PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrKEVZARA®

Sarilumab injection

solution for subcutaneous injection

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

interleukin-6 (IL-6) receptor antagonist, L04AC14

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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RECENT MAJOR LABEL CHANGES

7 WARNING AND PRECAUTIONS	10/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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 14 CLINICAL TRIALS).

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.

1.1 Pediatrics

Pediatrics (<18 years of age):

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age):

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

2 CONTRAINDICATIONS

Sarilumab is contraindicated in patients with known hypersensitivity to Kevzara or to any of the excipients. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING Section.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Patients treated with Kevzara are at increased risk for developing serious infections that may lead to hospitalization or death (see 7 WARNINGS AND PRECAUTIONS, 8 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 7 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.

4 DOSAGE AND ADMINISTRATION

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

4.2 Recommended Dose and Dosage Adjustment

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

Health Canada has not authorized an indication for pediatric use.

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 7 WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS Section).

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

Please refer to **Table 1**, **Table 2** and **Table 3** for the recommended dosage modifications in case of neutropenia, thrombocytopenia, or elevated liver enzyme.

Table 1: Recommended dosage modifications in case of neutropenia

Low Absolute Neutrophil Count (ANC) (see 7 WARNINGS AND PRECAUTIONS, and 10 CLINICAL PHARMACOLOGY Section).	
Lab Value (cells/L)	**Recommendation**
ANC greater than $1x10^9$/L	**Maintain current dose of Kevzara**
ANC 0.5-1 x 10^9/L	**Hold treatment with Kevzara until >$1x10^9$/L. 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 0.5 x 10^9/L	**Discontinue Kevzara**

ANC – Absolute Neutrophil Count

Table 2: Recommended dosage modifications in case of thrombocytopenia

Low Platelet Count (see 7 WARNINGS AND PRECAUTIONS Section).	
Lab Value (cells/µL)	**Recommendation**
50-100 x 10^3/µL	**Hold treatment with Kevzara until >100 x 10^3/µL. 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 x 10^3/µL	**If confirmed by repeat testing, discontinue Kevzara**

Table 3: Recommended dosage modifications in case of elevated liver enzyme

Liver Enzyme Abnormalities (see 7 WARNINGS AND PRECAUTIONS Section).	
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**

ALT - alanine aminotransferase, ULN – Upper limit of normal, DMARDs - Disease-Modifying Anti-Rheumatic Drugs

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.

4.4 Administration

General Considerations for Administration

Do not initiate treatment with Kevzara in patients with an absolute neutrophil count (ANC) below 2 x 10^9/L, platelet count below 150 x 10^3/µL, or who have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above 1.5 times the upper limit of normal (ULN). The concurrent use of Kevzara with biological DMARDs such as tumor necrosis factor (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 health 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. If using the pre-filled injection pen, allow the pen to sit at room temperature for 60 minutes prior to subcutaneous injection. Do not warm Kevzara in any other way.

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. Do not use if the solution is cloudy, discoloured or contains particles, or if any part of the pre-filled syringe or pre-filled pen appears to be damaged.

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.

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

4.5 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 health professional for instructions.

5 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, liver function tests (LFTs), and lipids were within normal range) as a consequence.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Injection: single-dose pre-filled syringe or pre-filled pen •200 mg/1.14 mL •150 mg/1.14 mL	Arginine, histidine, polysorbate 20, sucrose and water for injection. *For a complete listing see* 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Kevzara solution for subcutaneous administration is supplied as a sterile, colourless to pale yellow, preservative-free liquid solution of approximately pH 6.0. Each pre-filled syringe or pre-filled pen 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 or pre-filled pen are latex free (including the needle

cap).

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

Description

Kevzara (sarilumab) is a fully 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.

7 WARNINGS AND PRECAUTIONS

General

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 8 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 8 ADVERSE REACTIONS and 4 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.

Gastrointestinal

Gastrointestinal Perforation and Diverticulitis

Cases of gastrointestinal perforation and diverticulitis have been reported in association with sarilumab. Gastrointestinal perforation has been reported in patients with and without diverticulitis. Use Kevzara with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with new onset abdominal symptoms such as persistent pain with fever. (see 8 ADVERSE REACTIONS Section).

Hepatic/Biliary/Pancreatic

Treatment with Kevzara is not recommended in patients with active hepatic disease or hepatic impairment (see 7.1 Special Populations, and 8 ADVERSE REACTIONS Section).

Hypersensitivity

Hypersensitivity reactions have been reported in association with Kevzara (see section 8 ADVERSE REACTIONS). Injection site rash, rash, and urticaria were the most frequent hypersensitivity reactions. Patients should be advised to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If anaphylaxis or other hypersensitivity reaction occurs, administration of Kevzara should be stopped immediately. Kevzara should not be administered to patients with known hypersensitivity to sarilumab (see section 2 CONTRAINDICATIONS and 8 ADVERSE REACTIONS).

Immune

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 8 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 9 DRUG INTERACTIONS Section).

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 x 10^9/L. In patients who develop an ANC less than 0.5 x 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 10 CLINICAL PHARMACOLOGY Section). For recommended dose modifications based on ANC results see 4 DOSAGE AND ADMINISTRATION Section.
- Based on the pharmacodynamics of the changes in ANC (see 10 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 8 ADVERSE REACTIONS Section).

- Initiating treatment with Kevzara is not recommended in patients with a platelet count below 150 x 10^9/L. In patients who develop a platelet count less than 50 x 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 4 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 8 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 1.5x ULN. In patients who develop elevated ALT greater than 5x ULN, discontinue treatment with Kevzara (see 4 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 4 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 low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and/or triglycerides (see 8 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.

7.1 Special Populations

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 7 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 10 CLINICAL PHARMACOLOGY Section).

7.1.1 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 7.1 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 (i.e., 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 ≥5mg/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-6Rα 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 16 NON-CLINICAL 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

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age):
Safety and efficacy of Kevzara have not been established in children less than 18 years of age.

7.1.4 Geriatrics

Geriatrics (>65 years of age):
Of the total number of patients in clinical studies of Kevzara (see 14 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.

8 ADVERSE REACTIONS

8.1 Adverse reaction overview

The most frequently reported adverse reactions were neutropenia, upper respiratory tract infections, increased ALT, urinary tract infections, and injection site erythema. The most common serious adverse reactions were infections (see 7 WARNINGS AND PRECAUTIONS).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 7 WARNINGS AND PRECAUTIONS Section).

The most frequent adverse reactions (occurring in at least 2.5% 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 7 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. Gastrointestinal perforation was reported in patients with and without diverticulitis and included reports of 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 7 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/µL 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 /µL 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 4 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 7 WARNINGS AND PRECAUTIONS Section).

Platelet count

In the 12-week placebo-controlled population, decreases in platelet counts below 100 x 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 7 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 5. 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 4 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 7 WARNINGS AND PRECAUTIONS Section).

Table 5 : Incidence of Liver Enzyme Abnormalities in the Phase 3 Placebo-Controlled Efficacy Population through Week 12

	Placebo + DMARDs N=579	**Kevzara 150 mg + DMARDs N=579**	**Kevzara 200 mg + DMARDs N=582**
AST			
>ULN – 3x ULN	13.3%	25.1%	28%
>3x ULN – 5x ULN	0%	1.4%	1.0%
>5x ULN	0%	0.7%	0.2%
ALT			
>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%

AST- aspartate aminotransferase, ALT - alanine aminotransferase, DMARDs- Disease-modifying antirheumatic drugs, 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 7 WARNINGS AND PRECAUTIONS Section).

Other Adverse Reactions

Table 6: Adverse Reactions Occurring in 1% or More of Patients Administered Placebo + DMARD, 150 mg Kevzara + DMARD, or 200 mg Kevzara + DMARD

		Kevzara	
Primary System Organ Class Preferred Term	**Placebo + DMARD (N=579)**	**150 mg q2w + DMARD (N=579)**	**200 mg q2w + DMARD (N=582)**
Any class	242 (41.8%)	287 (49.6%)	306 (52.6%)
Blood and lymphatic system disorders	12 (2.1%)	38 (6.6%)	67 (11.5%)

Primary System Organ Class Preferred Term	Placebo + DMARD (N=579)	Kevzara 150 mg q2w + DMARD (N=579)	Kevzara 200 mg q2w + DMARD (N=582)
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%)
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%)
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%)
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%)
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%)
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%)

Primary System Organ Class Preferred Term	Placebo + DMARD (N=579)	Kevzara 150 mg q2w + DMARD (N=579)	Kevzara 200 mg q2w + DMARD (N=582)
Transaminases increased	2 (0.3%)	8 (1.4%)	5 (0.9%)
Metabolism and nutrition disorders	8 (1.4%)	26 (4.5%)	20 (3.4%)
Hypertriglyceridaemia	3 (0.5%)	15 (2.6%)	5 (0.9%)
Hypercholesterolaemia	0	6 (1.0%)	5 (0.9%)
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%)
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%)
Psychiatric disorders	6 (1.0%)	9 (1.6%)	11 (1.9%)
Insomnia	6 (1.0%)	4 (0.7%)	3 (0.5%)
Vascular disorders	15 (2.6%)	8 (1.4%)	13 (2.2%)
Hypertension	7 (1.2%)	4 (0.7%)	11 (1.9%)

DMARDs - Disease-modifying antirheumatic drugs, q2w: every two weeks

8.5 Post-market Adverse Reactions

The following adverse reaction has been identified post-market in patients receiving sarilumab:

Infections and infestations: diverticulitis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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 4 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-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.

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 10 CLINICAL PHARMACOLOGY Section).

9.4 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.

Live Vaccines

Avoid concurrent use of live vaccines during treatment with Kevzara (see 7 WARNINGS AND PRECAUTIONS Section).

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sarilumab binds 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 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.

10.2 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 7 WARNINGS AND PRECAUTIONS Section). Treatment with sarilumab resulted in decreases in fibrinogen and serum amyloid A, and increases in hemoglobin and serum albumin.

10.3 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 tmax 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. A summary of sarilumab pharmacokinetic parameters is included in Table 7.

Table 7: Summary of sarilumab pharmacokinetic parameters in adults with RA

Dose Regimen	$AUC_{\tau,ss}$ [a,c] (mg day/L)	$C_{max,ss}$ [a,c] (mg/L)	$C_{min,ss}$ [a,c] (mg/L)	T_{max} [b] (day)	V_d [c] (L)
150 mg q2w	202 ± 120	20.0 ± 9.20	6.35 ± 7.54	2 - 4	7.3
200 mg q2w	395 ± 207	35.6 ± 15.2	16.5 ± 14.1		

[a] mean ± SD; [b]range of median; [c]estimated by population PK analysis

$AUC_{t,ss}$: area under the concentration time curve from time 0 to t at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{min,ss}$: minimum concentration observed in the dosing interval during repeated dosing at steady state; T_{max} times to maximum concentration; V_d= volume of distribution; q2w-every two weeks

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.

11 STORAGE, STABILITY AND DISPOSAL

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.

12 SPECIAL HANDLING INSTRUCTIONS

Kevzara is supplied in a single-dose pre-filled syringe or pre-filled pen. 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. After removing the pre-filled pen from the refrigerator it should be allowed to reach room temperature by waiting for 60 minutes before injecting Kevzara.

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

Use the syringe or pen within 14 days after removing from the refrigerator. If the syringe or pen 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 discolouration prior to administration. If visibly opaque particles, discolouration 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.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Sarilumab

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-6Rα binding site within the antibody.

Kevzara has a molecular weight of approximately 144 kDa.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

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 every two weeks (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-a 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 α antagonists, when administered with background non-biologic DMARD treatment. The study was stratified by geographic region and the number of prior TNF α 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 8 - 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[a]	Phase 3, MTX-IR, R, DB, PC, rescue[b] 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

Study	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age ± SD (Range)	Gender
TARGET	Phase 3, TNF-IR[c], R, DB, PC, rescue[d] at 12 weeks DMARDs[e] 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

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

14.2 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 9. 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 9 - Clinical Response at Weeks 12, 24 and 52 in Placebo-Controlled Studies MOBILITY Part B and TARGET

	Percentage of Patients					
	MOBILITY Part B [b,c] MTX Inadequate Responders			TARGET [b,c,d] TNF Inhibitor Inadequate Responders		
	Placebo + MTX N = 398	Kevzara 150 mg + MTX N = 400	Kevzara 200 mg + MTX N = 399	Placebo + DMARD[a] N = 181	Kevzara 150 mg + DMARD [a] N =181	Kevzara 200 mg + DMARD [a] N = 184
ACR20						
Week 12	34.7%	54.0%	64.9%	37.6%	54.1%	62.5%

Percentage of Patients						
	MOBILITY Part B [b,c] MTX Inadequate Responders			TARGET [b,c,d] TNF Inhibitor Inadequate Responders		
	Placebo + MTX N = 398	Kevzara 150 mg + MTX N = 400	Kevzara 200 mg + MTX N = 399	Placebo + DMARD[a] N = 181	Kevzara 150 mg + DMARD [a] N =181	Kevzara 200 mg + DMARD [a] N = 184
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%)
Week 24[e]	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
Week 52	31.7%	53.5%	58.6%			
Difference from placebo, (97.5% CI)		21.9% (14.3%, 29.4%)	27.0% (19.5%, 34.6%)	NA[f]	NA[f]	NA[f]
ACR50						
Week 12	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%)
Week 24	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
Week 52	18.1%	40.0%	42.9%			
Difference from placebo, (97.5% CI)		21.9% (15.0%, 28.8%)	24.8% (17.8%, 31.8%)	NA[f]	NA[f]	NA[f]

Percentage of Patients						
	MOBILITY Part B [b,c] MTX Inadequate Responders			TARGET [b,c,d] TNF Inhibitor Inadequate Responders		
	Placebo + MTX N = 398	Kevzara 150 mg + MTX N = 400	Kevzara 200 mg + MTX N = 399	Placebo + DMARD[a] N = 181	Kevzara 150 mg + DMARD [a] N =181	Kevzara 200 mg + DMARD [a] N = 184
ACR70						
Week 12	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%)
Week 24	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
Week 52	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[f]	NA[f]	NA[f]
Major clinical response [g]						
Responders	3.0%	12.8%	14.8%	NA[f]	NA[f]	NA[f]
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			
DAS28-CRP < 2.6						
Week 24						
Responders	10.1%	27.8%	34.1%	7.2%	24.9%	28.8%

Percentage of Patients						
	MOBILITY Part B [b,c] MTX Inadequate Responders			TARGET [b,c,d] TNF Inhibitor Inadequate Responders		
	Placebo + MTX N = 398	Kevzara 150 mg + MTX N = 400	Kevzara 200 mg + MTX N = 399	Placebo + DMARD[a] N = 181	Kevzara 150 mg + DMARD [a] N =181	Kevzara 200 mg + DMARD [a] N = 184
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

[a] DMARDs in TARGET included MTX, sulfasalazine, leflunomide and hydroxychloroquine

[b] 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.

[c] 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.

[d] 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.

[e] Primary end point

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

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

DMARDs- Disease-modifying antirheumatic drugs, MTX=methotrexate, TNF=tumor necrosis factor

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

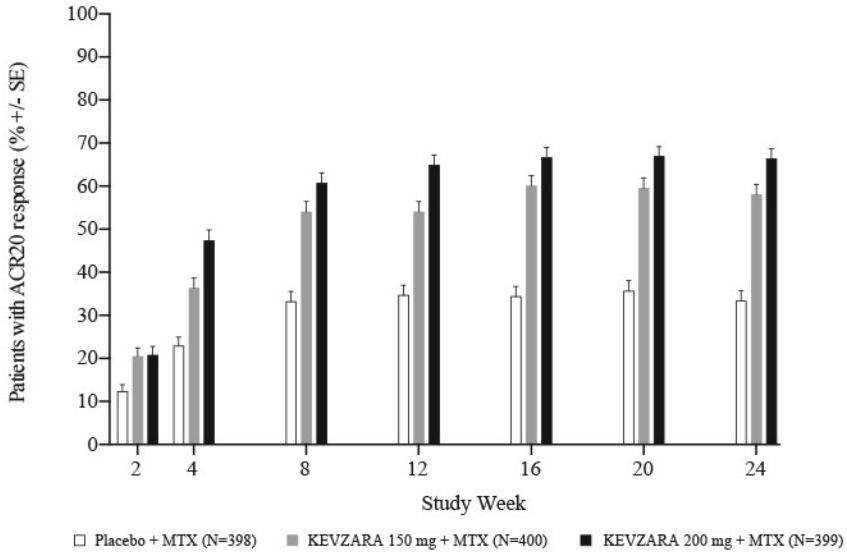
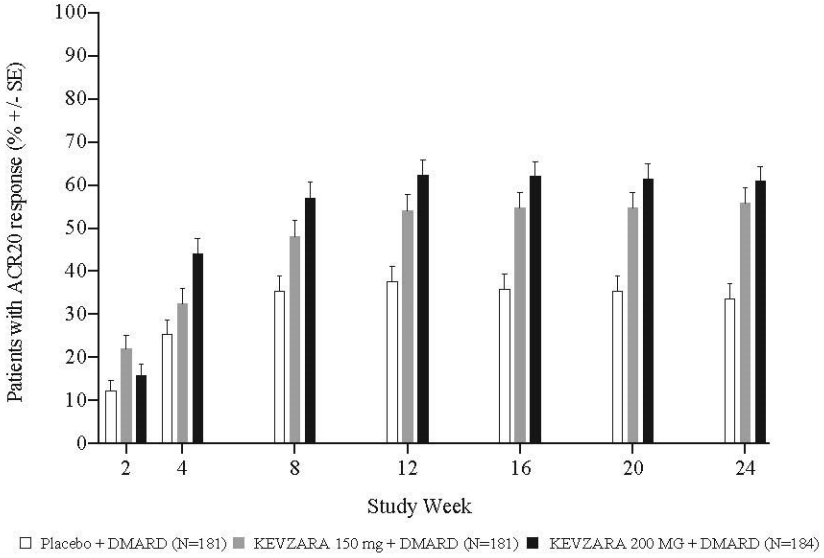


Figure 2: Percent of ACR20 Response by Visit for TARGET



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 10.

Table 10 - 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)
Tender Joints (0-68)						
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
Swollen Joints (0-66)						
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			
Change from baseline	-6.48	-9.81	-10.74	-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				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

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)
Physician global VAS* (0-100 mm)						
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
Patient global VAS* (0-100 mm)						
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
HAQ-DI (0-3)						
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
CRP (mg/L)						
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			

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	-0.18	-15.72	-19.01	-3.39	-14.24	-25.91

* VAS=visual analog scale, DMARDs- Disease-modifying antirheumatic drugs, MTX=methotrexate, TNF=tumor necrosis factor, HAQ-DI- health assessment questionnaire-disability index, CRP- C reactive protein

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 11).

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 11 - Mean Radiographic Change from Baseline at Weeks 24 and Week 52 in MOBILITY Part B [a, b]

	MOBILITY Part B		
	Placebo + MTX (N=398)	Kevzara 150 mg q2w + MTX (N=400)	Kevzara 200 mg q2w + MTX (N=399)
Modified Total Sharp Score (mTSS)			
Week 24			
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)
Week 52 [c]			
Mean change	2.03	0.58	0.16

	MOBILITY Part B		
	Placebo + MTX (N=398)	**Kevzara 150 mg q2w + MTX (N=400)**	**Kevzara 200 mg q2w + MTX (N=399)**
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
Erosion score (0-280)			
Week 24			
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)
Week 52			
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)
Joint space narrowing score			
Week 24			
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)
Week 52			
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)

[a] 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.

[b] 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.

[c] Primary end point

CI=confidence interval; LS=least squares; MTX=methotrexate, q2w: every two weeks

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

	MOBILITY Part B			TARGET [b]		
	Placebo + MTX N = 398	Kevzara 150 mg + MTX N = 400	Kevzara 200 mg + MTX N = 399	Placebo + DMARD [a] N = 181	Kevzara 150 mg + DMARD [a] N =181	Kevzara 200 mg + DMARD [a] N = 184
HAQ-DI Week 12						
LS mean				-0.28	-0.47	-0.47
Difference from placebo, (97.5% CI) [c]					-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 [d]				35.9%	47%	51.1%
HAQ-DI Week 16						
Change mean	-0.31	-0.52	-0.53			
Difference from placebo, (97.5% CI) [c]		-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 [d]	42.5%	53.8%	57.4%			

[a] DMARDs in TARGET included MTX, sulfasalazine, leflunomide and hydroxychloroquine

[b] 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.

[c] 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.
[d] Change from baseline greater than 0.3 units.
DMARDs- Disease-modifying antirheumatic drugs, MTX=methotrexate, TNF=tumor necrosis factor, HAQ-DI- health assessment questionnaire-disability index, LS- least squares, CI- confidence interval

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-6Rα 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-6Rα complexes in cells that express gp130 but not membrane-bound IL-6Rα.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL 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 ≥5mg/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.

Carcinogenicity:

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

KEVZARA®

sarilumab injection

Read this carefully before you start taking **Kevzara** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. 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
- Pre-filled pen, each containing 150 mg of Kevzara for subcutaneous injection
- Pre-filled pen, 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 take 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, bl 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.

Tell your healthcare provider if you:

- Develop symptoms such as nausea and vomiting, constipation, or less commonly diarrhea
- Have ever had any type of cancer. Kevzara may decrease the activity of your immune system. Medicines that affect the immune system may increase your risk of certain cancers.

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.
- Fever and stomach-area pain that does not go away

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 or pen. 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, or a person you are caring for, have taken too much Kevzara, contact a 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 of 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?

These are not all the possible side effects you may have when taking Kevzara. If you experience any side effects not listed here, tell your healthcare professional.

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

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNCOMMON			
Diverticulitis (a condition of the lower bowel) often with stomach (abdominal) pain, nausea and vomiting, fever, constipation, or less commonly diarrhea)		**X**	
COMMON			
Upper respiratory tract infections such as coughs and cold, sore throat, runny nose, nasal congestion, sneezing, coughing	**X**		
Urinary tract infection: burning when you urinate or urinating more often than normal		**X**	

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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:

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 or pen 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 pre-filled pen should be left at room temperature for 60 minutes prior to use. The syringe or pen should be used within 14 days after being taken out of the refrigerator. 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 pre-filled pen disposal, and caution against reuse of these items.

Keep out of reach and sight of children.

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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.ca, or by calling 1-800-589-6215.

This leaflet was prepared by Sanofi Canada Inc.

Last Revised: October 21, 2022

KEVZARA is a registered trademark of Sanofi Biotechnology.

INSTRUCTIONS FOR USE

KEVZARA®

(sarilumab)

Injection, for Subcutaneous Injection

Single-Dose Pre-Filled Syringe

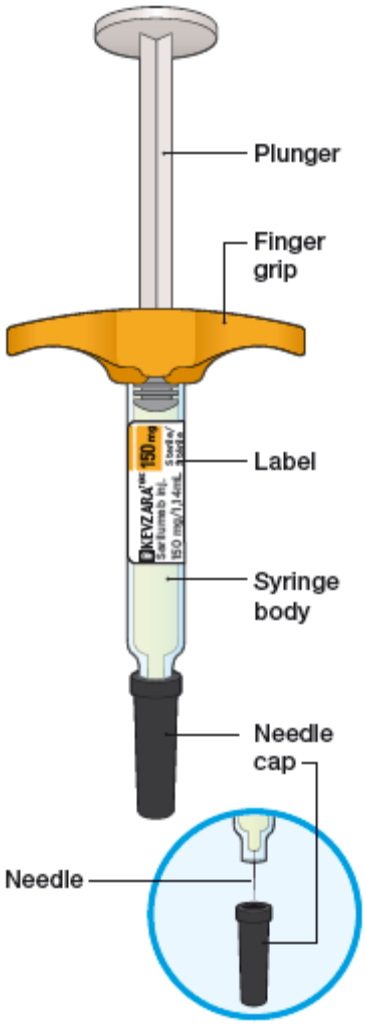
Important information

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.

Do	Do not
✓ Read all of the instructions carefully before using a syringe. ✓ Keep unused syringes in the original carton and store in the refrigerator between 2ºC and 8ºC (36ºF and 46ºF). ✓ Keep the carton in an insulated bag with an ice pack when traveling. ✓ Let the syringe warm up at room temperature for at least 30 minutes before using. ✓ Use the syringe within 14 days after taking it out of the refrigerator or insulated bag. ✓ Keep the syringe out of the reach of children.	✗ Do not use the syringe if it has been damaged or the needle cap is missing or not attached. ✗ Do not remove the needle cap until just before you are ready to inject. ✗ Do not touch the needle. ✗ Do not re-use or try to put the cap back on the syringe. ✗ Do not freeze or heat up the syringe. ✗ Do not expose the syringe to direct sunlight. ✗ Do not inject through your clothes.

Keep these instructions for future use.
If you have any further questions, ask your healthcare provider or call 1-800-589-6215.



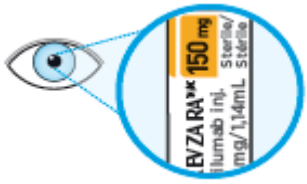
Step A: Get ready for an injection

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.

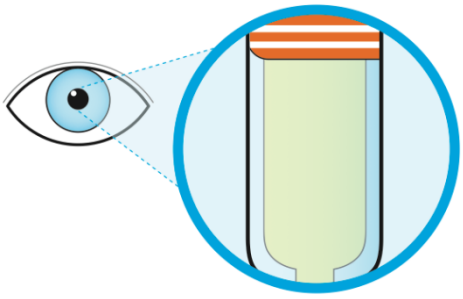
2. Look at the label.

- 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.



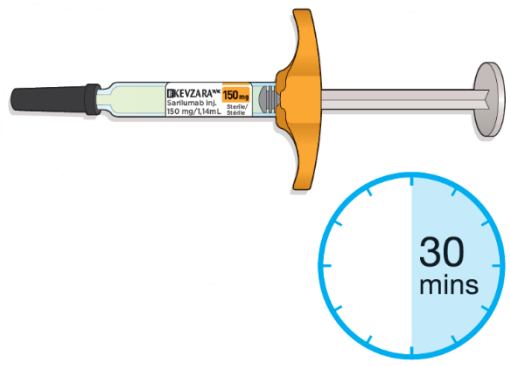
3. Look at the medicine.

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



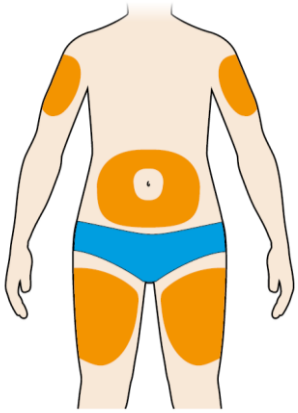
4. Lay the syringe on a flat surface and allow it to warm up at room temperature for at least 30 minutes.

- 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

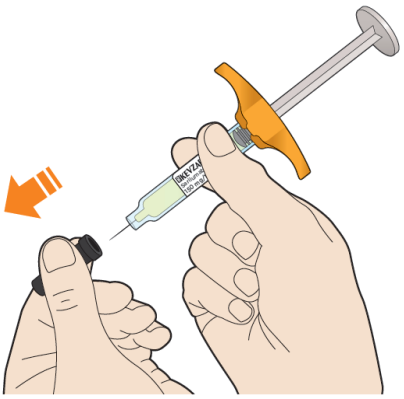
6. Prepare the injection site.

- 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"

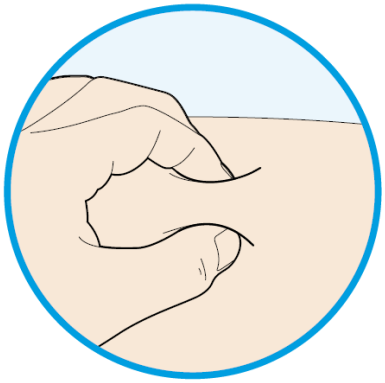
1. Pull off the needle cap.

- 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.

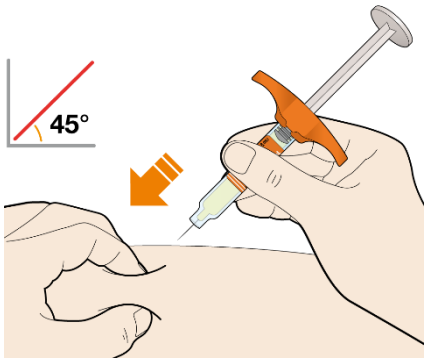


2. Pinch the skin.

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

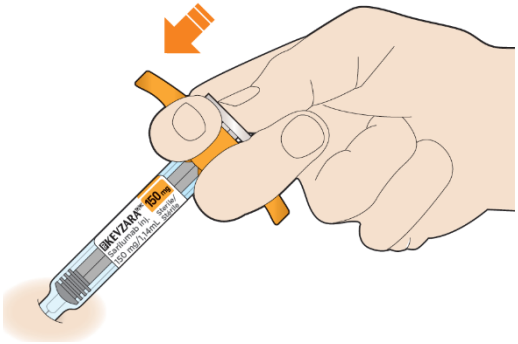


3. Insert the needle into the fold of skin at roughly a 45º angle.



4. Push the plunger down.

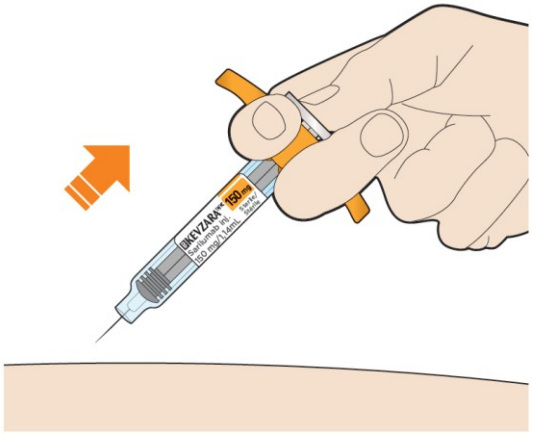
- Slowly push the plunger down as far as it will go until the syringe is empty.



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

- Pull the needle out at the same angle it was injected.
- If you see any blood, press a cotton ball or gauze on the site.

✗ **Do not** rub your skin after the injection.

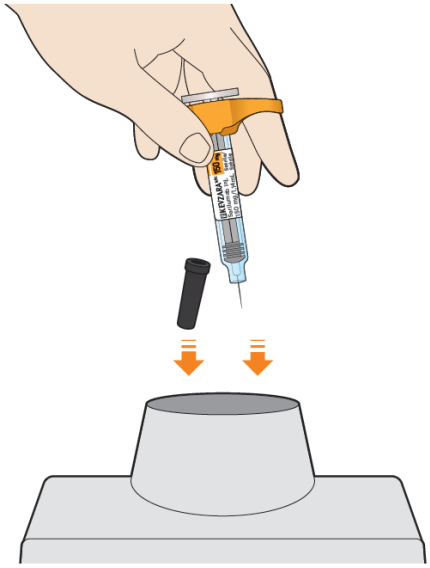


6. Put your used syringe and the cap into a puncture-resistant container.

- 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.



Last Revised: October 21, 2022

INSTRUCTIONS FOR USE

KEVZARA®

(sarilumab)

Injection, for Subcutaneous Injection

Single-Dose Pre-Filled Pen

Important information

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

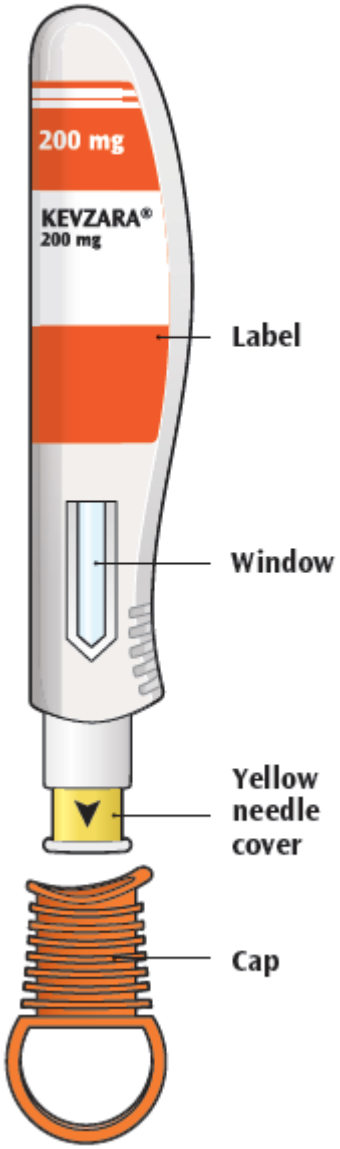
Ask your healthcare provider to show you the right way to use the pen before you inject for the first time.

Do	Do not
✓ Read all of the instructions carefully before using a pen. ✓ Keep unused pens in the original carton and store in the refrigerator between 2ºC and 8ºC (36ºF and 46ºF). ✓ Keep the carton in an insulated bag with an ice pack when traveling. ✓ Let the pen warm up at room temperature for at least 60 minutes before using. ✓ Use the pen within 14 days after taking it out of the refrigerator or insulated bag. ✓ Keep the pen out of the reach of children.	✗ Do not use the pen if it has been damaged or the needle cap is missing or not attached. ✗ Do not remove the needle cap until just before you are ready to inject. ✗ Do not press or touch the yellow needle cover with your fingers. ✗ Do not try to put the cap back on a pen. ✗ Do not re-use the pen. ✗ Do not freeze or heat up the pen. ✗ Once removed from the refrigerator, do not store the pen above 25ºC ✗ Do not expose the pen to direct sunlight. ✗ Do not inject through your clothes.

Keep these instructions for future use.

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

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



Step A: Get ready for an injection

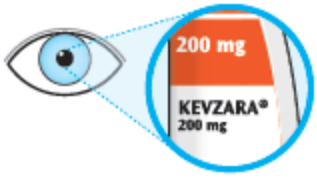
1. Prepare all the equipment you will need on a clean, flat working surface.

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

2. Look at the label.

- Check that you have the correct medicine and the correct dose.
- Check the expiration date (EXP), this is shown on the side of the pens.

✗ **Do not** use the syringe if the date has passed.

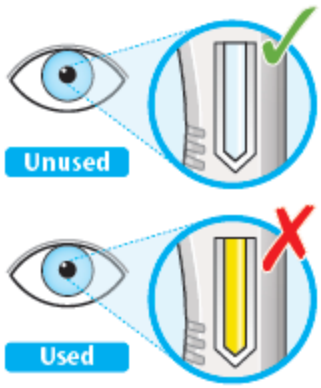


3. Look at the medicine.

- Check if the liquid is clear and colourless to pale yellow.
- You may see an air bubble, this is normal.

✗ **Do not** inject if the liquid is cloudy, discoloured or contains particles.

✗ **Do not** use if the window is solid yellow.



4. Lay the pen on a flat surface and allow it to warm up at room temperature for at least 60 minutes.

- Using the pen at room temperature may make the injection more comfortable.

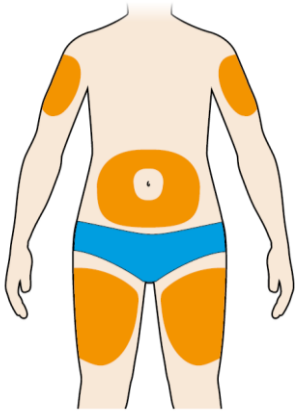
✗ **Do not** use the pen if it has been out of the refrigerator for more than 14 days.

✗ **Do not** heat the pen; let it warm up on its own.

✗ **Do not** expose the pen to direct sunlight.

5. Select the injection site.

- You can inject into your thigh or belly (abdomen) – except for the 5 cm (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.



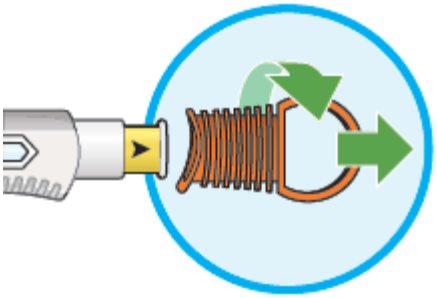
6. Prepare the injection site.

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

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

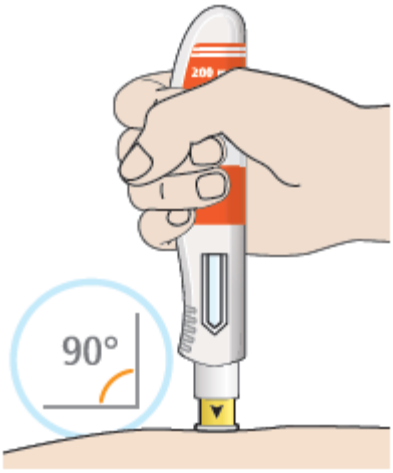
1. Twist or pull off the orange cap.

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



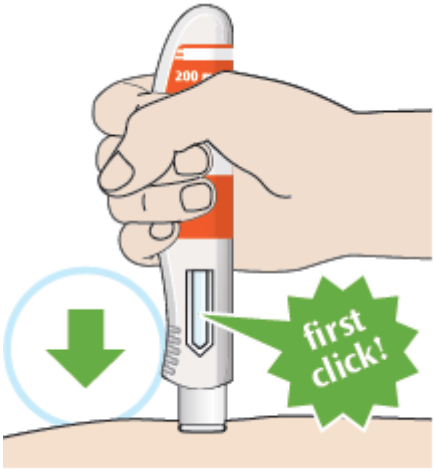
2. Put the yellow needle cover on your skin at roughly a 90º angle.

- Make sure you can see the window.



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

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



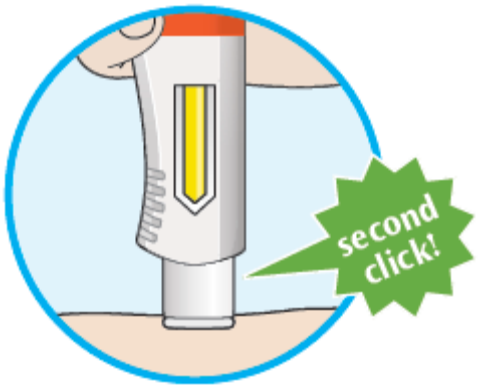
4. Keep holding the pen firmly against your skin.

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

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

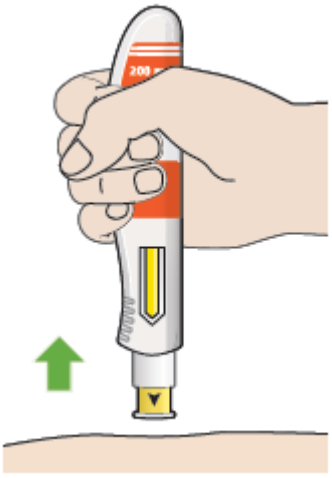
- If you do not hear a second click, you should still check to see if the window has turned fully yellow.

✗ If the window does not turn fully yellow, **do not** give yourself a second dose without speaking to your healthcare



6. Pull the pen away from your skin.

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



7. Put your used pen and the cap into a puncture-resistant container.

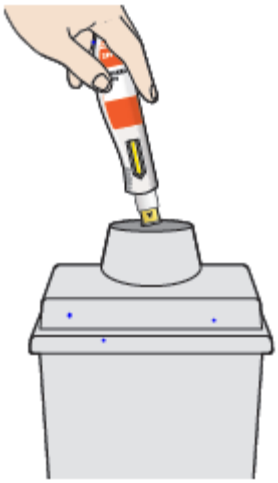
- Put your used pen and the cap in a puncture resistant container right away after use.
- Always keep the container out of the sight and reach of children.

✗ **Do not** put the cap back on.

✗ **Do not** throw away the used pens in the household waste.

✗ **Do not** recycle your used puncture-resistant container.

✗ **Do not** dispose of your used puncture-resistant container in your household waste unless your local guidelines permit this. Ask your doctor, pharmacist or nurse how to throw away the container.



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