16. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis [Internet]*. 2013 Mar [cited 2015 Nov 17];73(3):492-509.
17. Srirangan S, Choy EH. The role of interleukin 6 in the pathophysiology of rheumatoid arthritis. *Ther Adv Musculoskelet Dis* 2010;2:247–56.
18. Sugiyama E, Kuroda A, Hori F, Hori T, Taki H, Arai N, et al. Serum interleukin-6 level is a sensitive parameter of disease activity in rheumatoid arthritis. *J Clin Rheumatol* 1995;1:93–8.
19. Upchurch KS, Kay J. Evolution of treatment for rheumatoid arthritis. *Rheumatology (Oxford)* 2012;51 Suppl 6:vi28–36. 2.
20. Van der Heijde DM. Radiographic imaging: the ‘gold standard’ for assessment of disease progression in rheumatoid arthritis. *Rheumatology (Oxford)* 2000;39 Suppl 1:9–16.
21. Ware JE, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. *J Clin Epidemiol* 1998; 51(11):903-12.
22. Wang LH, Xue Y, Liu X, Luo F, Kelly L, Huang T, et al. Preclinical development of sarilumab, the first fully human monoclonal antibody (mAb) against IL-6Ra: utilization and value of double humanized animal model. *Ann Rheum Dis* 2013;72 Suppl 3:375.

## READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PART III: PATIENT MEDICATION INFORMATION

#### **KEVZARA™ sarilumab injection**

Read this carefully before you start using **KEVZARA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this medication. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KEVZARA**.

#### **Serious Warnings and Precautions**

##### **Risk of serious Infections**

KEVZARA is a medicine that affects your immune system. KEVZARA can lower the ability of your immune system to fight infections. Some people have serious infections while taking KEVZARA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

#### **What is KEVZARA used for?**

KEVZARA is used to treat adult patients with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a Disease Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well or caused side effects that led you to stop taking the medicine.

#### **How does KEVZARA work?**

KEVZARA (also known as sarilumab) is an injectable prescription medicine which blocks a protein, Interleukin-6 (IL-6), that is found at high levels in people diagnosed with RA. IL-6 plays a major role in the signs and symptoms of rheumatoid arthritis (RA). KEVZARA is a medicine that helps keep the immune system from attacking healthy tissues in the body. A normal immune system leaves healthy body tissues alone. In people with rheumatoid arthritis, the immune system attacks normal body tissues causing damage and inflammation, especially in the tissues of your joints and possibly other organs (such as heart, liver and bones). KEVZARA interferes with an important step in this attack (blocks a cytokine called IL-6 which is found at high levels in the joints affected by rheumatoid arthritis).

#### **What are the ingredients in KEVZARA?**

Medicinal ingredients: sarilumab

Non-medicinal ingredients: arginine, histidine, polysorbate 20, sucrose, water for injection.

The components of the prefilled syringe are latex free (including the needle cap).

**KEVZARA comes in the following dosage forms:**

- Pre-filled syringes, each containing 150 mg of KEVZARA for subcutaneous injection
- Pre-filled syringes, each containing 200 mg of KEVZARA for subcutaneous injection

**Do not use KEVZARA if:**

- you are allergic to sarilumab or any of the ingredients in KEVZARA (see section titled ‘What are the ingredients in KEVZARA?’).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you use KEVZARA. Talk about any health conditions or problems you may have, including if you:**

- have had an allergic reaction to KEVZARA
- think you have an infection or have symptoms of an infection, with or without a fever, such as sweating or chills, muscle aches, cough, shortness of breath, blood in phlegm, weight loss, warm, red, or painful skin or sores on your body, diarrhea or stomach pain, burning when you urinate or urinating more often than normal, feeling very tired
- are being treated for an infection, get a lot of infections or have repeated infections
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance of getting infections.
- have tuberculosis (TB), or have been in close contact with someone with TB
- live or have lived, or have traveled to certain parts of the country where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidiomycosis, or blastomycosis). These infections may happen more often or worsen if you use KEVZARA. Ask your healthcare provider, if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B or hepatitis C or other liver problems
- have or have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people using KEVZARA get tears (perforations) in their stomach or intestine. This happens most often in people who also take medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- have or have had any type of cancer
- have recently received or are scheduled to receive a vaccine
- have a surgery or a medical procedure planned
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if KEVZARA will harm your unborn baby.

Pregnancy Registry: Sanofi has a registry for pregnant women who use KEVZARA to gather information about the outcomes of pregnancies. If you are pregnant or become pregnant while using KEVZARA, talk to your healthcare provider about how you can join this pregnancy registry or call 1-877-311-8972 to enroll.

- plan to breast-feed or are breast-feeding. You and your healthcare provider should decide if you will use KEVZARA or breast-feed. You should not do both.

After starting KEVZARA, call your healthcare provider right away if you have any symptoms of an infection. KEVZARA may make you more likely to get an infection or worsen any infection you have.

Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away.

KEVZARA may decrease the activity of your immune system. Medicines that affect the immune system may increase your risk of certain cancers. Tell your healthcare provider if you have ever had any type of cancer.

**Other warnings you should know about:**

- Changes to laboratory tests:

Your healthcare provider should do blood tests before you start KEVZARA, 4 to 8 weeks after starting KEVZARA, and then approximately every 3 months during treatment to check for the following:

- low neutrophil count. Neutrophils are white blood cells that help the body fight off bacterial infections.
- low platelet count. Platelets are blood cells that help with blood clotting and stop bleeding.
- increase in certain liver function tests.

Your healthcare provider may not prescribe KEVZARA if your neutrophil or platelet counts are too low or your liver function tests are too high.

Your healthcare provider may interrupt your KEVZARA treatment for a period of time and/or decrease your dose of medicine if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider may do blood tests to check your cholesterol levels while you are taking KEVZARA.

- Tears (perforations) of the stomach or intestines:

Tell your healthcare provider if you have had a condition known as diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking KEVZARA get tears in their stomach or intestine. This happens most often in people who also take medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.

Call your healthcare provider right away if you have fever and stomach (abdominal) pain that does not go away.

- Cancer

KEVZARA may decrease the activity of your immune system. Medicines that affect the immune system may increase your risk of certain cancers. Tell your healthcare provider if you have ever had any type of cancer.

See “What are the possible side effects from using KEVZARA?” for more information about side effects.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with KEVZARA:**

- any other medicines to treat your RA. You should not take rituximab (Rituxan®), etanercept (Enbrel®), infliximab (Remicade®), anakinra (Kineret®), adalimumab (Humira®), abatacept (Orencia®), certolizumab (Cimzia®), golimumab (Simponi®), tocilizumab (Actemra®), or tofacitinib (Xeljanz®) while you are taking KEVZARA. Using KEVZARA with these medicines may increase your risk of infection.
- medicines that affect the way your liver works. Ask your healthcare provider if you are not sure if your medicine is one of these.

**How to take KEVZARA:**

- **See the detailed Instructions for Use that comes with this Patient Medication Information for instructions about the right way to prepare and give your KEVZARA injections.**
- KEVZARA is given as an injection under the skin (subcutaneous injection).
- KEVZARA comes as a single-dose (1 time) pre-filled syringe. Your healthcare provider will prescribe the dose that is best for you.
- If your healthcare provider decides that you or a caregiver can give the injections of KEVZARA, you or your caregiver should receive training on the right way to prepare and inject KEVZARA. Do not try to inject KEVZARA until you have been shown the right way to give the injections by your healthcare provider.

**Usual dose:**

KEVZARA should be injected every two weeks. The usual recommended dose is 200mg. Your healthcare provider may interrupt your KEVZARA treatment for a period of time and/or decrease your dose of KEVZARA to 150mg every two weeks.

**Overdose:**

If you think you have used too much KEVZARA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss a dose of KEVZARA and it has been 3 days or less since the missed dose, take your



dose as soon as you can. Then take your next dose at your regularly scheduled time. If it has been 4 days or more, or you are unsure when to take your next dose of KEVZARA, call your healthcare provider for instructions.

**What are possible side effects from using KEVZARA?**

Like all medicines, KEVZARA, can cause unwanted effects. These are not all the possible side effects you may feel when using KEVZARA. If you experience any side effects not listed here, contact your healthcare professional.

- Injection site redness
- Upper respiratory tract infection
- Nasal congestion, sore throat, and runny nose
- Cold sores

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b> Upper respiratory tract infections such as coughs and cold, sore throat, runny nose, nasal congestion, sneezing, coughing	<b>X</b>		
Urinary tract infection: burning when you urinate or urinating more often than normal		<b>X</b>	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

### **Reporting Side Effects**

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

#### **3 ways to report:**

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
Health Canada, Postal Locator 0701E  
Ottawa, ON  
K1A 0K9Postage paid labels and the Patient Side Effect Reporting Form are available at [MedEffect](#).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

### **Storage:**

Keep out of reach and sight of children.

Do not use this medicine after the expiry date which is stated on the label and carton.

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the syringe in the outer carton in order to protect from light.

Do not expose to intense heat.

The pre-filled syringe should be left at room temperature for 30 minutes prior to use. The syringe should be used within 14 days after being taken out of the refrigerator. A puncture-resistant container for disposal of syringes 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 disposal, and caution against reuse of these items.

### **If you want more information about KEVZARA:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website [sanofigenzyme.ca](#), or by calling 1-800-589-6215.

This leaflet was prepared by Sanofi Canada Inc.

KEVZARA is a registered trademark of Sanofi Biotechnology.

Last Revised: January 12, 2017

## INSTRUCTIONS FOR USE

**KEVZARA™**  
(sarilumab)

**Injection, for Subcutaneous Injection**  
**Single-Dose Pre-Filled Syringe**

### Important information

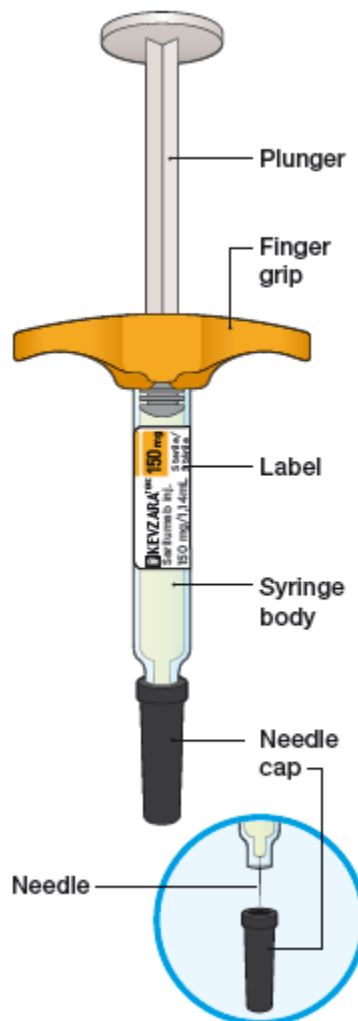
This device is a single-dose pre-filled syringe (called “syringe” in these instructions). It contains KEVZARA for injection under the skin (subcutaneous injection) once every two weeks.

Ask your healthcare provider to show you the right way to use the syringe before you inject for the first time.

<b>Do</b>	<b>Do not</b>
<ul style="list-style-type: none"><li>✓ Read all of the instructions carefully before using a syringe.</li><li>✓ Keep unused syringes in the original carton and store in the refrigerator between 2°C and 8°C (36°F and 46°F).</li><li>✓ Keep the carton in an insulated bag with an ice pack when traveling.</li><li>✓ Let the syringe warm up at room temperature for at least 30 minutes before using.</li><li>✓ Use the syringe within 14 days after taking it out of the refrigerator or insulated bag.</li><li>✓ Keep the syringe out of the reach of children.</li></ul>	<ul style="list-style-type: none"><li>✗ Do not use the syringe if it has been damaged or the needle cap is missing or not attached.</li><li>✗ Do not remove the needle cap until just before you are ready to inject.</li><li>✗ Do not touch the needle.</li><li>✗ Do not re-use or try to put the cap back on the syringe.</li><li>✗ Do not freeze or heat up the syringe.</li><li>✗ Do not expose the syringe to direct sunlight.</li><li>✗ Do not inject through your clothes.</li></ul>

Keep these instructions for future use.

If you have any further questions, ask your healthcare provider or call 1-800-589-6215.



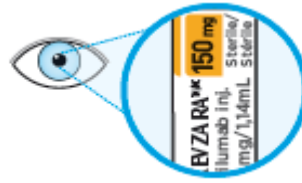
### Step A: Get ready for an injection

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

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

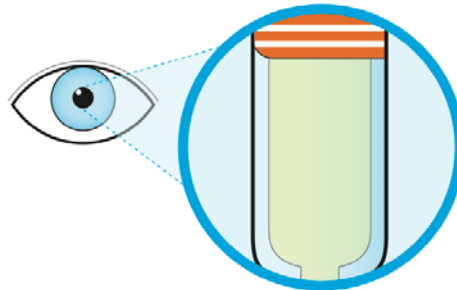
## 2. Look at the label.

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



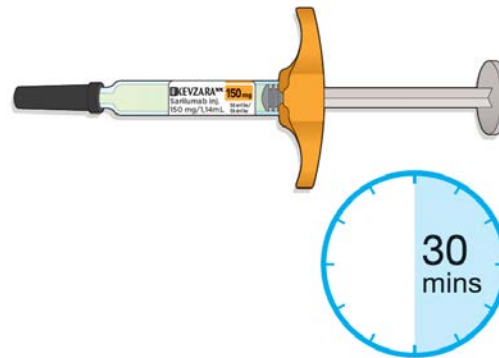
## 3. Look at the medicine.

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



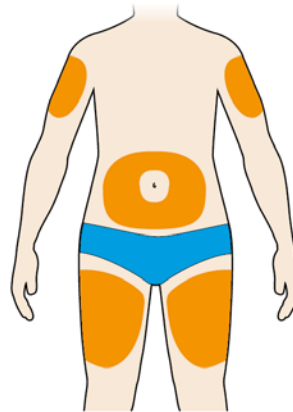
## 4. Lay the syringe on a flat surface and allow it to warm up at room temperature for at least 30 minutes.

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



## 5. Select the injection site.

- You can inject into your thigh or belly (abdomen) – except for the 5 cm (2 inches) around your belly button (navel). If somebody else gives you the injection, you can also use the upper arm.
- Change injection site each time you inject.
- ✗ **Do not** inject into skin that is tender, damaged or has bruises or scars.



● Injection sites

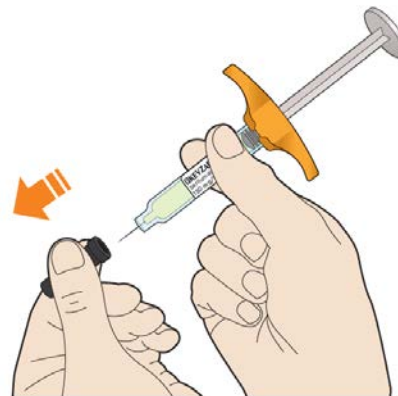
## 6. Prepare the injection site.

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

## Step B: Perform the injection – Perform Step B only after completing Step A “Get ready for an injection”

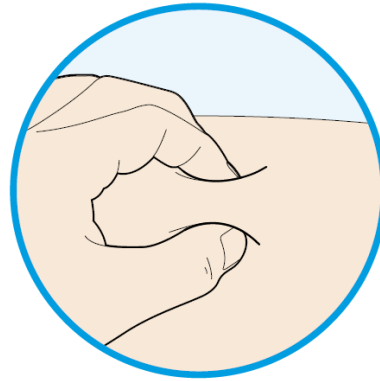
### 1. Pull off the needle cap.

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

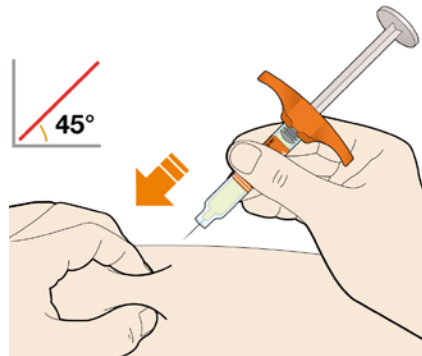


## 2. Pinch the skin.

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

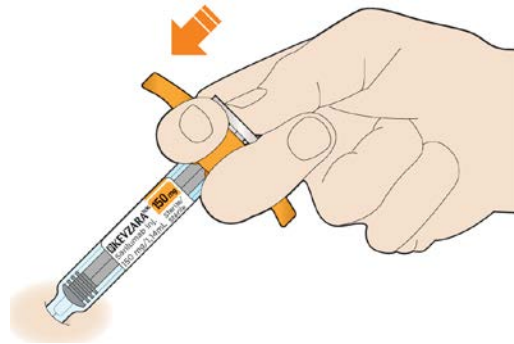


## 3. Insert the needle into the fold of skin at roughly a 45° angle.



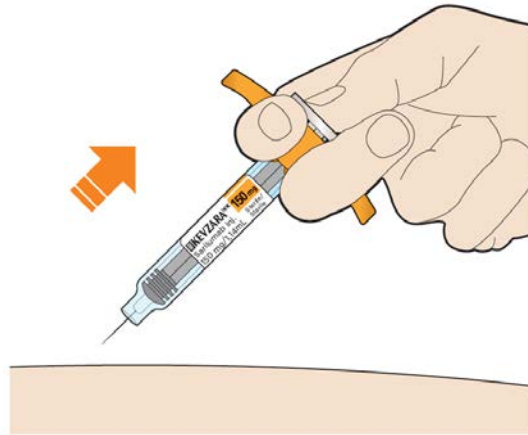
## 4. Push the plunger down.

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



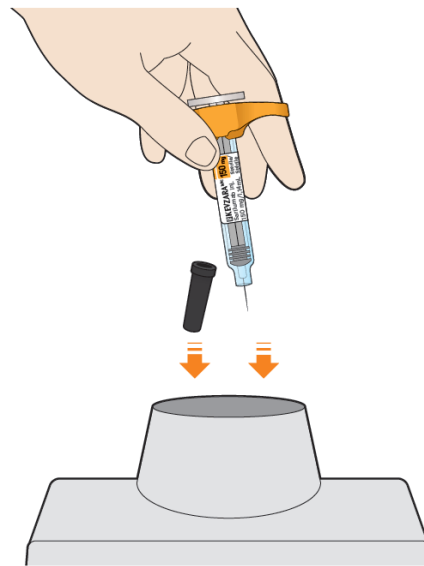
**5. Before you remove the needle, check that the syringe is empty.**

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



**6. Put your used syringe and the cap into a puncture-resistant container.**

- Always keep the container out of reach of children.
- ✗ **Do not** put the needle cap back on.
- ✗ **Do not** throw away the used syringe in the household trash.



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