

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**PrREMSIMA™ SC**  
(infliximab injection)

Solution for Subcutaneous Injection, 120 mg / ml

**Professed Standard**

Biological Response Modifier

Manufactured by:  
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## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

REMSIMA SC (infliximab injection) is indicated for:

- use in combination with methotrexate for the reduction in signs and symptoms, inhibition of the progression of structural damage and improvement in physical function in adult patients with moderately to severely active rheumatoid arthritis.

REMSIMA SC should be used as maintenance therapy after the completion of an induction period with intravenous infliximab (see **4 DOSAGE AND ADMINISTRATION**).

**REMSIMA SC should be used by physicians who have sufficient knowledge of rheumatoid arthritis and who have fully familiarized themselves with the efficacy/safety profile of REMSIMA SC.**

#### 1.1 Pediatrics (< 18 years of age)

No data on the safety and efficacy of subcutaneous infliximab in children aged below 18 years of age are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics (≥ 65 years of age)

Clinical studies with REMSIMA SC did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Geriatric patients treated with intravenous infliximab had similar efficacy and safety profiles to younger patients.

### 2 CONTRAINDICATIONS

REMSIMA SC is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- Patients with severe infections such as sepsis, abscesses, tuberculosis and opportunistic infections (see **WARNINGS AND PRECAUTIONS, Risk of Infections**).
- Patients with moderate or severe (NYHA Class III/IV) congestive heart failure (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS, Congestive Heart Failure**).
- Patients with history of hypersensitivity to infliximab, to other murine proteins, or to any excipients. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section of the product monograph.

### 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

#### Serious Warnings and Precautions

##### RISK OF INFECTIONS

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving infliximab. Some of these infections have been fatal.

Patients must be evaluated for the risk of tuberculosis, including latent tuberculosis, prior to initiation of REMSIMA SC. This evaluation should include a detailed medical history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray (if indicated), should be performed in all patients. Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised. Treatment of latent tuberculosis infection should be initiated prior to therapy with REMSIMA SC (see WARNINGS AND PRECAUTIONS, Risk of Infections).

##### Hepatosplenic T-cell Lymphoma

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with tumour necrosis factor (TNF)-blockers including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

### 4 DOSAGE AND ADMINISTRATION

#### 4.1 Dosing Considerations

It is important to check the product labels to ensure that the correct formulation of infliximab (intravenous or subcutaneous) is being administered to the patient, as prescribed. REMSIMA SC is not intended for intravenous administration and should be administered via a subcutaneous injection only. REMSIMA SC is intended for use as maintenance therapy after the completion of a dose-induction phase using an intravenous (IV) formulation of infliximab, see **4.3 Administration**.

#### 4.2 Recommended Dose and Dosage Adjustment

##### Rheumatoid Arthritis

*For patients initiating treatment with infliximab:*

Treatment with REMSIMA SC administered subcutaneously in adult patients with moderately to severely active rheumatoid arthritis should be initiated as maintenance therapy 4 weeks following a dose-induction phase, see **4.3 Administration**. The recommended dose for

REMSIMA SC is 120 mg once every 2 weeks. REMSIMA SC should be given in combination with methotrexate.

*For patients already receiving intravenous infliximab maintenance therapy:*

For patients who have been on maintenance therapy with intravenous infliximab and who are switching to REMSIMA SC maintenance therapy, the first dose of REMSIMA SC may be administered 8 weeks after the last infliximab intravenous infusion. There is insufficient information regarding efficacy and safety of REMSIMA SC in patients who received intravenous infusions of infliximab higher than 3 mg/kg every 8 weeks. Information regarding switching patients from the subcutaneous formulation to intravenous infliximab is not available.

#### Pediatrics

Health Canada has not authorized an indication for pediatric use (**see INDICATIONS**).

### **4.3 Administration**

REMSIMA SC 120 mg solution for subcutaneous injection is provided with a pre-filled syringe or in a pre-filled pen, and administered by subcutaneous (under the skin) injection only. Full instructions for use are provided in the **PATIENT MEDICATION INFORMATION**.

*Dose-induction for initiation of infliximab therapy:*

REMSIMA SC is intended for maintenance therapy only; intravenous formulations of infliximab are available for dose-induction. For patients beginning infliximab therapy, the initial two intravenous infliximab infusions will be given intravenously by the physician or nurse. See detailed instructions in the appropriate labelling for the selected intravenous infliximab preparation.

*REMSIMA SC maintenance therapy:*

The first dose of REMSIMA SC may be administered under the supervision of the physician or nurse 4 weeks after the second infusion in a dose-induction regimen (i.e. at Week 6 following two IV infusion doses at Weeks 0 & 2) or 8 weeks after the most recent infusion for patients already receiving infliximab maintenance therapy. The physician or nurse should ensure appropriate follow-up of patients for any systemic injection reaction(s) and localized injection site reaction(s).

For subsequent REMSIMA SC injections and after proper training in subcutaneous injection technique, patients may self-inject with REMSIMA SC if their physician determines that it is appropriate. Adequate medical follow-up should be provided by the physician as necessary. Suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions. REMSIMA SC should be discontinued in patients who have experienced a serious systemic allergic or hypersensitivity reaction.

REMSIMA SC should be refrigerated at 2-8°C. **Do not freeze.** REMSIMA SC may be stored at temperatures up to a maximum of 25°C for a period of up to 28 days. REMSIMA SC must be discarded if not used within the 28-day period (See **STORAGE, STABILITY AND DISPOSAL**).

#### 4.4 Missed Dose

##### Missed dose for up to 7 days

If the patient misses a dose of REMSIMA SC for up to 7 days after the original scheduled dose, the missed dose should be taken immediately. The next dose should be administered as per the originally planned date and thereafter on the original bi-weekly schedule.

##### Missed dose for 8 days or more

If the patient misses a dose of REMSIMA SC for 8 days or more after the original scheduled dose, the missed dose should not be taken. The next dose should be administered as per the next originally planned date and thereafter on the original bi-weekly schedule.

#### 5 OVERDOSAGE

Repeated doses of subcutaneous infliximab up to 240 mg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects. Appropriate symptomatic treatment should be instituted immediately.

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

#### 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table - Dosage Forms, Strengths, Composition and Packaging**

<b>Route of Administration</b>	<b>Dosage Form / Strength/Composition</b>	<b>Non-medicinal Ingredients</b>
Subcutaneous injection	1 mL sterile solution / 120 mg/ pre-filled syringe 1 mL sterile solution / 120 mg/ pre-filled syringe with automatic needle guard 1 mL sterile solution / 120 mg/ pre-filled pen	Acetic acid, sodium acetate trihydrate, sorbitol, polysorbate 80, water for injection

#### 7 DESCRIPTION

REMSIMA SC (infliximab injection) consists of a chimeric immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to the human tumor necrosis factor alpha (TNF $\alpha$ ).

The REMSIMA SC drug product is formulated as a clear to opalescent, colorless to pale brown solution which is supplied as a single use pre-filled syringe or pre-filled pen. Each syringe or pen is designed to deliver a single dose of 120 mg infliximab active substance. The components of a single syringe or pen of the drug product REMSIMA SC are: infliximab, acetic acid, sodium acetate trihydrate, sorbitol, polysorbate 80, water for injection.

#### 8 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

## General

To help ensure the traceability of biologic products, health professionals, caregivers and patients should recognize 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.

### **Risk of Infections**

**Serious infections due to bacterial (including sepsis and pneumonia), invasive fungal, viral, and other opportunistic pathogens, have been reported in patients receiving TNF-blocking agents. Some of these infections have been fatal. Many of the serious infections in patients treated with infliximab have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections.**

**REMSIMA SC should not be given to patients with a clinically important active infection, including tuberculosis. Caution should be exercised when considering the use of REMSIMA SC in patients with a chronic infection or a history of recurrent infection. Patients should be monitored for signs and symptoms of infection while on or after treatment with REMSIMA SC. New infections should be closely monitored. If a patient develops a serious infection, REMSIMA SC therapy should be discontinued (see ADVERSE REACTIONS, Infections).**

**Cases of histoplasmosis, coccidioidomycosis, blastomycosis, listeriosis, pneumocystosis, and tuberculosis have been observed in patients receiving infliximab. For patients who have resided in or travelled to regions where histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of REMSIMA SC treatment should be carefully considered before initiation or continuation of REMSIMA SC therapy.**

### **Invasive Fungal Infections**

In patients treated with REMSIMA SC, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localized disease, and antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. The decision to administer empiric antifungal therapy should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

### **Tuberculosis**

Cases of active tuberculosis have occurred in patients treated with infliximab during and after treatment for latent tuberculosis. Patients receiving REMSIMA SC should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis infection. The possibility of undetected latent tuberculosis should be considered, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with REMSIMA SC should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with infliximab. Anti-



tuberculosis therapy should be considered prior to initiation of REMSIMA SC in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating REMSIMA SC should also be considered in patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis. The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

### **Opportunistic Infections**

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF-blockers, including infliximab. Patients have frequently presented with disseminated rather than localized disease.

### **Concurrent Administration of TNF-alpha Inhibitor and Anakinra**

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF $\alpha$ -blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF $\alpha$ -blocking agents. Therefore, the combination of REMSIMA SC and anakinra is not recommended.

### **Concurrent Administration of REMSIMA SC with Abatacept**

In clinical studies, concurrent administration of TNF-blocking agents and abatacept has been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Because of the nature of the adverse events seen with the combination of TNF-blocking agents and abatacept therapy, the combination of REMSIMA SC and abatacept is not recommended.

### **Concurrent Administration with other Biological Therapeutics**

There is insufficient information regarding the concomitant use of REMSIMA SC with other biological therapeutics used to treat the same conditions as REMSIMA SC. The concomitant use of REMSIMA SC with these biologics is not recommended because of the possibility of an increased risk of infection.

### **Switching between Biological Therapeutics**

When switching from one biologic to another, patients should continue to be monitored, since overlapping biological activity may further increase the risk of infection.

### **Carcinogenesis and Mutagenesis**

#### **Lymphoma**

Lymphomas have been observed in patients treated with TNF-blocking agents, including infliximab. In clinical trials, patients treated with infliximab had a higher incidence of lymphoma than the expected rate in the general population. Patients with rheumatoid arthritis, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) for the development of lymphoma than the general

population, even in the absence of TNF-blocking therapy. The role of TNF-blockers in the development of malignancy is not known.

### **Hepatosplenic T-cell lymphoma**

Post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blockers including infliximab. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker. The vast majority of infliximab cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. Cases of hepatosplenic T-cell lymphoma have also occurred in Crohn's disease and ulcerative colitis patients receiving azathioprine or 6-mercaptopurine who were not treated with infliximab. The causal relationship of hepatosplenic T-cell lymphoma to infliximab therapy remains unclear.

### **Leukemia**

Cases of acute and chronic leukemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

### **Non-lymphoma malignancy**

In the controlled portions of clinical trials of some TNF-blocking agents, including infliximab, more malignancies (excluding lymphoma and non-melanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients (see **ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease**). The rate of non-lymphoma malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate among control patients was lower than expected.

In an exploratory clinical trial evaluating the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking.

### **Cervical cancer**

A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. A causal relationship between infliximab and cervical cancer cannot be excluded. Periodic screening should continue in women treated with REMSIMA SC, including those over 60 years of age.

### **Skin cancers**

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including infliximab. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

The potential role of TNF-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy (see **ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease**).

Long-term studies in animals have not been performed to evaluate the carcinogenic potential. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. Tumorigenicity studies in mice deficient in TNF $\alpha$  demonstrated no increase in tumors when challenged with known tumor initiators and/or promoters.

### **Cardiovascular**

**REMSIMA SC should be used with caution in patients with mild heart failure (NYHA Class I/II). Patients should be closely monitored, and REMSIMA SC must not be continued in patients who develop new or worsening symptoms of heart failure (see CONTRAINDICATIONS and ADVERSE REACTIONS, Congestive Heart Failure).**

The results of a randomized study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg intravenous infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg.

### **Driving and Operating Machinery**

REMSIMA SC may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of REMSIMA SC.

### **Hematologic**

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab. Caution should be exercised in patients treated with REMSIMA SC who have a current or past history of significant cytopenia. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of REMSIMA SC therapy should be considered in patients with confirmed significant hematologic abnormalities.

### **Hepatic/Biliary/Pancreatic**

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience with infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between infliximab and these events has not been established. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations  $\geq 5$  times the upper limit of normal develop, REMSIMA SC should be discontinued immediately, and a thorough investigation of the abnormality should be undertaken. As also observed with the use of other immunosuppressive drugs, reactivation of hepatitis B has occurred very rarely in patients receiving infliximab who are chronic carriers of this virus (i.e., surface antigen positive). Patients should be tested for hepatitis B virus (HBV) infection before initiating treatment with immunosuppressants, including REMSIMA SC. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B should be appropriately evaluated prior to the initiation of REMSIMA SC therapy and monitored closely during treatment and for several months following discontinuation of therapy.

## **Immune**

### **Hypersensitivity Reactions**

Infliximab has been associated with hypersensitivity reactions that vary in their time of onset. Hypersensitivity reactions, which include urticaria, dyspnea, and/or bronchospasm, laryngeal edema and hypotension, have occurred during or within 2 hours of intravenous infliximab infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease and rheumatoid arthritis patients 3 to 12 days after infliximab therapy was reinstated following an extended period without infliximab treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMSIMA SC should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see **ADVERSE REACTIONS, Hypersensitivity Reactions**).

### **Delayed Hypersensitivity Reactions**

In clinical studies, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab-free interval. Patients should be advised to seek immediate medical advice if they experience any delayed adverse reaction. If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

### **Hypersensitivity Reactions following Readministration of Infliximab**

In a rheumatoid arthritis clinical trial where subjects were receiving low dose methotrexate resulted in a higher incidence of serious and severe infusion reactions during the reinduction regimen than had been observed in rheumatoid arthritis and Crohn's disease trials in which a period of no drug treatment was followed by regular maintenance therapy without reinduction. Most of these reactions occurred during the second reinduction infusion at Week 2. The serious infusion reactions included anaphylaxis, urticaria, facial edema, chills and itching. Retreatment with a reinduction regimen after a period of no treatment is not recommended. There are no data on readministration in patients treated with REMSIMA SC maintenance therapy.

### **Autoimmunity**

Treatment with infliximab may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with infliximab, treatment should be discontinued (see **ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome**).

### **Immunogenicity**

Treatment with infliximab can be associated with the development of antibodies to infliximab (see **WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions**).

In a Phase III study of rheumatoid arthritis (CT-P13 3.5 Part 2) in patients who received concomitant MTX, anti-infliximab antibodies occurred at Week 30 in 48.4% and 57.1% following the subcutaneous infliximab and intravenous infliximab, respectively. Patients who were antibody-positive were more likely to have higher rates of clearance than patients who were antibody negative.

Immunogenicity tests are generally product-specific. Comparison of antibody rates to those from other products, or comparison of the incidence of antibodies between different tests without cross-validation is not appropriate.

### **Vaccinations**

It is recommended that all patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating REMSIMA SC therapy.

### **Live Vaccines/Therapeutic Infectious Agents**

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with REMSIMA SC is not recommended.

Fatal outcome due to disseminated Bacille Calmette-Guérin (BCG) infection has been reported in an infant who received BCG vaccine after *in utero* exposure to infliximab. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with REMSIMA SC.

### **Non-Live Vaccines**

In a subset of patients from a study of intravenous infliximab in RA patients, a similar proportion of patients in each treatment group mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine indicating that infliximab did not interfere with T-cell independent humoral immune responses.

### **Neurologic**

Infliximab and other agents that inhibit TNF have been associated with seizure, and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMSIMA SC in patients with these neurological disorders, and should consider discontinuation of REMSIMA SC if these disorders develop.

Physicians should alert patients to the presence of the Patient Package Insert, provide this information to them, and ensure full understanding of the content.

### **Peri-Operative Considerations**

There is limited safety experience of infliximab in patients who have undergone surgical procedures, including arthroplasty. The long half-life of infliximab should be taken in to consideration if a surgical procedure is planned. A patient who requires surgery while on REMSIMA SC should be closely monitored for infections, and appropriate actions should be taken.

## **Sexual Health** **Reproduction**

It is unknown whether infliximab can impair fertility in humans.

### **8.1 Special Populations**

#### **8.1.1 Pregnant Women**

Women of childbearing potential must use adequate contraception to prevent pregnancy and continue to do so for at least 6 months after the last REMSIMA SC treatment.

There are no adequate and well-controlled studies in pregnant women. As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 6 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including disseminated infection that can become fatal (see **WARNINGS AND PRECAUTIONS, Live Vaccines/Therapeutic Infectious Agents and Non-Live Vaccines**).

#### **8.1.2 Breast-feeding**

It is unknown if infliximab is excreted in human milk or absorbed systemically after ingestion. Because immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from infliximab, breast feeding is not recommended during treatment and for 6 months after the last dose of REMSIMA SC. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

#### **8.1.4 Geriatrics (≥ 65 years of age)**

Specific studies of subcutaneous infliximab in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies with intravenous infliximab and this suggests that the use in geriatric population is associated with no overall differences in safety and efficacy and the same is expected for subcutaneous infliximab. Studies with intravenous infliximab indicated a potentially greater risk of serious infections in patients 65 years and older; there are inadequate data to determine whether the use of REMSIMA SC is associated with differences in safety profile in older adults.

## **9 ADVERSE REACTIONS**

### **9.1 Adverse Reaction Overview**

The most common adverse drug reactions reported from both clinical trials and post-marketing reports are infections, allergic reactions and infusion-related reactions. Less common adverse drug reactions from these sources, which may be serious and clinically relevant include hepatobiliary events (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**), demyelinating disorders (see **WARNINGS AND PRECAUTIONS, Neurological Events**), and lymphoma (see **WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis**).

## 9.2 Clinical Trial Adverse Reactions

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

### Description of Data Sources

Clinical studies involving intravenous and subcutaneous formulations of infliximab were conducted in 474 patients with rheumatoid arthritis (343 patients exposed), Crohn's disease (53 patients exposed) and ulcerative colitis (78 patients exposed). Overall, treatment-emergent adverse events (TEAEs) were reported in 62% of patients (60% of subcutaneous infliximab-treated patients vs 65% of intravenous infliximab-treated patients) and treatment-emergent serious adverse events (TESAEs) were reported in 6% of patients (5% of subcutaneous infliximab-treated patients vs 8% of intravenous infliximab-treated patients).

Study CT-P13 3.5 Part 2 was a randomised, parallel-group, multi-dose, 64-week study to evaluate efficacy, PK and safety of subcutaneous infliximab in RA patients. The study was conducted to establish therapeutic non-inferiority of subcutaneous infliximab compared with intravenous infliximab in 343 RA patients.

**Table 1: Number of RA Patients with 1 or More Treatment-Emergent Adverse Events (Frequency of at Least 3 Patients Overall) during the Maintenance Phase of RA trial (Study CT-P13 3.5 Part 2)**

	Week 6 to < Week 30		Week 6 to Week 64	
	Intravenous Infliximab (N=175)	Subcutaneous Infliximab (N=168)	Intravenous Infliximab <sup>a</sup> (N=175)	Subcutaneous Infliximab (N=168)
Patient with 1 or more adverse events	71 (40.6)	54 (32.1)	117 (66.9)	92 (54.8)
System organ class/preferred term				
Blood and lymphatic system disorders				
Anemia	1 (0.6)	2 (1.2)	2 (1.1)	2 (1.2)
Leukopenia	3 (1.7)	3 (1.8)	4 (2.3)	3 (1.8)
Neutropenia	3 (1.7)	4 (2.4)	3 (1.7)	6 (3.6)
Gastrointestinal disorders				
Abdominal pain	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)
Diarrhea	0	1 (0.6)	1 (0.6)	4 (2.4)
Nausea	0	0	1 (0.6)	2 (1.2)
Toothache	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)
General disorders and administration site conditions				
Injection site reaction	4 (2.3)	11 (6.5)	22 (12.6)	30 (17.9)
Infections and infestations				
Asymptomatic bacteriuria	0	0	2 (1.1)	3 (1.8)
Bronchitis	3 (1.7)	3 (1.8)	4 (2.3)	5 (3.0)
Cystitis	2 (1.1)	0	3 (1.7)	0
Latent tuberculosis	1 (0.6)	1 (0.6)	10 (5.7)	8 (4.8)
Nasopharyngitis	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)
Oral herpes	2 (1.1)	3 (1.8)	3 (1.7)	4 (2.4)
Pharyngitis	1 (0.6)	3 (1.8)	2 (1.1)	3 (1.8)
Pneumonia	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)
Rhinitis	1 (0.6)	1 (0.6)	2 (1.1)	1 (0.6)
Tonsillitis	1 (0.6)	0	3 (1.7)	1 (0.6)

	Week 6 to < Week 30		Week 6 to Week 64	
	Intravenous Infiximab (N=175)	Subcutaneous Infiximab (N=168)	Intravenous Infiximab <sup>a</sup> (N=175)	Subcutaneous Infiximab (N=168)
Upper respiratory tract infection	6 (3.4)	4 (2.4)	13 (7.4)	8 (4.8)
Urinary tract infection	4 (2.3)	3 (1.8)	7 (4.0)	9 (5.4)
Viral upper respiratory tract infection	6 (3.4)	7 (4.2)	14 (8.0)	10 (6.0)
Injury, poisoning and procedural complications				
Systemic reaction	8 (4.6)	1 (0.6)	10 (5.7)	5 (3.0)
Investigations				
Alanine aminotransferase increased	5 (2.9)	4 (2.4)	9 (5.1)	7 (4.2)
Aspartate aminotransferase increased	3 (1.7)	1 (0.6)	6 (3.4)	2 (1.2)
Blood creatine phosphokinase increased	0	0	2 (1.1)	2 (1.2)
Gamma-glutamyltransferase increased	3 (1.7)	1 (0.6)	3 (1.7)	3 (1.8)
Transaminases increased	2 (1.1)	0	3 (1.7)	1 (0.6)
Musculoskeletal and connective tissue disorders				
Back pain	2 (1.1)	1 (0.6)	4 (2.3)	2 (1.2)
Rheumatoid arthritis	4 (2.3)	2 (1.2)	6 (3.4)	7 (4.2)
Spinal osteoarthritis	1 (0.6)	1 (0.6)	2 (1.1)	1 (0.6)
Nervous system disorders				
Dizziness	3 (1.7)	1 (0.6)	3 (1.7)	2 (1.2)
Headache	4 (2.3)	2 (1.2)	7 (4.0)	6 (3.6)
Vascular disorders				
Hypertension	1 (0.6)	1 (0.6)	4 (2.3)	1 (0.6)

Note: Data from Weeks 6 to <30 provide comparison of safety between subcutaneous infiximab and intravenous infiximab, while data from Weeks 6 to 64 provide the overall safety picture of subcutaneous infiximab or intravenous to subcutaneous maintenance therapy.

<sup>a</sup> Intravenous infiximab was switched to subcutaneous infiximab at Week 30

## **Subcutaneous Infiximab**

### **Hypersensitivity Reactions**

#### **Systemic Injection Reaction/ Localized Injection Site Reaction**

The safety profile of subcutaneous infiximab in combination with methotrexate was evaluated in a Phase I/III parallel group study in patients with active rheumatoid arthritis. The safety population consisted of 168 patients in the subcutaneous infiximab group and 175 patients in the intravenous infiximab group. For study details, see **PART II, Clinical Trials**.

The incidence of systemic injection reactions (e.g. rash, pruritus, flushing and edema) was 1.2 per 100 patient-years in the subcutaneous infiximab group (from Week 6) and 2.1 per 100 patient-years in the intravenous infiximab group who switched to subcutaneous infiximab administration (from Week 30). All systemic injection reactions were mild to moderate.

The incidence of localized injection site reactions (e.g. injection site erythema, pain, pruritus and swelling) was 17.6 per 100 patient-years in the subcutaneous infiximab group (from Week 6)



and 21.4 per 100 patient-years in those who switched to subcutaneous infliximab administration (from Week 30). Most of these reactions were mild to moderate.

### **Infections**

In subcutaneous infliximab studies, infections were reported in 30% of subcutaneous infliximab-treated patients and in 33% of intravenous infliximab-treated patients.

In Study CT-P13 3.5 Part 2, 29% of subcutaneous infliximab-treated RA patients had infections reported vs. 34% of intravenous infliximab-treated RA patients (up to 64 weeks of follow-up). The infections most frequently reported in the RA study were viral upper respiratory tract infection, upper respiratory tract infection and latent tuberculosis.

No increased risk of serious infections was observed with subcutaneous infliximab compared with intravenous infliximab.

In subcutaneous infliximab studies, latent tuberculosis was reported in 4% of infliximab-treated patients.

### **Hepatobiliary Events**

In subcutaneous infliximab clinical trials, hepatobiliary disorders were reported in 1% of subcutaneous infliximab-treated patients and in 2% of intravenous infliximab-treated patients.

In Study CT-P13 3.5 Part 2, there was one subcutaneous infliximab-treated RA patient with cholecystitis chronic and four intravenous infliximab-treated RA patients with chronic hepatitis, hepatic steatosis, hepatomegaly and liver disorders (up to 64 weeks of follow-up).

Mild or moderate elevations of ALT and AST have been observed in patients receiving subcutaneous infliximab or intravenous infliximab without progression to severe hepatic injury. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved in most patients without discontinuation of infliximab treatment.

### **Malignancies/Lymphoproliferative Disease**

The potential role of TNF-blocking therapy in the development of malignancies is not known. Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering infliximab treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving infliximab.

In subcutaneous infliximab clinical studies, one RA patient developed malignant ovarian cyst amongst 168 RA patients administered with subcutaneous infliximab, which is at a rate of 0.586 cases per 100 patient-years. The rate of malignancies among subcutaneous infliximab-treated patients was similar to rates observed in previous controlled clinical trials with infliximab.

## **Congestive Heart Failure**

In subcutaneous infliximab clinical trials, no mortality related to congestive heart failure was reported. There was one case of moderate cardiac failure in one UC patient, who was administered with subcutaneous infliximab. There is no experience with Remsima SC in patients with NYHA Class III or IV heart failure, severe uncontrolled cardiac disease, or history of myocardial infarction.

## **Intravenous Infliximab**

The following information reflects the use of intravenous infliximab in clinical trials. There are inadequate data to determine whether these findings apply to the use of subcutaneous infliximab, therefore these should be considered as potential risks.

## **Autoantibodies/Lupus-like Syndrome**

Approximately 55% of 1598 intravenous infliximab-treated patients in clinical trials (primarily RA and CD) who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately 20% of 265 placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 19% of 2116 intravenous infliximab-treated patients compared with 0% of 422 placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

In a study of intravenous infliximab in RA patients through Week 102, 62% of intravenous infliximab-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared with 27% of placebo-treated patients. In another study of intravenous infliximab in RA patients through Week 58, 66% of intravenous infliximab-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared with 21% of placebo-treated patients. In both RA studies, anti-dsDNA antibodies developed in approximately 15% of intravenous infliximab-treated patients, compared to none of the placebo-treated patients. No association was seen between intravenous infliximab dose/schedule and development of ANA or anti-dsDNA antibodies.

Of Crohn's disease patients treated with intravenous infliximab who were evaluated for antinuclear antibodies (ANA), 40% developed ANA between screening and last evaluation. Anti-dsDNA antibodies developed in approximately 20% of Crohn's disease patients treated with intravenous infliximab. The development of anti-dsDNA antibodies was not related to either the dose or duration of intravenous infliximab treatment. However, baseline therapy with an immunosuppressant in Crohn's disease patients was associated with reduced development of anti-dsDNA antibodies (3% compared to 21% in patients not receiving any immunosuppressant). Crohn's disease patients were approximately 2 times more likely to develop anti-dsDNA antibodies if they were ANA-positive at study entry.

In clinical studies, 6 patients were diagnosed with a possible lupus-like syndrome, four with Crohn's disease and two with rheumatoid arthritis. All patients improved following discontinuation of therapy and/or appropriate medical treatment. No patients had renal involvement. The lupus-like syndrome in one patient with rheumatoid arthritis remained ongoing at the end of the study. One case of a lupus-like reaction has been observed in a Crohn's disease patient in up to three years of long-term follow-up (see **WARNINGS AND PRECAUTIONS, Autoimmunity**).

## Hepatobiliary Events

In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving intravenous infliximab (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving intravenous infliximab without progression to severe hepatic injury. Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving intravenous infliximab than in controls, both when intravenous infliximab was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of intravenous infliximab, or modification of concomitant medications.

## Malignancies/Lymphoproliferative Disease

The potential role of TNF-blocking therapy in the development of malignancies is not known. Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering infliximab treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving infliximab.

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF-blocker compared with control patients. In the controlled and open-label portions of intravenous infliximab clinical trials, 5 patients developed lymphomas among 5780 patients treated with intravenous infliximab (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, ankylosing spondylitis, and ulcerative colitis, 5 lymphomas were observed for a rate of 0.09 cases per 100 patient-years of follow-up, which is approximately 4-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several-fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

In the controlled portions of clinical trials of some TNF-blocking agents including intravenous infliximab, more cases of non-lymphoma malignancies have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of intravenous infliximab trials in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, psoriasis, ankylosing spondylitis, and ulcerative colitis, 14 patients were diagnosed with non-lymphoma malignancies among 4019 intravenous infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among intravenous infliximab-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for intravenous infliximab-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of non-lymphoma malignancies among intravenous

infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with intravenous infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age.

### **Congestive Heart Failure**

In a phase II study evaluating intravenous infliximab in NYHA Class III/IV CHF patients (left ventricular ejection fraction  $\leq 35\%$ ), higher incidences of mortality and hospitalization due to worsening heart failure were seen in intravenous infliximab-treated patients, especially those treated with 10 mg/kg. One hundred and fifty patients were treated with 3 infusions of intravenous infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 28 weeks, 4 of 101 patients treated with intravenous infliximab (1 at 5 mg/kg and 3 at 10 mg/kg) died compared with no deaths among the 49 placebo-treated patients. In follow-up, at 38 weeks, 9 patients treated with intravenous infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared with one death among the placebo-treated patients. At 28 weeks, 14 of 101 patients treated with intravenous infliximab (3 at 5 mg/kg and 11 at 10 mg/kg) were hospitalized for worsening CHF compared with 5 of the 49 placebo-treated patients (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Cardiovascular**).

There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

### **9.3 Less Common Clinical Trial Adverse Drug Reactions**

#### **Subcutaneous Infliximab**

Other medically relevant adverse events occurring in less than 3 patients overall in patients treated with REMSIMA SC for any indication were as follows, presented by body system:

**Blood and lymphatic system disorders:** antiphospholipid syndrome, erythropenia, hypereosinophilic syndrome, hypochromic anemia, iron deficiency anemia, lymphadenopathy, lymphadenopathy mediastinal, lymphopenia, polycythemia, thrombocytopenia

**Cardiac disorders:** arrhythmia, bradycardia, bundle branch block right, cardiac arrest, cardiac failure, mitral valve incompetence, myocardial infarction, sinus bradycardia, subendocardial ischemia, tachycardia, tricuspid valve incompetence, ventricular extrasystoles

**Congenital, familial and genetic disorders:** hereditary hemochromatosis, Lown-Ganong-Levine syndrome

**Ear and labyrinth disorders:** middle ear inflammation, tinnitus

**Endocrine disorders:** cushingoid

**Eye disorders:** chalazion, eye pruritus

**Gastrointestinal disorders:** abdominal distension, abdominal pain upper, anal fissure, anal fistula, chronic gastritis, colitis, constipation, duodenal ulcer hemorrhage, dyschezia, flatulence, gastritis, glossitis, hemorrhoids, hypoesthesia oral, inguinal hernia, intestinal obstruction, lip erythema, rectal tenesmus

**General disorders and administration site conditions:** asthenia, chest pain, enanthema, influenza-like illness, non-cardiac chest pain, edema peripheral, peripheral swelling, soft tissue inflammation, sudden death

**Hepatobiliary disorders:** cholecystitis chronic, chronic hepatitis, hepatic steatosis, hepatomegaly, hyperbilirubinemia, liver disorder

**Immune system disorders:** seasonal allergy

**Infections and infestations:** abscess intestinal, acarodermatitis, acne pustular, acute sinusitis, adenoviral upper respiratory infection, anal abscess, angular cheilitis, appendicitis, bronchitis hemophilus, conjunctivitis bacterial, cystitis, eczema infected, enterobiasis, furuncle, gastroenteritis salmonella, gingivitis, herpes ophthalmic, herpes zoster, impetigo, lower respiratory tract infection, oral bacterial infection, otosalpingitis, pharyngotonsillitis, pilonidal cyst, pneumonia legionella, pulmonary tuberculosis, respiratory tract infection, salpingo-oophoritis, sinobronchitis, staphylococcal skin infection, tooth abscess, tooth infection, tracheobronchitis, vaginal infection, varicella, vulvovaginal candidiasis, wound infection

**Injury, poisoning and procedural complications:** animal bite, arthropod bite, burns second degree, contusion, foot fracture, joint injury, limb injury, spinal compression fracture, synovial rupture

**Investigations:** beta-2 glycoprotein antibody positive, blood alkaline phosphatase increased, blood bilirubin increased, blood triglycerides increased, body mass index increased, creatinine renal clearance decreased, electrocardiogram repolarization abnormality, glucose urine, hepatic enzyme increased, interferon gamma release assay positive, neutrophil count decreased, platelet count decreased, weight decreased, weight increased, white blood cell count decreased

**Metabolism and nutrition disorders:** diabetes mellitus, hyperkalemia, hypokalemia

**Musculoskeletal and connective tissue disorders:** arthritis, arthritis enteropathic, bursitis, connective tissue inflammation, intervertebral disc disorder, intervertebral disc protrusion, myalgia, osteoarthritis, osteonecrosis, spinal osteoarthritis, spinal pain

**Neoplasms benign, malignant and unspecified (incl cysts and polyps):** malignant ovarian cyst, non-small cell lung cancer, seborrheic keratosis, skin papilloma

**Nervous system disorders:** carotid artery stenosis, dementia Alzheimer's type, hypoesthesia, neuralgia, paresthesia

**Product issues:** device loosening

**Psychiatric disorders:** anxiety, insomnia, irritability

**Renal and urinary disorders:** chronic kidney disease, hematuria, nephrolithiasis, pollakiuria, renal amyloidosis

**Reproductive system and breast disorders:** balanoposthitis, cervical polyp, prostatitis

**Respiratory, thoracic and mediastinal disorders:** bronchiectasis, cough, nasal congestion, pleurisy, pulmonary mass, sleep apnea syndrome

**Skin and subcutaneous tissue disorders:** acne, butterfly rash, dermal cyst, dermatitis, dermatitis allergic, dermatitis atopic, dry skin, eczema, erythema, erythema nodosum, hidradenitis, lichen planus, night sweats, pruritus, psoriasis, rash follicular, rash papular, seborrheic dermatitis, urticaria

**Vascular disorders:** phlebitis superficial, varicose vein

### **Intravenous Infliximab**

Other medically relevant adverse events occurring at a frequency <1% in patients treated with intravenous infliximab were as follows, presented by body system:

**Administration / application site:** injection site inflammation, injection site ecchymosis, injection site swelling, injection site infection

**Autonomic Nervous System:** fecal incontinence

**Body as a whole:** anaphylactoid reaction, diaphragmatic hernia, generalized edema, surgical/procedural sequela, substernal chest pain, rigors

**Blood:** pancytopenia, splenomegaly

**Cardiovascular:** circulatory failure, hypotension postural, pallor  
**Collagen:** LE syndrome, anti-DNA antibodies, positive antinuclear factor test, anticardiolipin antibodies  
**Ear and Hearing:** otitis externa  
**Endocrine:** adrenal insufficiency, hypothyroidism  
**Eye and Vision:** lacrimation abnormal, iritis, scleritis, eye pain, glaucoma  
**Gastrointestinal:** ileus, intestinal stenosis, pancreatitis, peritonitis, rectal hemorrhage, appetite increased, anal fistula, diarrhea bloody, gastritis, intestinal obstruction, intestinal perforation  
**Central & Peripheral Nervous:** meningitis, neuritis, optic neuritis, peripheral neuropathy, neuralgia, ataxia, dysesthesia, tremor, hyperkinesia  
**Heart Rate and Rhythm:** arrhythmia, bradycardia, cardiac arrest, palpitations  
**Liver and Biliary:** cholelithiasis, hepatitis, bilirubinemia, cholecystitis, hepatocellular damage, elevated GGT, fatty liver, hepatomegaly  
**Metabolic and Nutritional:** hypercholesterolemia  
**Musculoskeletal:** intervertebral disk herniation, tendon disorder, joint stiffness  
**Myo-, Endo-, Pericardial and Coronary Valve:** myocardial infarction, mitral insufficiency, heart murmur, cardiac failure  
**Platelet, Bleeding and Clotting:** thrombocytopenia  
**Neoplasms:** adenocarcinoma, basal cell carcinoma, breast cancer, lymphoma, malignant melanoma, squamous cell carcinoma, bladder carcinoma, rectal carcinoma, uterine cancer, pulmonary carcinoma  
**Psychiatric:** confusion, suicide attempt, irritability, nervousness, amnesia  
**Red Blood Cell:** iron deficiency anemia, hemolytic anemia  
**Reproductive:** menstrual irregularity, dysmenorrhea, menorrhagia, breast fibroadenosis, amenorrhea, female breast pain  
**Resistance Mechanism:** sepsis, serum sickness, tuberculosis, fungal infection, viral infection, sarcoid-like reaction  
**Respiratory:** Adult respiratory distress syndrome, respiratory tract infection, pleural effusion, lobar pneumonia, pulmonary edema, respiratory insufficiency, bronchospasm, asthma, hemoptysis, epistaxis, laryngitis  
**Skin and Appendages:** erythema nodosum, rash maculopapular, rash pustular, photosensitivity reaction, edema periorbital, fasciitis  
**Special Senses, Other:** taste perversion, taste loss  
**Urinary:** renal failure, dysuria, renal calculus, pyelonephritis  
**Vascular (Extracardiac):** brain infarction, thrombophlebitis, vasculitis, brain ischemia, pulmonary embolism  
**White Cell and Reticuloendothelial:** neutropenia, neutrophilia, lymphocytosis

#### **9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data**

Hematologic adverse reactions observed in clinical trials in more than 1 patient include: anemia, iron deficiency anemia, leukopenia, lymphadenopathy, lymphopenia, neutropenia, thrombocytopenia.

The proportion of patients with abnormal ALT levels in response to infliximab is presented in **Table 2**.

**Table 2: Proportion of patients with elevated ALT in subcutaneous infliximab Clinical Trials**

	Proportion of patients with elevated ALT					
	>1 to 3 X ULN		>3 to 5 X ULN		>5 X ULN	
	Intravenous Infliximab	Subcutaneous Infliximab	Intravenous Infliximab	Subcutaneous Infliximab	Intravenous Infliximab	Subcutaneous Infliximab
RA <sup>1</sup>	28.0%	46.4%	5.1%	2.4%	1.1%	0.0%

<sup>1</sup> Note: All patients received induction dosing with intravenous infliximab 3 mg/kg at Weeks 0 and 2 then from Weeks 6 to 30, patients received maintenance dose of intravenous infliximab 3 mg/kg or subcutaneous infliximab 120 mg. From Week 30 onward, all patients received subcutaneous infliximab 120 mg.

## 9.5 Post-Market Adverse Reactions

There are no post-market data available for subcutaneous infliximab.

## 10 DRUG INTERACTIONS

### 10.1 Overview

Specific drug interaction studies have not been conducted. All RA patients that received REMSIMA SC were on concomitant methotrexate therapy.

### 10.2 Drug-Drug Interactions

#### Concurrent Use of REMSIMA SC with other Biological Therapeutics

The combination of REMSIMA SC with other biological therapeutics used to treat the same conditions as REMSIMA SC, including anakinra or abatacept, is not recommended (see **WARNINGS AND PRECAUTIONS, Risk of Infections**).

#### Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with REMSIMA SC. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for at least 6 months following birth (see **WARNINGS AND PRECAUTIONS**).

It is recommended that therapeutic infectious agents not be given concurrently with REMSIMA SC (see **WARNINGS AND PRECAUTIONS**).

#### Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF $\alpha$ , IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of REMSIMA SC in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

Interactions with other drugs have not been established.

### 10.3 Drug-Food Interactions

Interactions with food have not been established.

## 10.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

## 10.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10.6 Drug-Lifestyle Interactions

Interactions with lifestyle have not been established.

# 11 ACTION AND CLINICAL PHARMACOLOGY

## 11.1 Mechanism of Action

Infliximab is a chimeric IgG1 $\kappa$  monoclonal antibody that binds specifically to human TNF $\alpha$ . Infliximab binds to the soluble and transmembrane forms of TNF $\alpha$  with high affinity, thereby neutralizing the biological activity of TNF $\alpha$ . Infliximab was also shown to bind to Fc $\gamma$  receptors [Fc $\gamma$ RI, Fc $\gamma$ RIIa, Fc $\gamma$ RIIb, Fc $\gamma$ RIIIa (V and F) and Fc $\gamma$ RIIIb], FcRn, and C1q. Following binding, cells expressing transmembrane TNF $\alpha$  can be lysed in vitro by complement or effector cell-mediated mechanisms. Infliximab was shown to inhibit the functional activity of TNF $\alpha$  in a wide variety of in vitro bioassays, which demonstrated the following: induction of complement dependent cytotoxicity (CDC), induction of antibody-dependent cell-mediated cytotoxicity (ADCC), inhibition of transmembrane TNF $\alpha$ -dependent apoptosis, suppression of pro-inflammatory cytokine secretion [interleukin 6 (IL-6) and IL-8], and induction of regulatory macrophages.

## 11.2 Pharmacodynamics

There are no relevant data on the pharmacodynamic effects of subcutaneously administered infliximab.

## 11.3 Pharmacokinetics

**Table 3: Summary of Infliximab Pharmacokinetic Parameters in RA Population at Steady State**

	C <sub>trough</sub> ( $\mu$ g/mL)	C <sub>max</sub> ( $\mu$ g/mL)	AUC (hr* $\mu$ g/mL)
Subcutaneous Infliximab (120 mg Q2W)	12.22 $\pm$ 6.60	17.78 $\pm$ 7.241	20974.1 $\pm$ 9479.62
Intravenous Infliximab (3 mg/kg Q8W)	1.51 $\pm$ 2.50	71.88 $\pm$ 12.185	14302.3 $\pm$ 6603.79

**Absorption:** Single subcutaneous injections of 120, 180 and 240 mg of infliximab yielded approximately dose proportional increases in the maximum serum concentration (C<sub>max</sub>) and area under the concentration-time curve (AUC).



After single doses of 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects, the mean  $C_{max}$  values were 10.0, 15.1 and 23.1  $\mu\text{g/mL}$ , respectively, and for all doses infliximab could be detected in the serum for at least 12 weeks thereafter.

After administration of infliximab 120 mg subcutaneously every 2 weeks (from Week 6 after 2 doses of intravenous infliximab at Weeks 0 and 2) to patients with active rheumatoid arthritis who were concomitantly treated with MTX, the median (CV%)  $C_{trough}$  level at Week 22 was 12.8  $\mu\text{g/mL}$  (80.1%) at steady state.

Estimated by a population PK model, the bioavailability of subcutaneous infliximab was 58% (95% CI: 54% - 62%).

**Distribution:** The apparent volume of distribution during the terminal phase (mean of 7.3 to 8.8 litres) was not dependent on the administered dose of subcutaneous infliximab.

**Metabolism:** It is believed that infliximab is metabolized in a similar manner to other proteins in the body. It is probably hydrolysed into its component amino acids and recycled or catabolized.

**Elimination:** The elimination pathways for infliximab have not been characterised. Unchanged infliximab was not detected in urine.

In studies in healthy subjects, the mean ( $\pm$  SD) apparent clearance of infliximab 120 mg administered subcutaneously was  $19.3 \pm 6.9$  mL/hr.

In the rheumatoid arthritis patients, the mean ( $\pm$  SD) clearance of infliximab 120 mg subcutaneous at Week 22 was  $18.8 \pm 8.3$  mL/hr at steady state.

The mean terminal half-life ranged from 11.3 days to 13.7 days for 120, 180 and 240 mg of subcutaneous infliximab administered to healthy subjects.

### **Special Populations and Conditions**

It is not known if age differences, gender differences, genetic polymorphism, renal insufficiency or hepatic insufficiency have effects on clearance or volume of distribution of subcutaneous infliximab.

## **12 STORAGE, STABILITY AND DISPOSAL**

Store in a refrigerator (2°C - 8°C).

Do not freeze. Keep the medicinal product in its outer carton in order to protect from light.

The medicinal product may be stored at temperatures up to a maximum of 25°C for a period of up to 28 days. The medicinal product must be discarded if not used within the 28-day period.

## **13 SPECIAL HANDLING INSTRUCTIONS**

REMSIMA SC is a solution that is clear to opalescent, colourless to pale brown. Do not use if the solution is cloudy, discoloured or contains visible particulate matter.

After use, place the pre-filled syringe/ pre-filled syringe with automatic needle guard/ pre-filled pen into a puncture resistant container and discard as required by local regulations. Do not

recycle the injecting device. Always keep the medicinal product out of the sight and reach of children.

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

## PART II: SCIENTIFIC INFORMATION

### 14 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Infliximab

Chemical name: Infliximab

Molecular mass: 149,100 daltons

Structural formula: The infliximab molecule contains 1328 amino acids and consists of 2 identical H chains and 2 identical L chains which associate by non-covalent H-H and H-L interactions and covalent H-H and H-L disulfide bonds. Infliximab is a glycoprotein consisting of 5 major glycoforms, each containing 2 (1 on each H chain) asparagine-linked (N-linked) asialo-, core-fucosylated, biantennary oligosaccharide chains with terminal galactose microheterogeneity. The oligosaccharide is bound exclusively to Asn-300 in the C<sub>H2</sub> region of both H chains.

Physicochemical properties: REMSIMA SC is a clear to opalescent, colorless to pale brown solution for subcutaneous injection.

#### Product Characteristics

Infliximab drug substance is a purified, recombinant DNA-derived, chimeric human-mouse IgG monoclonal antibody (MAb) which binds to and neutralizes human tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) with high affinity ( $K_a=1 \times 10^{10} \text{ M}^{-1}$ ). Infliximab contains murine heavy (H) and light (L) chain variable regions (VH and VL, respectively) derived from the murine anti-TNF $\alpha$  MAb, A2, and genomic DNA-derived human H and L chain constant regions (C<sub>H</sub> and C<sub>L</sub>, respectively).

### 15 CLINICAL TRIALS

#### 15.1 Trial Design and Study Demographics

REMSIMA SC is a subcutaneous formulation of infliximab, a drug which is usually administered via intravenous (IV) infusion. REMSIMA SC is intended to be a choice for maintenance therapy with infliximab after the completion of a 6-week dose-loading period using the IV formulation.

A comparative efficacy and safety study (CT-P13 3.5 Part 2) in 343 patients with rheumatoid arthritis (RA) was conducted in support of the indication for maintenance treatment using REMSIMA SC.

An overview of the study design and demographic characteristics of patients enrolled in the clinical study is presented in **Table 4**.

**Table 4: Summary of trial design and patient demographics**

Study	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
CT-P13 3.5 Part 2	Prospective Phase 3, randomized, double-blind, multicentre, multiple single-dose subcutaneous injection, parallel-group in rheumatoid arthritis	<p><b>&lt;Dose-loading phase&gt; - Week 0 to 6</b> Two doses of intravenous infliximab 3 mg/kg at Weeks 0 and 2 for all patients</p> <p><b>&lt;Maintenance phase&gt; - Week 6 to 64</b></p> <ul style="list-style-type: none"> <li>• IV Arm: Further 3 doses of intravenous infliximab were administered at Week 6 and every 8 weeks thereafter up to Week 22 with placebo SC at Week 6 and every 2 weeks thereafter through Week 28. Intravenous infliximab was then switched to subcutaneous infliximab 120 mg at Week 30. Further doses of study treatment with subcutaneous infliximab 120 mg every 2 weeks were given up to Week 54.</li> <li>• SC arm: First subcutaneous infliximab 120 mg via PFS at Week 6 and then every 2 weeks up to Week 54 with placebo IV at Weeks 6, 14 and 22.</li> </ul>	343	51.4 (18 to 74)	74 (21.6%) male 269 (78.4%) female

## 15.2 Study Results

### 15.2.1 Efficacy

The efficacy of subcutaneous infliximab in rheumatoid arthritis patients was assessed in a randomized, parallel-group pivotal Phase I/III study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of efficacy of subcutaneous infliximab compared to intravenous infliximab maintenance treatment.

All patients in Parts 1 and 2 of the study received dose-loading with intravenous infliximab at a dose of 3 mg/kg at Week 0 and Week 2. In Part 2 of this study, 167 patients were randomized to receive subcutaneous infliximab 120 mg at Week 6 and every 2 weeks up to Week 54, while 176 patients were randomized to receive intravenous infliximab 3 mg/kg at Weeks 6, 14 and 22 and then switched to subcutaneous infliximab at Week 30 once-every 2 weeks up to Week 54. Methotrexate was given concomitantly.

The primary endpoint of the study was the treatment difference of the change from baseline of DAS28 (CRP) at Week 22. The estimate of treatment difference was 0.27 with corresponding lower limit of the two-sided 95% confidence interval [CI] of 0.02 (95% CI: 0.02, 0.52), which was greater than the pre-specified non-inferiority margin of -0.6 indicating non-inferiority of subcutaneous infliximab to intravenous infliximab.

**Table 5: Mean (SD) Actual Values of DAS28 (CRP and ESR)**

	Subcutaneous Infliximab (N=165)	Intravenous Infliximab <sup>b</sup> (N=174)
DAS28 (CRP)		
Baseline	6.0 (0.8)	5.9 (0.8)
Week 6	4.0 (1.2)	4.1 (1.2)
Week 22	3.3 (1.1) <sup>a</sup>	3.5 (1.2) <sup>a</sup>
Week 54	2.8 (1.1)	2.9 (1.2) <sup>b</sup>

Note: All patients received induction dosing with intravenous infliximab 3 mg/kg at Weeks 0 and 2 then from Weeks 6 to <30, patients received maintenance dose of intravenous infliximab 3 mg/kg or subcutaneous infliximab 120 mg. From Week 30 onward, all patients received subcutaneous infliximab 120 mg.

<sup>a</sup> Two-sided 95% CI for difference in the mean change from baseline for DAS28 (CRP) at Week 22 was above the pre-defined non-inferiority margin of -0.6

<sup>b</sup> Intravenous infliximab was switched to subcutaneous infliximab at Week 30

The analysis of other efficacy endpoints showed that the efficacy profile of subcutaneous infliximab compared to intravenous infliximab in RA patients was generally comparable in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to Week 54.

**Table 6: Proportions of Patients Achieving Clinical Response According to the ACR Criteria**

	Subcutaneous Infliximab (N=165)	Intravenous Infliximab <sup>a</sup> (N=174)
ACR20		
Week 6	107 (64.8%)	103 (59.2%)
Week 22	139 (84.2%)	137 (78.7%)
Week 54	132 (80.0%)	125 (71.8%) <sup>a</sup>
ACR50		
Week 6	47 (28.5%)	45 (25.9%)
Week 22	85 (51.5%)	90 (51.7%)
Week 54	108 (65.5%)	101 (58.0%) <sup>a</sup>

	Subcutaneous Infliximab (N=165)	Intravenous Infliximab <sup>a</sup> (N=174)
ACR70		
Week 6	19 (11.5%)	18 (10.3%)
Week 22	46 (27.9%)	49 (28.2%)
Week 54	77 (46.7%)	68 (39.1%) <sup>a</sup>

Note: All patients received induction dosing with intravenous infliximab 3 mg/kg at Weeks 0 and 2 then from Weeks 6 to <30, patients received maintenance dose of intravenous infliximab 3 mg/kg or subcutaneous infliximab 120 mg. From Week 30 onward, all patients received subcutaneous infliximab 120 mg.

<sup>a</sup> Intravenous infliximab was switched to subcutaneous infliximab at Week 30

### 15.2.2 Immunogenicity

In Study CT-P13 3.5 Part 2, samples that were positive for anti-drug antibody (ADA) were tested for neutralizing capacity. The proportion of patients who had ADA positive results at Week 30 was lower for subcutaneous infliximab-treated RA patients compared to intravenous infliximab-treated RA patients: 29.2% vs 61.1%. Among the patients who had ADA positive results at Week 30, 69.4% of subcutaneous infliximab-treated RA patients showed neutralizing antibody (NAb) positive response vs 60.7% of intravenous infliximab-treated RA patients.

The proportion of patients who had ADA positive results at Week 54 was lower for subcutaneous infliximab-treated RA patients compared to intravenous infliximab-treated RA patients: 28.6% vs 36.6%. Among the patients who had ADA positive results at Week 54, 75.0% of subcutaneous infliximab-treated RA patients showed NAb positive response vs 67.2% of intravenous infliximab-treated RA patients.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology

Two repeat-dose toxicity studies were performed in rats where intravenous infliximab were administered on Days 1 and 8 to assess for off-target toxicities. In the first study, the doses administered were 0, 10, or 40 mg/kg/dose, and in the second study, the doses administered were 0, 10, or 50 mg/kg/dose. In the first study, slight increases in absolute reticulocyte counts in males and platelet counts in males and females were observed at 40 mg/kg/dose. Minimal Kupffer cell hyperplasia was also observed in the livers of both males and females at 10 and 40 mg/kg/dose. All findings were considered non-adverse due to minimal severity. In the second study, transient subdued behavior following dosing, slight increases in reticulocyte counts and total protein levels, slight decreases in creatine kinase levels and the albumin/globulin ratio, and increased liver weights (females only) were observed in males and females at 50 mg/kg/dose; however, there were no test article-related histopathological correlates and the findings were considered non-adverse.

### Carcinogenicity

Studies have not been conducted to evaluate the carcinogenic potential of subcutaneous infliximab.

### Genotoxicity

Studies have not been conducted to evaluate the genotoxic potential of subcutaneous infliximab.

## **Reproductive and Developmental Toxicity**

Studies have not been conducted to evaluate the potential reproductive or developmental toxicity of subcutaneous infliximab.

## **Local Tolerance**

A single-dose study was conducted in rabbits in which animals were administered a single dose of 80.4 mg of infliximab by a single SC injection. The concentration of the formulation administered was 120 mg/mL, which corresponds to the clinical subcutaneous dosing concentration. No notable abnormal signs were observed during clinical inspection of the injection site. In addition, no adverse macroscopic or histopathological findings were observed at the injection site. It was concluded that subcutaneous administration of infliximab was locally well-tolerated in rabbits at a concentration of 120 mg/mL.

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

### PATIENT MEDICATION INFORMATION

Pr**REMSIMA™ SC** (pronounced) <<Rem-see-mah>>  
(infliximab for subcutaneous injection)

**Sterile Solution, 120 mg / pre-filled syringe**

Read this carefully before you start taking **REMSIMA SC** 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 **REMSIMA SC**.

#### Serious Warnings and Precautions

- Serious infections, including sepsis, tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and opportunistic infections (such as systemic fungal, viral, and bacterial infections) have been reported in patients, especially in those 65 years and older, receiving infliximab and other similar medicines. Some patients with these infections have died. Prior to treatment with **REMSIMA SC**, you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or traveled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common. These infections are caused by fungus that can affect the lungs or other parts of your body. Ask your doctor if you don't know if these infections are common in the area in which you have lived or traveled. If you develop an infection during treatment with **REMSIMA SC**, you should tell your doctor right away.
- Prior to treatment with **REMSIMA SC**, you should tell your doctor if you have had tuberculosis, or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated with **REMSIMA SC**.
- Treatment with **REMSIMA SC** must be interrupted if you develop a serious infection or sepsis. Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking **REMSIMA SC** and for 6 months after you receive the medicine.
- If you need surgery, tell your doctor that you have taken **REMSIMA SC**.
- Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF- blockers, including infliximab. Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage or young adult males and most had either Crohn's disease or ulcerative colitis. This type of cancer often results in death. Almost all patients had also received drugs known as azathioprine or 6-mercaptopurine in addition to TNF-blockers. You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking **REMSIMA SC**.

#### What is **REMSIMA SC** used for?

- **REMSIMA SC** (pronounced) <<Rem-see-mah>> is a medicine that is used in people with moderate to severe rheumatoid arthritis (in combination with methotrexate). Your doctor has chosen to treat your rheumatoid arthritis with **REMSIMA SC** because you have moderately to severely active rheumatoid arthritis.

#### How does **REMSIMA SC** work?

Research has shown that in these diseases the body overproduces a substance known as tumor necrosis factor alpha (TNF alpha). The active ingredient in **REMSIMA SC** is called infliximab. Infliximab is a monoclonal antibody, a type of protein that recognizes and binds to other unique proteins. Infliximab binds to and neutralizes TNF alpha. Infliximab is made from mouse and human proteins.



**REMSIMA SC** is a medicine that affects your immune system. **REMSIMA SC** can lower the ability of your immune system to fight infections.

**What are the ingredients in REMSIMA SC?**

Medicinal ingredient: Infliximab

Non-medicinal ingredients: Acetic acid, polysorbate 80, sodium acetate trihydrate, sorbitol, water for injections.

No preservatives are present.

**REMSIMA SC comes in the following dosage forms:**

It is supplied as a solution for SC injection in individually-boxed single-use 1 mL pre-filled syringe of 120 mg infliximab.

**Do not use REMSIMA SC if:**

- you have a severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis or other serious infection.
- you have heart failure that is moderate or severe.
- you have an allergy to infliximab or any ingredient in **REMSIMA SC** (acetic acid, polysorbate 80, sodium acetate trihydrate and sorbitol), or if you have a history of allergies to mouse proteins.

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

- Congestive heart failure: If you have mild heart failure and you are being treated with **REMSIMA SC** your heart failure status must be closely monitored by your doctor. Tell your doctor immediately if you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet).
- Other heart problems: Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of receiving infliximab. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.
- Immediate allergic reactions: Some patients who have received infliximab have developed allergic reactions, including anaphylaxis. Some reactions can happen while you are getting your treatment or shortly afterwards. Some of these reactions have been serious. The symptoms include hives, difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop **REMSIMA SC** treatment for severe reactions. Your doctor can prescribe medicines to treat these effects.
- Delayed allergic reactions: Some allergic reactions can occur 1 to 12 days after **REMSIMA SC** treatment. The symptoms of this type of delayed reaction include muscle or joint pain with fever or rash. Tell your doctor if you notice any of these symptoms.
- Nervous system diseases: Tell your doctor if you have a disease that affects your nervous system, like multiple sclerosis, neuropathies, Guillain-Barré syndrome, or seizures, or you have been diagnosed with optic neuritis, or if you experience any numbness, tingling, or visual disturbances. Some patients have reported that their nervous system disease got worse after receiving infliximab.
- Autoimmune disease: Some patients treated with infliximab have developed symptoms that suggest an autoimmune disease called lupus-like syndrome. Tell your doctor if you notice symptoms of lupus-like syndrome, such as, prolonged chest discomfort or pain, shortness of breath, joint pain, or sun-sensitive rash on the cheeks or arms. Your doctor will evaluate your condition and may decide to stop your treatment with **REMSIMA SC**.
- Liver injury: There have been cases where people taking infliximab have developed liver problems. Signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever, and severe fatigue (tiredness). You should contact your doctor immediately if you develop any of these symptoms.
- Blood problems: In some instances, patients treated with TNF-blocking agents may develop low blood

counts, including a severely decreased number of white blood cells. If you develop symptoms such as persistent fever or infections, bleeding, or bruising, you should contact your doctor right away.

- Stroke: Some patients have experienced a stroke within approximately 24 hours of receiving infliximab. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body, sudden confusion, trouble speaking or understanding, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.
- Hepatitis B: Treatment with TNF-blocking agents such as **REMSIMA SC** may result in a reactivation of the hepatitis B virus in people who carry this virus. If you have or have had hepatitis B infection or know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with **REMSIMA SC**. Your doctor should do a blood test for hepatitis B virus before you start treatment with **REMSIMA SC**.
- Vaccination: Tell your doctor that you have received **REMSIMA SC** if you need to get a vaccination. It is not known if medicines like **REMSIMA SC** can interfere with vaccinations. You should not receive live vaccines while you are taking **REMSIMA SC**. The use of a 'live' vaccine may result in an infection caused by the 'live' vaccine or bacteria contained in the vaccine (when you have a weakened immune system). It is recommended that you be brought up to date with all vaccinations in agreement with current guidelines prior to starting **REMSIMA SC**.
- Therapeutic infectious agents: Tell your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
- Pregnancy, breast-feeding and ability to have children: If you are being treated with **REMSIMA SC**, you must avoid becoming pregnant by using adequate contraception during your treatment and for 6 months after your last **REMSIMA SC** injection. Tell your doctor if you think you may be pregnant, are breastfeeding, or planning to conceive a child. Your doctor will help you decide whether or not to use **REMSIMA SC**. If you have a baby and you were using **REMSIMA SC** during your pregnancy, it is important to tell your baby's doctor and other healthcare professionals about your **REMSIMA SC** use so they can decide when your baby should receive their vaccinations, including live vaccines, such as BCG (used to prevent tuberculosis). If you received **REMSIMA SC** while you were pregnant, your baby may be at higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your **REMSIMA SC** use before the baby receives any vaccine. Administration of BCG vaccine within 6 months after birth to the baby whose mother received **REMSIMA SC** while pregnant may result in infection in the newborn with severe complications, including death. For other types of vaccines, discuss with your doctor. Breast feeding is not recommended during treatment and for 6 months after the last dose of **REMSIMA SC**. Your doctor will help you decide whether or not to use **REMSIMA SC**. Severely decreased numbers of white blood cells have also been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately. It is not known if **REMSIMA SC** can affect your ability to have children in the future.

#### **Other warnings you should know about:**

Reports of a type of blood cancer called lymphoma in patients on infliximab or other TNF-blockers are rare but occur more often than expected for people in general. People who have been treated for rheumatoid arthritis for a long time, particularly those with highly active disease, may be more prone to develop lymphoma. Cancers, other than lymphoma have also been reported. There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of getting lymphoma or other cancers may increase.

Some patients treated with infliximab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking **REMSIMA SC**, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.

Patients with a specific type of lung disease called COPD (Chronic Obstructive Pulmonary Disease) may be at increased risk for cancer with **REMSIMA SC** treatment. If you have COPD you should discuss with your doctor whether **REMSIMA SC** is appropriate for you.

**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 REMSIMA SC:**

- Tell your doctor about all medicines that you have recently taken or are taking during your treatment with **REMSIMA SC**. These include any other medicines to treat rheumatoid arthritis. Drugs that may interact with **REMSIMA SC** include: prescription and non-prescription medicines, vitamins, and herbal supplements.
- Patients with rheumatoid arthritis often take other medicines that can cause side effects. Special studies have not been done to determine whether other medicines will react with **REMSIMA SC**.
- Especially, tell your doctor if you take KINERET® (anakinra) or ORENCIA® (abatacept). **REMSIMA SC** should not be taken together with anakinra or abatacept.
- If you have a baby while you are using **REMSIMA SC**, tell your baby's doctor about your **REMSIMA SC** use before the baby receives any live vaccines.

**How to take REMSIMA SC:**

- **REMSIMA SC** 120 mg solution for injection is administered by injection under the skin (subcutaneous use) only. It is important to check the product labels to ensure that the correct formulation is being given as prescribed.
- **REMSIMA SC** is intended to be used for maintenance therapy after you have already taken at least two infusions of intravenous infliximab. The initial two intravenous infusions will be given to you by your doctor or nurse.
- After the first two intravenous infusions, the first dose of **REMSIMA SC** will be administered under the supervision of your doctor.
- After proper training, if you feel you are well-trained and confident to inject **REMSIMA SC** yourself, your doctor may allow you to inject subsequent doses of **REMSIMA SC** yourself at home.
- Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed "Instructions for Use" at the end of this leaflet.

**Tell all doctors involved in your care that you take REMSIMA SC.**

**Usual dose:**

Rheumatoid Arthritis:

Your doctor will start your treatment with two intravenous infliximab infusion doses of 3 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). They are administered 2 weeks apart via intravenous infusion. After 4 weeks from the last intravenous infusion, you will be given **REMSIMA SC** via injection under the skin (subcutaneous injection).

The usual recommended dose of **REMSIMA SC** subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**Overdose**

Repeated doses of the subcutaneous infliximab up to 240 mg have been administered without direct toxic effects. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate treatment instituted immediately.

If you think you have taken too much <b>REMSIMA SC</b> , contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. Always have the outer carton of the medicine with you, even if it is empty.
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**Missed Dose**Missed dose for up to 7 days

If you miss a dose of **REMSIMA SC** for up to 7 days after the original scheduled dose, you should take the missed dose immediately. Take your next dose on the next originally planned date and thereafter bi-weekly.

Missed dose for 8 days or more

If you miss a dose of **REMSIMA SC** for 8 days or more after the original scheduled dose, you should not take the missed dose. Take your next dose on the next originally planned date and thereafter bi-weekly.

If you are not sure when to inject **REMSIMA SC**, call your doctor.

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

**What are possible side effects from using REMSIMA SC?**

These are not all the possible side effects you may feel when taking **REMSIMA SC**. If you experience any side effects not listed here, contact your healthcare professional.

Some patients had side effects that caused them to stop **REMSIMA SC** treatment. The most common reasons were shortness of breath, rash, and headache.

Other common side effects besides the ones already mentioned in this leaflet include abdominal pain, back pain, coughing, diarrhea, dizziness, fatigue, itchiness, pain, upper respiratory infections (such as bronchitis, sinusitis, cold, sore throat), upset stomach, and urinary tract infections. **REMSIMA SC** may have a minor influence on the ability to drive and use of machines. Dizziness may occur after receiving **REMSIMA SC**.

Some of the side effects of **REMSIMA SC** can be serious and may require treatment.

Tell your doctor if you experience any of the effects listed in this leaflet or any other side effects.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
Local injection site reaction: Symptoms of redness, pain, itching, swelling, hardness, bruising, bleeding, cold sensation, tingling sensation, irritation, rash, ulcer, hives and scab.		✓	
Serious infections: symptoms of fever, feel very tired, have a cough or have flu-like symptoms or develop an abscess.		✓	
Allergic reactions: Symptoms while you are getting your <b>REMSIMA SC</b> injection or shortly afterwards of hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure or symptoms 1 to 12 days after receiving <b>REMSIMA SC</b> including fever, rash, headache and muscle or joint pain.		✓	
<b>UNCOMMON</b>			
Liver injury: signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark		✓	

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
brown-coloured urine, right sided abdominal pain, fever and severe fatigue (tiredness).			
Heart failure: If you have been told that you have a heart problem called congestive heart failure, you will need to be closely monitored by your doctor. New or worse symptoms that are related to your heart condition, including shortness of breath or swelling of your ankles or feet.		✓	
Blood problems: symptoms of fever that doesn't go away, bruising or bleeding very easily or looking very pale.		✓	
Nervous system disorders: signs include changes in your vision, (including blindness), seizures, weakness in your arms and/or legs, and numbness or tingling in any part of your body.		✓	
Malignancy: if you have had or develop lymphoma or other cancers while you are taking <b>REMSIMA SC</b> .		✓	
Lupus: symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint pain, or a rash on the cheeks or arms that gets worse in the sun.		✓	
<b>RARE</b>			
Skin problems: skin rashes including redness, itching, skin peeling and blistering; Small pus-filled bumps that can spread over the body, sometimes with a fever (acute generalized exanthematous pustulosis); Itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes (lichenoid reactions)		✓	
Lung problems: symptoms of new or worsening shortness of breath.		✓	

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

#### **Reporting Side Effects**

You can 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/adverse-reaction-reporting.html) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.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 the carton after “EXP”. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the medicinal product in its outer carton to protect from light.
- This medicine can also be stored in the original carton outside of refrigerated storage up to a maximum of 25°C for a single period of up to 28 days, but not beyond the original expiry date. In this situation, do not return to refrigerated storage again. Write the new expiry date on the carton including day/month/year. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Keep out of reach and sight of children.

**If you want more information about REMSIMA SC:**

- 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). (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>).

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Republic of Korea

Last Revised:

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## Instructions for use

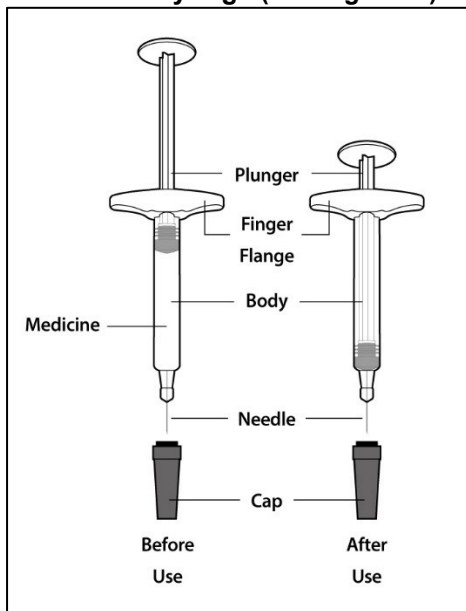
Read carefully these instructions before using the **REMSIMA SC** syringe. Consult your healthcare provider if you have questions about using the **REMSIMA SC** syringe.

## Important information

- Use the syringe **ONLY** if your healthcare provider has trained you on the right way to prepare for and to give an injection.
- Ask your healthcare provider how often you will need to give an injection.
- Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.
- **Do not** use the syringe if it has been dropped or is visibly damaged. A damaged syringe may not function properly.
- **Do not** reuse the syringe.
- **Do not** shake the syringe at any time.

## About the REMSIMA SC syringe

### Parts of the syringe (see *Figure A*):



*Figure A*

- **Do not** remove the cap until you are ready to inject. Once you remove the cap, **do not** recap the syringe.

## Prepare for the injection

### 1. Gather the supplies for the injection.

- a. Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.
- b. Remove the syringe from the carton stored in your refrigerator by holding the middle of the syringe body.
- c. Ensure you have the following supplies:
  - Syringe
  - Alcohol swab
  - Cotton ball or gauze\*
  - Adhesive bandage\*

- Sharps disposal container\*  
\*Items not included in the carton.

## 2. Inspect the syringe.

**Do not** use the syringe if:

- It is cracked or damaged.
- The expiration date has passed.

## 3. Inspect the medicine (see **Figure B**).

**Do not** use the syringe if the liquid is different to clear colourless or pale brown or contains particles in it.

*Note: You may see air bubbles in the liquid. This is normal.*

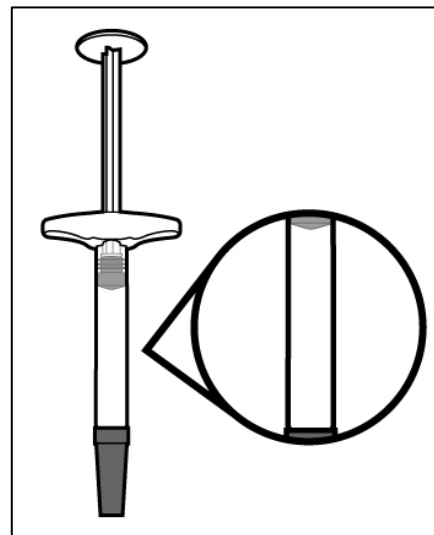


Figure B

## 4. Wait 30 minutes.

- Leave the syringe at room temperature for 30 minutes to allow it to naturally warm up.

**Do not** warm the syringe using heat sources such as hot water or a microwave.

## 5. Choose an injection site (see **Figure C**).

- Select an injection site. You may inject into:
  - The front of the thighs.
  - The abdomen except for the 5 cm around the belly button (navel).
  - The outer area of the upper arms (caregiver ONLY).

**Do not** inject into skin that is within 5 cm of your belly button (navel), or is tender, damaged, bruised, or scarred.

*Note: Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.*

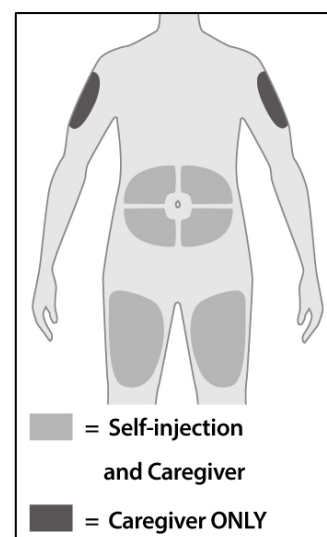


Figure C

## 6. Wash your hands.

- Wash your hands with soap and water and dry them thoroughly.



**7. Clean the injection site.**

- a. Clean the injection site with an alcohol swab.
- b. Let the skin dry before injecting.

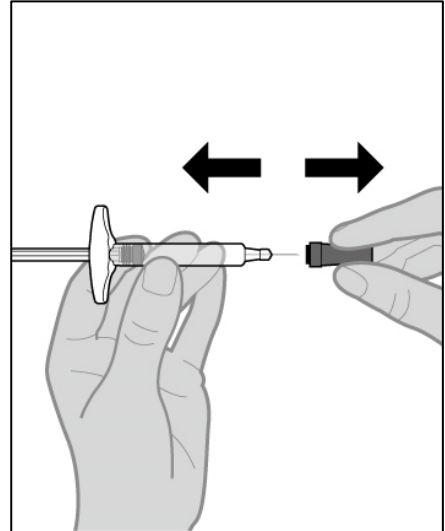
**Do not** blow on or touch the injection site again before giving the injection.

**Give the injection**

**8. Remove the cap (see *Figure D*).**

- a. Pull the cap straight off and set it aside.

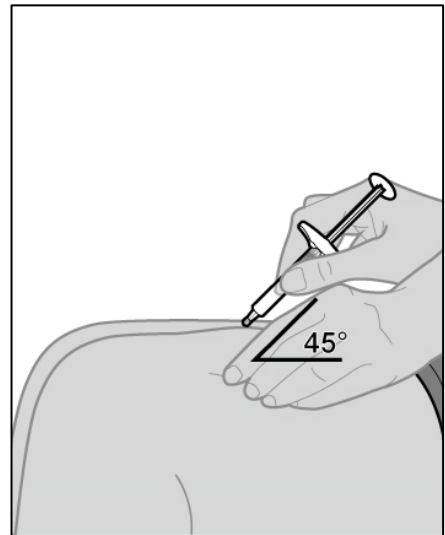
**Do not** touch the needle. Doing so may result in a needle stick injury.



*Figure D*

**9. Insert the syringe into the injection site (see *Figure E*).**

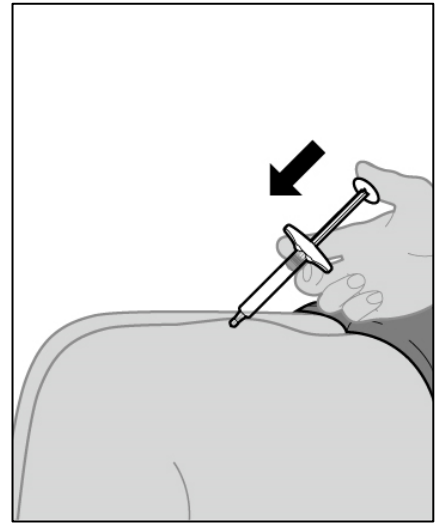
- a. Hold the syringe by its body in one hand between your thumb and index finger.
- b. Using your other hand, gently pinch a fold of skin you cleaned.
- c. With a quick and “dart-like” motion, insert the needle completely into the fold of the skin at a 45-degree angle.



*Figure E*

**10. Give the injection (see *Figure F*).**

- a. After the needle is inserted, let go of the pinched skin.
- b. Push the plunger down slowly and as far as it will go until the syringe is empty.

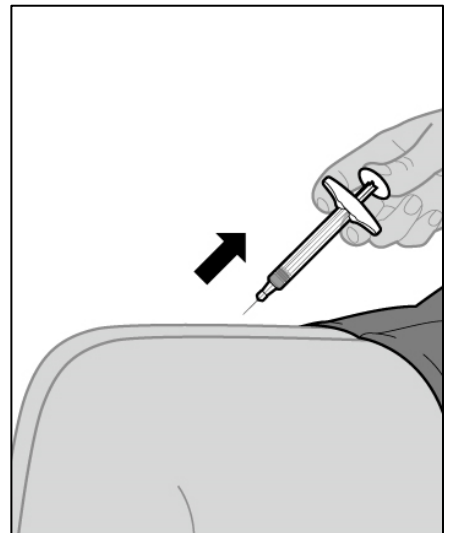


*Figure F*

**11. Remove the needle from the injection site (see *Figure G*).**

- a. Remove the needle from the skin at the same angle it was inserted.
- b. Gently press a cotton ball or gauze over the injection site and hold for 10 seconds.
- c. Apply an adhesive bandage, if necessary.

**Do not** rub the injection site.



*Figure G*

## After the injection

### 12. Dispose of the syringe (see *Figure H*).

- a. Put the used syringe in an approved sharps disposal container immediately after use.
- b. If you do not have an approved sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic;
  - able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
  - upright and stable during use;
  - leak-resistant; and
  - properly labelled to warn of hazardous waste inside the container.
- c. When your sharps disposal container is almost full, it should be disposed of in accordance with local requirements.

**Do not** recap the syringe.

*Note: Keep the syringe and sharps disposal container out of the sight and reach of children.*

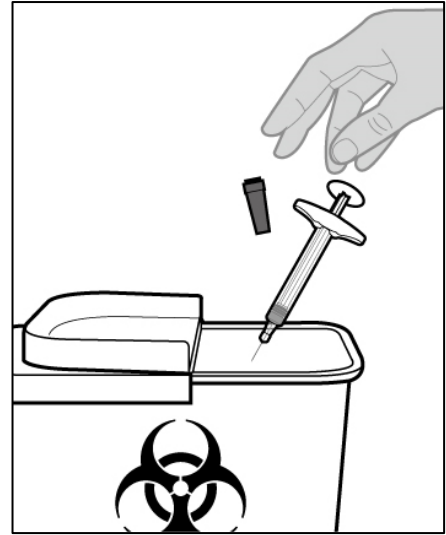


Figure H

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

### PATIENT MEDICATION INFORMATION

Pr**REMSIMA™ SC** (pronounced) <<Rem-see-mah>>  
(infliximab for subcutaneous injection)

**Sterile Solution, 120 mg / pre-filled syringe with needle guard**

Read this carefully before you start taking **REMSIMA SC** 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 **REMSIMA SC**.

#### Serious Warnings and Precautions

- Serious infections, including sepsis, tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and opportunistic infections (such as systemic fungal, viral, and bacterial infections) have been reported in patients, especially in those 65 years and older, receiving infliximab and other similar medicines. Some patients with these infections have died. Prior to treatment with **REMSIMA SC**, you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or traveled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common. These infections are caused by fungus that can affect the lungs or other parts of your body. Ask your doctor if you don't know if these infections are common in the area in which you have lived or traveled. If you develop an infection during treatment with **REMSIMA SC**, you should tell your doctor right away.
- Prior to treatment with **REMSIMA SC**, you should tell your doctor if you have had tuberculosis, or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated with **REMSIMA SC**.
- Treatment with **REMSIMA SC** must be interrupted if you develop a serious infection or sepsis. Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking **REMSIMA SC** and for 6 months after you receive the medicine.
- If you need surgery, tell your doctor that you have taken **REMSIMA SC**.
- Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF- blockers, including infliximab. Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage or young adult males and most had either Crohn's disease or ulcerative colitis. This type of cancer often results in death. Almost all patients had also received drugs known as azathioprine or 6-mercaptopurine in addition to TNF-blockers. You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking **REMSIMA SC**.

#### What is **REMSIMA SC** used for?

- **REMSIMA SC** (pronounced) <<Rem-see-mah>> is a medicine that is used in people with moderate to severe rheumatoid arthritis (in combination with methotrexate). Your doctor has chosen to treat your rheumatoid arthritis with **REMSIMA SC** because you have moderately to severely active rheumatoid arthritis.

#### How does **REMSIMA SC** work?

Research has shown that in these diseases the body overproduces a substance known as tumor necrosis factor alpha (TNF alpha). The active ingredient in **REMSIMA SC** is called infliximab. Infliximab is a monoclonal antibody, a type of protein that recognizes and binds to other unique proteins. Infliximab binds to and neutralizes TNF alpha. Infliximab is made from mouse and human proteins.

**REMSIMA SC** is a medicine that affects your immune system. **REMSIMA SC** can lower the ability of your immune system to fight infections.

**What are the ingredients in REMSIMA SC?**

Medicinal ingredient: Infliximab

Non-medicinal ingredients: Acetic acid, polysorbate 80, sodium acetate trihydrate, sorbitol, water for injections.

No preservatives are present.

**REMSIMA SC comes in the following dosage forms:**

It is supplied as a solution for SC injection in individually-boxed single-use 1 mL pre-filled syringe with needle guard of 120 mg infliximab.

**Do not use REMSIMA SC if:**

- you have a severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis or other serious infection.
- you have heart failure that is moderate or severe.
- you have an allergy to infliximab or any ingredient in **REMSIMA SC** (acetic acid, polysorbate 80, sodium acetate trihydrate and sorbitol), or if you have a history of allergies to mouse proteins.

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

- Congestive heart failure: If you have mild heart failure and you are being treated with **REMSIMA SC** your heart failure status must be closely monitored by your doctor. Tell your doctor immediately if you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet).
- Other heart problems: Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of receiving infliximab. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.
- Immediate allergic reactions: Some patients who have received infliximab have developed allergic reactions, including anaphylaxis. Some reactions can happen while you are getting your treatment or shortly afterwards. Some of these reactions have been serious. The symptoms include hives, difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop **REMSIMA SC** treatment for severe reactions. Your doctor can prescribe medicines to treat these effects.
- Delayed allergic reactions: Some allergic reactions can occur 1 to 12 days after **REMSIMA SC** treatment. The symptoms of this type of delayed reaction include muscle or joint pain with fever or rash. Tell your doctor if you notice any of these symptoms.
- Nervous system diseases: Tell your doctor if you have a disease that affects your nervous system, like multiple sclerosis, neuropathies, Guillain-Barré syndrome, or seizures, or you have been diagnosed with optic neuritis, or if you experience any numbness, tingling, or visual disturbances. Some patients have reported that their nervous system disease got worse after receiving infliximab.
- Autoimmune disease: Some patients treated with infliximab have developed symptoms that suggest an autoimmune disease called lupus-like syndrome. Tell your doctor if you notice symptoms of lupus-like syndrome, such as, prolonged chest discomfort or pain, shortness of breath, joint pain, or sun-sensitive rash on the cheeks or arms. Your doctor will evaluate your condition and may decide to stop your treatment with **REMSIMA SC**.
- Liver injury: There have been cases where people taking infliximab have developed liver problems. Signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever, and severe fatigue (tiredness). You should contact your doctor immediately if you develop any of these symptoms.
- Blood problems: In some instances, patients treated with TNF-blocking agents may develop low blood

counts, including a severely decreased number of white blood cells. If you develop symptoms such as persistent fever or infections, bleeding, or bruising, you should contact your doctor right away.

- Stroke: Some patients have experienced a stroke within approximately 24 hours of receiving infliximab. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body, sudden confusion, trouble speaking or understanding, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.
- Hepatitis B: Treatment with TNF-blocking agents such as **REMSIMA SC** may result in a reactivation of the hepatitis B virus in people who carry this virus. If you have or have had hepatitis B infection or know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with **REMSIMA SC**. Your doctor should do a blood test for hepatitis B virus before you start treatment with **REMSIMA SC**.
- Vaccination: Tell your doctor that you have received **REMSIMA SC** if you need to get a vaccination. It is not known if medicines like **REMSIMA SC** can interfere with vaccinations. You should not receive live vaccines while you are taking **REMSIMA SC**. The use of a 'live' vaccine may result in an infection caused by the 'live' vaccine or bacteria contained in the vaccine (when you have a weakened immune system). It is recommended that you be brought up to date with all vaccinations in agreement with current guidelines prior to starting **REMSIMA SC**.
- Therapeutic infectious agents: Tell your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
- Pregnancy, breast-feeding and ability to have children: If you are being treated with **REMSIMA SC**, you must avoid becoming pregnant by using adequate contraception during your treatment and for 6 months after your last **REMSIMA SC** injection. Tell your doctor if you think you may be pregnant, are breastfeeding, or planning to conceive a child. Your doctor will help you decide whether or not to use **REMSIMA SC**. If you have a baby and you were using **REMSIMA SC** during your pregnancy, it is important to tell your baby's doctor and other healthcare professionals about your **REMSIMA SC** use so they can decide when your baby should receive their vaccinations, including live vaccines, such as BCG (used to prevent tuberculosis). If you received **REMSIMA SC** while you were pregnant, your baby may be at higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your **REMSIMA SC** use before the baby receives any vaccine. Administration of BCG vaccine within 6 months after birth to the baby whose mother received **REMSIMA SC** while pregnant may result in infection in the newborn with severe complications, including death. For other types of vaccines, discuss with your doctor. Breast feeding is not recommended during treatment and for 6 months after the last dose of **REMSIMA SC**. Your doctor will help you decide whether or not to use **REMSIMA SC**. Severely decreased numbers of white blood cells have also been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately. It is not known if **REMSIMA SC** can affect your ability to have children in the future.

#### **Other warnings you should know about:**

Reports of a type of blood cancer called lymphoma in patients on infliximab or other TNF-blockers are rare but occur more often than expected for people in general. People who have been treated for rheumatoid arthritis for a long time, particularly those with highly active disease, may be more prone to develop lymphoma. Cancers, other than lymphoma have also been reported. There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of getting lymphoma or other cancers may increase.

Some patients treated with infliximab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking **REMSIMA SC**, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.

Patients with a specific type of lung disease called COPD (Chronic Obstructive Pulmonary Disease) may be at increased risk for cancer with **REMSIMA SC** treatment. If you have COPD you should discuss with your doctor whether **REMSIMA SC** is appropriate for you.

**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 REMSIMA SC:**

- Tell your doctor about all medicines that you have recently taken or are taking during your treatment with **REMSIMA SC**. These include any other medicines to treat rheumatoid arthritis. Drugs that may interact with **REMSIMA SC** include: prescription and non-prescription medicines, vitamins, and herbal supplements.
- Patients with rheumatoid arthritis often take other medicines that can cause side effects. Special studies have not been done to determine whether other medicines will react with **REMSIMA SC**.
- Especially, tell your doctor if you take KINERET® (anakinra) or ORENCIA® (abatacept). **REMSIMA SC** should not be taken together with anakinra or abatacept.
- If you have a baby while you are using **REMSIMA SC**, tell your baby's doctor about your **REMSIMA SC** use before the baby receives any live vaccines.

**How to take REMSIMA SC:**

- **REMSIMA SC** 120 mg solution for injection is administered by injection under the skin (subcutaneous use) only. It is important to check the product labels to ensure that the correct formulation is being given as prescribed.
- **REMSIMA SC** is intended to be used for maintenance therapy after you have already taken at least two infusions of intravenous infliximab. The initial two intravenous infusions will be given to you by your doctor or nurse.
- After the first two intravenous infusions, the first dose of **REMSIMA SC** will be administered under the supervision of your doctor.
- After proper training, if you feel you are well-trained and confident to inject **REMSIMA SC** yourself, your doctor may allow you to inject subsequent doses of **REMSIMA SC** yourself at home.
- Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed "Instructions for Use" at the end of this leaflet.

**Tell all doctors involved in your care that you take REMSIMA SC.**

**Usual dose:**

Rheumatoid Arthritis:

Your doctor will start your treatment with two intravenous infliximab infusion doses of 3 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). They are administered 2 weeks apart via intravenous infusion. After 4 weeks from the last intravenous infusion, you will be given **REMSIMA SC** via injection under the skin (subcutaneous injection).

The usual recommended dose of **REMSIMA SC** subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**Overdose**

Repeated doses of the subcutaneous infliximab up to 240 mg have been administered without direct toxic effects. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate treatment instituted immediately.

If you think you have taken too much **REMSIMA SC**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. Always have the outer carton of the medicine with you, even if it is empty.

**Missed Dose**

Missed dose for up to 7 days

If you miss a dose of **REMSIMA SC** for up to 7 days after the original scheduled dose, you should take the missed dose immediately. Take your next dose on the next originally planned date and thereafter bi-weekly.

Missed dose for 8 days or more

If you miss a dose of **REMSIMA SC** for 8 days or more after the original scheduled dose, you should not take the missed dose. Take your next dose on the next originally planned date and thereafter bi-weekly.

If you are not sure when to inject **REMSIMA SC**, call your doctor.

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

**What are possible side effects from using REMSIMA SC?**

These are not all the possible side effects you may feel when taking **REMSIMA SC**. If you experience any side effects not listed here, contact your healthcare professional.

Some patients had side effects that caused them to stop **REMSIMA SC** treatment. The most common reasons were shortness of breath, rash, and headache.

Other common side effects besides the ones already mentioned in this leaflet include abdominal pain, back pain, coughing, diarrhea, dizziness, fatigue, itchiness, pain, upper respiratory infections (such as bronchitis, sinusitis, cold, sore throat), upset stomach, and urinary tract infections. **REMSIMA SC** may have a minor influence on the ability to drive and use of machines. Dizziness may occur after receiving **REMSIMA SC**.

Some of the side effects of **REMSIMA SC** can be serious and may require treatment.

Tell your doctor if you experience any of the effects listed in this leaflet or any other side effects.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
Local injection site reaction: Symptoms of redness, pain, itching, swelling, hardness, bruising, bleeding, cold sensation, tingling sensation, irritation, rash, ulcer, hives and scab.		✓	
Serious infections: symptoms of fever, feel very tired, have a cough or have flu-like symptoms or develop an abscess.		✓	
Allergic reactions: Symptoms while you are getting your <b>REMSIMA SC</b> injection or shortly afterwards of hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure or symptoms 1 to 12 days after receiving <b>REMSIMA SC</b> including fever, rash, headache and muscle or joint pain.		✓	
<b>UNCOMMON</b>			
Liver injury: signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-coloured urine, right sided		✓	



<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
abdominal pain, fever and severe fatigue (tiredness).			
Heart failure: If you have been told that you have a heart problem called congestive heart failure, you will need to be closely monitored by your doctor. New or worse symptoms that are related to your heart condition, including shortness of breath or swelling of your ankles or feet.		✓	
Blood problems: symptoms of fever that doesn't go away, bruising or bleeding very easily or looking very pale.		✓	
Nervous system disorders: signs include changes in your vision, (including blindness), seizures, weakness in your arms and/or legs, and numbness or tingling in any part of your body.		✓	
Malignancy: if you have had or develop lymphoma or other cancers while you are taking <b>REMSIMA SC</b> .		✓	
Lupus: symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint pain, or a rash on the cheeks or arms that gets worse in the sun.		✓	
<b>RARE</b>			
Skin problems: skin rashes including redness, itching, skin peeling and blistering; Small pus-filled bumps that can spread over the body, sometimes with a fever (acute generalized exanthematous pustulosis); Itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes (lichenoid reactions)		✓	
Lung problems: symptoms of new or worsening shortness of breath.		✓	

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

#### **Reporting Side Effects**

You can 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/adverse-reaction-reporting.html) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.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 the carton after “EXP”. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the medicinal product in its outer carton to protect from light.
- This medicine can also be stored in the original carton outside of refrigerated storage up to a maximum of 25°C for a single period of up to 28 days, but not beyond the original expiry date. In this situation, do not return to refrigerated storage again. Write the new expiry date on the carton including day/month/year. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Keep out of reach and sight of children.

**If you want more information about REMSIMA SC:**

- 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). (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>).

This leaflet was prepared by:  
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Last Revised:

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## Instructions for use

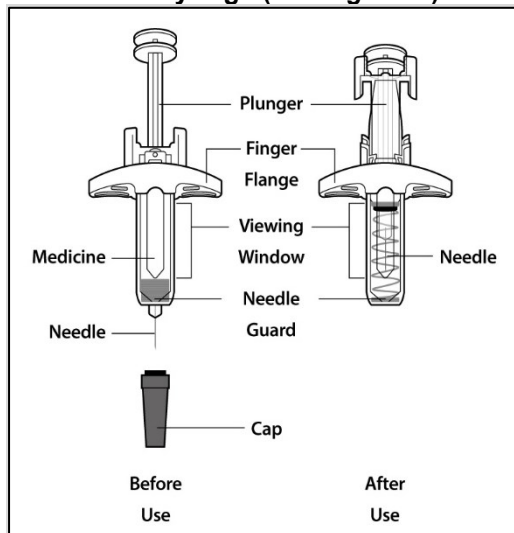
Read carefully these instructions before using the **REMSIMA SC** syringe. Consult your healthcare provider if you have questions about using the **REMSIMA SC** syringe.

## Important information

- Use the syringe **ONLY** if your healthcare provider has trained you on the right way to prepare for and to give an injection.
- Ask your healthcare provider how often you will need to give an injection.
- Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.
- **Do not** use the syringe if it has been dropped or is visibly damaged. A damaged syringe may not function properly.
- **Do not** reuse the syringe.
- **Do not** shake the syringe at any time.

## About the REMSIMA SC syringe

### Parts of the syringe (see *Figure A*):



*Figure A*

- **Do not** remove the cap until you are ready to inject. Once you remove the cap, **do not** recap the syringe.

## Prepare for the injection

### 1. Gather the supplies for the injection.

- Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.
- Remove the syringe from the carton stored in your refrigerator by holding the middle of the syringe body.
- Ensure you have the following supplies:
  - Syringe
  - Alcohol swab
  - Cotton ball or gauze\*
  - Adhesive bandage\*
  - Sharps disposal container\*

*\*Items not included in the carton.*

## 2. Inspect the syringe.

**Do not** use the syringe if:

- It is cracked or damaged.
- The expiration date has passed.

## 3. Inspect the medicine (see *Figure B*).

**Do not** use the syringe if the liquid is different to clear colourless or pale brown or contains particles in it.

*Note: You may see air bubbles in the liquid. This is normal.*

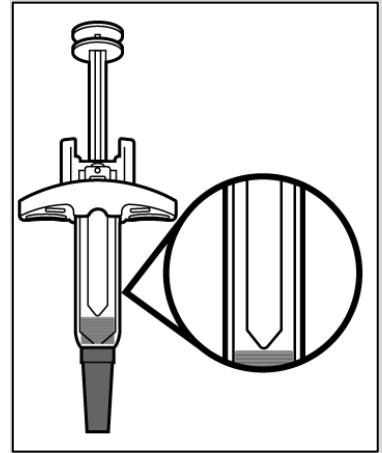


Figure B

## 4. Wait 30 minutes.

- a. Leave the syringe at room temperature for 30 minutes to allow it to naturally warm up.

**Do not** warm the syringe using heat sources such as hot water or a microwave.

## 5. Choose an injection site (see *Figure C*).

- a. Select an injection site. You may inject into:
  - The front of the thighs.
  - The abdomen except for the 5 cm around the belly button (navel).
  - The outer area of the upper arms (caregiver ONLY).

**Do not** inject into skin that is within 5 cm of your belly button (navel), or is tender, damaged, bruised, or scarred.

*Note: Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.*

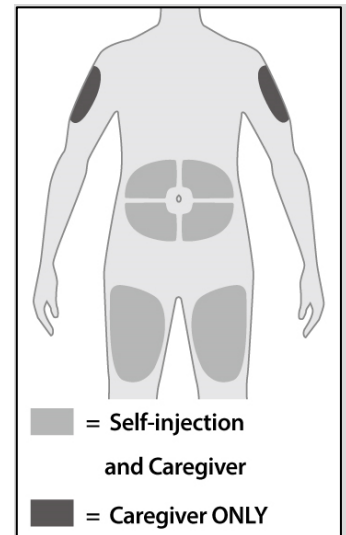


Figure C

## 6. Wash your hands.

- a. Wash your hands with soap and water and dry them thoroughly.

## 7. Clean the injection site.

- a. Clean the injection site with an alcohol swab.
- b. Let the skin dry before injecting.

**Do not** blow on or touch the injection site again before giving the injection.

## Give the injection

### 8. Remove the cap (see *Figure D*).

- a. Pull the cap straight off and set it aside.

**Do not** touch the needle. Doing so may result in a needle stick injury.

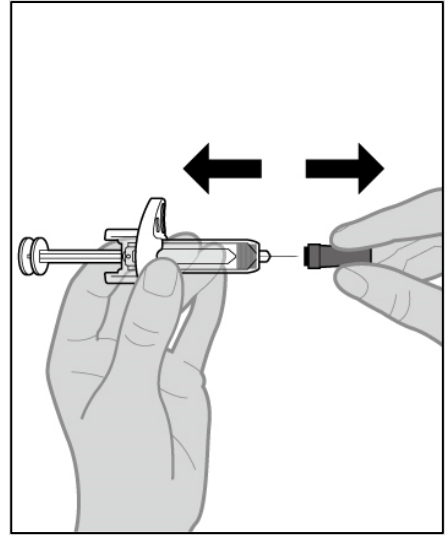


Figure D

### 9. Insert the syringe into the injection site (see *Figure E*).

- a. Hold the syringe by its body in one hand between your thumb and index finger.
- b. Using your other hand, gently pinch a fold of skin you cleaned.
- c. With a quick and “dart-like” motion, insert the needle completely into the fold of the skin at a 45-degree angle.

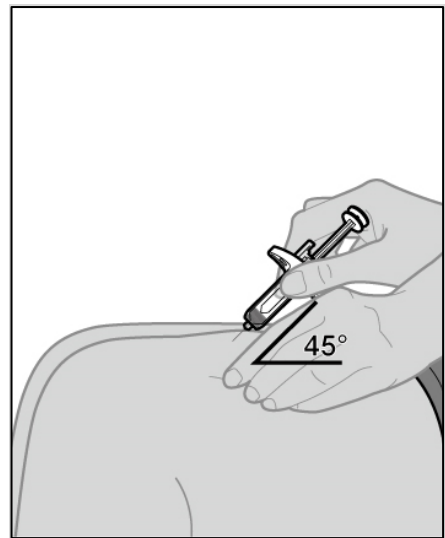
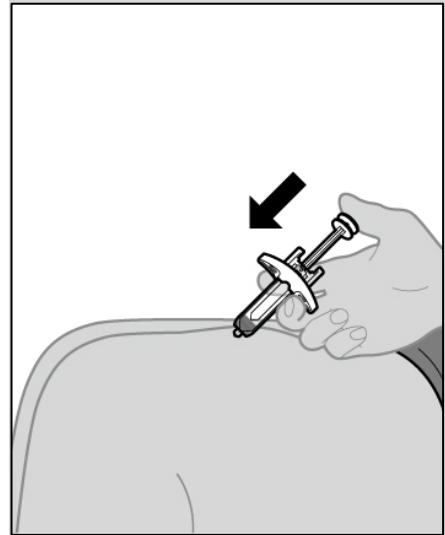


Figure E

**10. Give the injection (see *Figure F*).**

- a. After the needle is inserted, let go of the pinched skin.
- b. Push the plunger down slowly and as far as it will go until the syringe is empty.

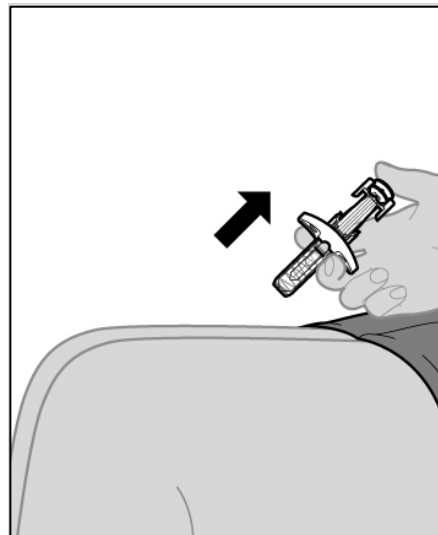


*Figure F*

**11. Remove the syringe from the injection site (see *Figure G*).**

- a. After the syringe is empty, slowly lift your thumb from the plunger until needle is completely covered by the automatic needle guard.
- b. Gently press a cotton ball or gauze over the injection site and hold for 10 seconds.
- c. Apply an adhesive bandage, if necessary.

**Do not** rub the injection site.



*Figure G*

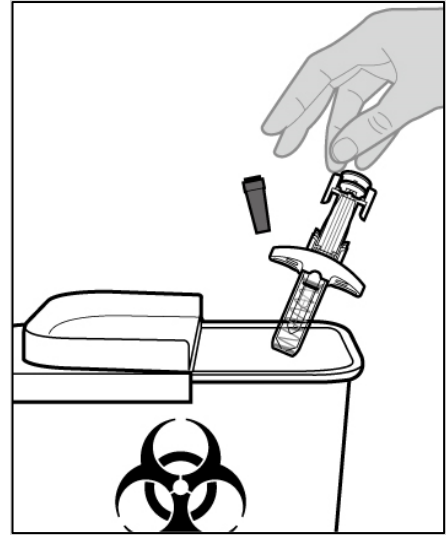
## After the injection

### 12. Dispose of the syringe (see *Figure H*).

- a. Put the used syringe in an approved sharps disposal container immediately after use.
- b. If you do not have an approved sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic;
  - able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
  - upright and stable during use;
  - leak-resistant; and
  - properly labelled to warn of hazardous waste inside the container.
- c. When your sharps disposal container is almost full, it should be disposed of in accordance with local requirements.

**Do not** recap the syringe.

*Note: Keep the syringe and sharps disposal container out of the sight and reach of children.*



*Figure H*

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

### PATIENT MEDICATION INFORMATION

Pr**REMSIMA™ SC** (pronounced) <<Rem-see-mah>>  
(infliximab for subcutaneous injection)

**Sterile Solution, 120 mg / pre-filled pen**

Read this carefully before you start taking **REMSIMA SC** 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 **REMSIMA SC**.

#### Serious Warnings and Precautions

- Serious infections, including sepsis, tuberculosis, legionellosis (a serious form of bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and opportunistic infections (such as systemic fungal, viral, and bacterial infections) have been reported in patients, especially in those 65 years and older, receiving infliximab and other similar medicines. Some patients with these infections have died. Prior to treatment with **REMSIMA SC**, you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or traveled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common. These infections are caused by fungus that can affect the lungs or other parts of your body. Ask your doctor if you don't know if these infections are common in the area in which you have lived or traveled. If you develop an infection during treatment with **REMSIMA SC**, you should tell your doctor right away.
- Prior to treatment with **REMSIMA SC**, you should tell your doctor if you have had tuberculosis, or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated with **REMSIMA SC**.
- Treatment with **REMSIMA SC** must be interrupted if you develop a serious infection or sepsis. Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking **REMSIMA SC** and for 6 months after you receive the medicine.
- If you need surgery, tell your doctor that you have taken **REMSIMA SC**.
- Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF- blockers, including infliximab. Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage or young adult males and most had either Crohn's disease or ulcerative colitis. This type of cancer often results in death. Almost all patients had also received drugs known as azathioprine or 6-mercaptopurine in addition to TNF-blockers. You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking **REMSIMA SC**.

#### What is **REMSIMA SC** used for?

- **REMSIMA SC** (pronounced) <<Rem-see-mah>> is a medicine that is used in people with moderate to severe rheumatoid arthritis (in combination with methotrexate). Your doctor has chosen to treat your rheumatoid arthritis with **REMSIMA SC** because you have moderately to severely active rheumatoid arthritis.

#### How does **REMSIMA SC** work?

Research has shown that in these diseases the body overproduces a substance known as tumor necrosis factor alpha (TNF alpha). The active ingredient in **REMSIMA SC** is called infliximab. Infliximab is a monoclonal antibody, a type of protein that recognizes and binds to other unique proteins. Infliximab binds to and neutralizes TNF alpha. Infliximab is made from mouse and human proteins.



**REMSIMA SC** is a medicine that affects your immune system. **REMSIMA SC** can lower the ability of your immune system to fight infections.

**What are the ingredients in REMSIMA SC?**

Medicinal ingredient: Infliximab

Non-medicinal ingredients: Acetic acid, polysorbate 80, sodium acetate trihydrate, sorbitol, water for injections.

No preservatives are present.

**REMSIMA SC comes in the following dosage forms:**

It is supplied as a solution for SC injection in individually-boxed single-use 1 mL pre-filled pen of 120 mg infliximab.

**Do not use REMSIMA SC if:**

- you have a severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis or other serious infection.
- you have heart failure that is moderate or severe.
- you have an allergy to infliximab or any ingredient in **REMSIMA SC** (acetic acid, polysorbate 80, sodium acetate trihydrate and sorbitol), or if you have a history of allergies to mouse proteins.

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

- Congestive heart failure: If you have mild heart failure and you are being treated with **REMSIMA SC** your heart failure status must be closely monitored by your doctor. Tell your doctor immediately if you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet).
- Other heart problems: Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of receiving infliximab. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.
- Immediate allergic reactions: Some patients who have received infliximab have developed allergic reactions, including anaphylaxis. Some reactions can happen while you are getting your treatment or shortly afterwards. Some of these reactions have been serious. The symptoms include hives, difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop **REMSIMA SC** treatment for severe reactions. Your doctor can prescribe medicines to treat these effects.
- Delayed allergic reactions: Some allergic reactions can occur 1 to 12 days after **REMSIMA SC** treatment. The symptoms of this type of delayed reaction include muscle or joint pain with fever or rash. Tell your doctor if you notice any of these symptoms.
- Nervous system diseases: Tell your doctor if you have a disease that affects your nervous system, like multiple sclerosis, neuropathies, Guillain-Barré syndrome, or seizures, or you have been diagnosed with optic neuritis, or if you experience any numbness, tingling, or visual disturbances. Some patients have reported that their nervous system disease got worse after receiving infliximab.
- Autoimmune disease: Some patients treated with infliximab have developed symptoms that suggest an autoimmune disease called lupus-like syndrome. Tell your doctor if you notice symptoms of lupus-like syndrome, such as, prolonged chest discomfort or pain, shortness of breath, joint pain, or sun-sensitive rash on the cheeks or arms. Your doctor will evaluate your condition and may decide to stop your treatment with **REMSIMA SC**.
- Liver injury: There have been cases where people taking infliximab have developed liver problems. Signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever, and severe fatigue (tiredness). You should contact your doctor immediately if you develop any of these symptoms.
- Blood problems: In some instances, patients treated with TNF-blocking agents may develop low blood

counts, including a severely decreased number of white blood cells. If you develop symptoms such as persistent fever or infections, bleeding, or bruising, you should contact your doctor right away.

- Stroke: Some patients have experienced a stroke within approximately 24 hours of receiving infliximab. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body, sudden confusion, trouble speaking or understanding, sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.
- Hepatitis B: Treatment with TNF-blocking agents such as **REMSIMA SC** may result in a reactivation of the hepatitis B virus in people who carry this virus. If you have or have had hepatitis B infection or know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with **REMSIMA SC**. Your doctor should do a blood test for hepatitis B virus before you start treatment with **REMSIMA SC**.
- Vaccination: Tell your doctor that you have received **REMSIMA SC** if you need to get a vaccination. It is not known if medicines like **REMSIMA SC** can interfere with vaccinations. You should not receive live vaccines while you are taking **REMSIMA SC**. The use of a 'live' vaccine may result in an infection caused by the 'live' vaccine or bacteria contained in the vaccine (when you have a weakened immune system). It is recommended that you be brought up to date with all vaccinations in agreement with current guidelines prior to starting **REMSIMA SC**.
- Therapeutic infectious agents: Tell your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
- Pregnancy, breast-feeding and ability to have children: If you are being treated with **REMSIMA SC**, you must avoid becoming pregnant by using adequate contraception during your treatment and for 6 months after your last **REMSIMA SC** injection. Tell your doctor if you think you may be pregnant, are breastfeeding, or planning to conceive a child. Your doctor will help you decide whether or not to use **REMSIMA SC**. If you have a baby and you were using **REMSIMA SC** during your pregnancy, it is important to tell your baby's doctor and other healthcare professionals about your **REMSIMA SC** use so they can decide when your baby should receive their vaccinations, including live vaccines, such as BCG (used to prevent tuberculosis). If you received **REMSIMA SC** while you were pregnant, your baby may be at higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your **REMSIMA SC** use before the baby receives any vaccine. Administration of BCG vaccine within 6 months after birth to the baby whose mother received **REMSIMA SC** while pregnant may result in infection in the newborn with severe complications, including death. For other types of vaccines, discuss with your doctor. Breast feeding is not recommended during treatment and for 6 months after the last dose of **REMSIMA SC**. Your doctor will help you decide whether or not to use **REMSIMA SC**. Severely decreased numbers of white blood cells have also been reported in infants born to women treated with infliximab during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately. It is not known if **REMSIMA SC** can affect your ability to have children in the future.

#### **Other warnings you should know about:**

Reports of a type of blood cancer called lymphoma in patients on infliximab or other TNF-blockers are rare but occur more often than expected for people in general. People who have been treated for rheumatoid arthritis or Crohn's disease for a long time, particularly those with highly active disease, may be more prone to develop lymphoma. Cancers, other than lymphoma have also been reported. There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death. For children and adults taking TNF-blocker medicines, the chances of getting lymphoma or other cancers may increase.

Some patients treated with infliximab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Some women being treated for rheumatoid arthritis with infliximab have developed cervical cancer. For women taking **REMSIMA SC**, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.

Patients with a specific type of lung disease called COPD (Chronic Obstructive Pulmonary Disease) may be at increased risk for cancer with **REMSIMA SC** treatment. If you have COPD you should discuss with your doctor whether **REMSIMA SC** is appropriate for you.

**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 REMSIMA SC:**

- Tell your doctor about all medicines that you have recently taken or are taking during your treatment with **REMSIMA SC**. These include any other medicines to treat rheumatoid arthritis. Drugs that may interact with **REMSIMA SC** include: prescription and non-prescription medicines, vitamins, and herbal supplements.
- Patients with rheumatoid arthritis often take other medicines that can cause side effects. Special studies have not been done to determine whether other medicines will react with **REMSIMA SC**.
- Especially, tell your doctor if you take KINERET® (anakinra) or ORENCIA® (abatacept). **REMSIMA SC** should not be taken together with anakinra or abatacept.
- If you have a baby while you are using **REMSIMA SC**, tell your baby's doctor about your **REMSIMA SC** use before the baby receives any live vaccines.

**How to take REMSIMA SC:**

- **REMSIMA SC** 120 mg solution for injection is administered by injection under the skin (subcutaneous use) only. It is important to check the product labels to ensure that the correct formulation is being given as prescribed.
- **REMSIMA SC** is intended to be used for maintenance therapy after you have already taken at least two infusions of intravenous infliximab. The initial two intravenous infusions will be given to you by your doctor or nurse.
- After the first two intravenous infusions, the first dose of **REMSIMA SC** will be administered under the supervision of your doctor.
- After proper training, if you feel you are well-trained and confident to inject **REMSIMA SC** yourself, your doctor may allow you to inject subsequent doses of **REMSIMA SC** yourself at home.
- Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed "Instructions for Use" at the end of this leaflet.

**Tell all doctors involved in your care that you take REMSIMA SC.**

**Usual dose:**

Rheumatoid Arthritis:

Your doctor will start your treatment with two intravenous infliximab infusion doses of 3 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). They are administered 2 weeks apart via intravenous infusion. After 4 weeks from the last intravenous infusion, you will be given **REMSIMA SC** via injection under the skin (subcutaneous injection).

The usual recommended dose of **REMSIMA SC** subcutaneous injection is 120 mg once every 2 weeks regardless of weight.

**Overdose**

Repeated doses of the subcutaneous infliximab up to 240 mg have been administered without direct toxic effects. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate treatment instituted immediately.

If you think you have taken too much **REMSIMA SC**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms. Always have the outer carton of the medicine with you, even if it is empty.

**Missed Dose**

Missed dose for up to 7 days

If you miss a dose of **REMSIMA SC** for up to 7 days after the original scheduled dose, you should take the missed dose immediately. Take your next dose on the next originally planned date and thereafter bi-weekly.

Missed dose for 8 days or more

If you miss a dose of **REMSIMA SC** for 8 days or more after the original scheduled dose, you should not take the missed dose. Take your next dose on the next originally planned date and thereafter bi-weekly.

If you are not sure when to inject **REMSIMA SC**, call your doctor.

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

**What are possible side effects from using REMSIMA SC?**

These are not all the possible side effects you may feel when taking **REMSIMA SC**. If you experience any side effects not listed here, contact your healthcare professional.

Some patients had side effects that caused them to stop **REMSIMA SC** treatment. The most common reasons were shortness of breath, rash, and headache.

Other common side effects besides the ones already mentioned in this leaflet include abdominal pain, back pain, coughing, diarrhea, dizziness, fatigue, itchiness, pain, upper respiratory infections (such as bronchitis, sinusitis, cold, sore throat), upset stomach, and urinary tract infections. **REMSIMA SC** may have a minor influence on the ability to drive and use of machines. Dizziness may occur after receiving **REMSIMA SC**.

Some of the side effects of **REMSIMA SC** can be serious and may require treatment.

Tell your doctor if you experience any of the effects listed in this leaflet or any other side effects.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>COMMON</b>			
Local injection site reaction: Symptoms of redness, pain, itching, swelling, hardness, bruising, bleeding, cold sensation, tingling sensation, irritation, rash, ulcer, hives and scab.		✓	
Serious infections: symptoms of fever, feel very tired, have a cough or have flu-like symptoms or develop an abscess.		✓	
Allergic reactions: Symptoms while you are getting your <b>REMSIMA SC</b> injection or shortly afterwards of hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure or symptoms 1 to 12 days after receiving <b>REMSIMA SC</b> including fever, rash, headache and muscle or joint pain.		✓	
<b>UNCOMMON</b>			
Liver injury: signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-coloured urine, right sided		✓	

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
abdominal pain, fever and severe fatigue (tiredness).			
Heart failure: If you have been told that you have a heart problem called congestive heart failure, you will need to be closely monitored by your doctor. New or worse symptoms that are related to your heart condition, including shortness of breath or swelling of your ankles or feet.		✓	
Blood problems: symptoms of fever that doesn't go away, bruising or bleeding very easily or looking very pale.		✓	
Nervous system disorders: signs include changes in your vision, (including blindness), seizures, weakness in your arms and/or legs, and numbness or tingling in any part of your body.		✓	
Malignancy: if you have had or develop lymphoma or other cancers while you are taking <b>REMSIMA SC</b> .		✓	
Lupus: symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint pain, or a rash on the cheeks or arms that gets worse in the sun.		✓	
<b>RARE</b>			
Skin problems: skin rashes including redness, itching, skin peeling and blistering; Small pus-filled bumps that can spread over the body, sometimes with a fever (acute generalized exanthematous pustulosis); Itchy reddish-purple skin rash and/or threadlike white-grey lines on mucous membranes (lichenoid reactions)		✓	
Lung problems: symptoms of new or worsening shortness of breath.		✓	

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

#### **Reporting Side Effects**

You can 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/adverse-reaction-reporting.html) (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.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 the carton after “EXP”. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the medicinal product in its outer carton to protect from light.
- This medicine can also be stored in the original carton outside of refrigerated storage up to a maximum of 25°C for a single period of up to 28 days, but not beyond the original expiry date. In this situation, do not return to refrigerated storage again. Write the new expiry date on the carton including day/month/year. Discard this medicine if not used by the new expiry date or the expiry date printed on the carton, whichever is earlier.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Keep out of reach and sight of children.

**If you want more information about REMSIMA SC:**

- 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). (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>).

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Last Revised: January 28, 2021

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## Instructions for use

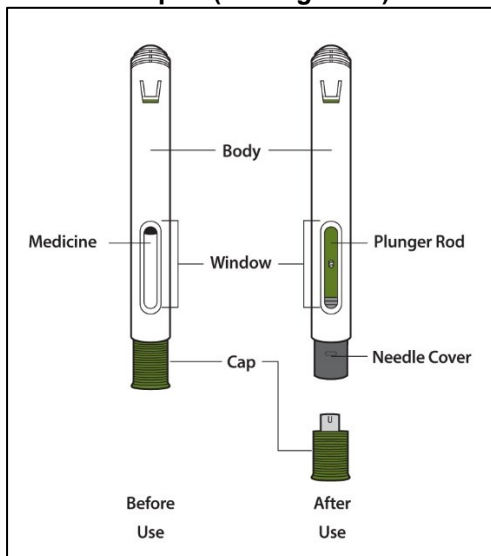
Read carefully these instructions before using the **REMSIMA SC** pen. Consult your healthcare provider if you have questions about using the **REMSIMA SC** pen.

## Important information

- Use the pen **ONLY** if your healthcare provider has trained you on the right way to prepare for and to give an injection.
- Ask your healthcare provider how often you will need to give an injection.
- Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.
- **Do not** use the pen if it has been dropped or is visibly damaged. A damaged pen may not function properly.
- **Do not** reuse the pen.
- **Do not** shake the pen at any time.

## About the REMSIMA SC pen

### Parts of the pen (see *Figure A*):



*Figure A*

- **Do not** remove the cap until you are ready to inject. Once you remove the cap, **do not** recap the pen.

## Prepare for the injection

### 1. Gather the supplies for the injection.

- a. Prepare a clean, flat surface, such as a table or countertop, in a well-lit area.
- b. Remove the pen from the carton stored in your refrigerator.
- c. Ensure you have the following supplies:
  - Pen
  - Alcohol swab
  - Cotton ball or gauze\*
  - Adhesive bandage\*
  - Sharps disposal container\*

*\*Items not included in the carton.*

## 2. Inspect the pen.

**Do not** use the pen if:

- It is cracked or damaged.
- The expiration date has passed.

## 3. Inspect the medicine (see *Figure B*).

**Do not** use the pen if the liquid is different to clear colourless or pale brown or contains particles in it.

*Note: You may see air bubbles in the liquid. This is normal.*

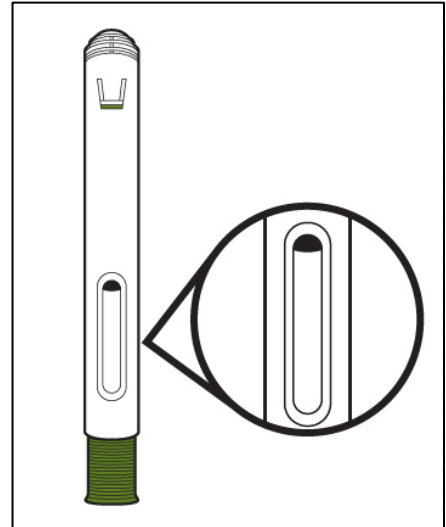


Figure B

## 4. Wait 30 minutes.

- a. Leave the pen at room temperature for 30 minutes to allow it to naturally warm up.

**Do not** warm the pen using heat sources such as hot water or a microwave.

## 5. Choose an injection site (see *Figure C*).

- a. Select an injection site. You may inject into:
  - The front of the thighs.
  - The abdomen except for the 5 cm around the belly button (navel).
  - The outer area of the upper arms (caregiver ONLY).

**Do not** inject into skin that is within 5 cm of your belly button (navel), or is tender, damaged, bruised, or scarred.

*Note: Rotate the injection site each time you give an injection. Each new injection site should be at least 3 cm away from the previous injection site.*

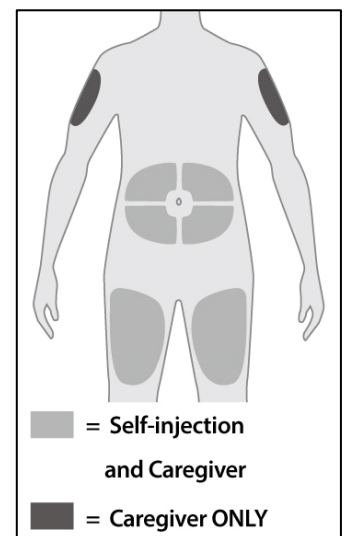


Figure C

## 6. Wash your hands.

- a. Wash your hands with soap and water and dry them thoroughly.



**7. Clean the injection site.**

- a. Clean the injection site with an alcohol swab.
- b. Let the skin dry before injecting.

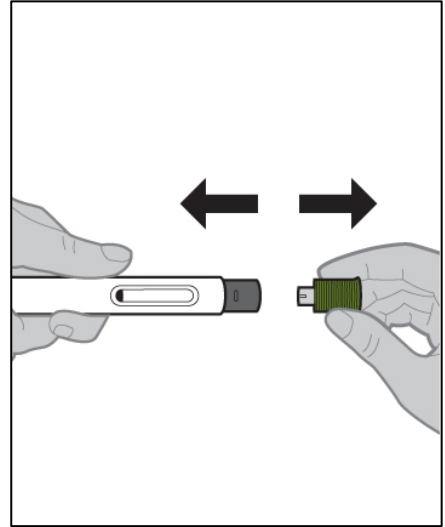
**Do not** blow on or touch the injection site again before giving the injection.

**Give the injection**

**8. Remove the cap (see *Figure D*).**

- a. Pull the olive green cap straight off and set it aside.

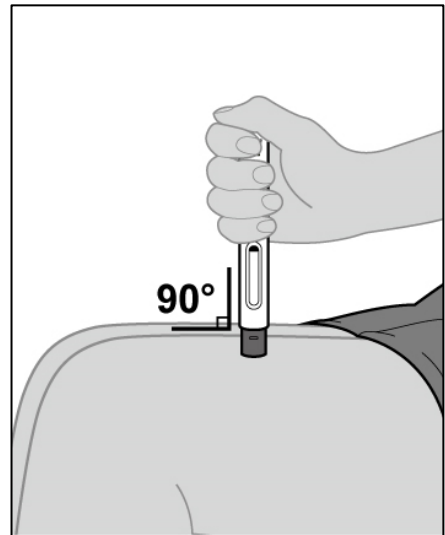
**Do not** touch the needle cover. Doing so may result in a needle stick injury.



*Figure D*

**9. Place the pen on the injection site (see *Figure E*).**

- a. Hold the pen so that you can see the window.
- b. Without pinching or stretching the skin, place the pen over the injection site at a 90-degree angle.



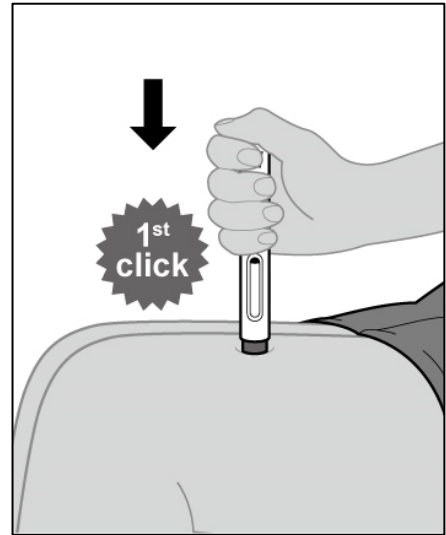
*Figure E*

**10. Start the injection (see *Figure F*).**

- a. Press the pen **firmly** against the skin.

*Note: When the injection starts you will hear the 1<sup>st</sup> loud “click” and the olive green plunger rod will begin to fill the window.*

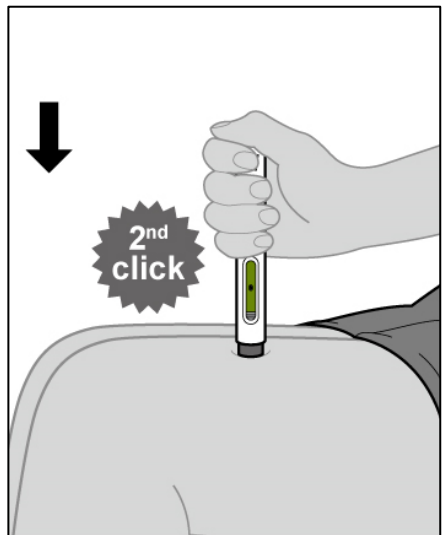
- b. Keep holding the pen **firmly** against the skin and listen for the 2<sup>nd</sup> loud “click.”



*Figure F*

**11. Finish the injection (see *Figure G*).**

- a. After you hear the 2<sup>nd</sup> loud “click,” **continue to hold the pen firmly against the skin and count slowly to at least five** to ensure you inject the full dose.



*Figure G*

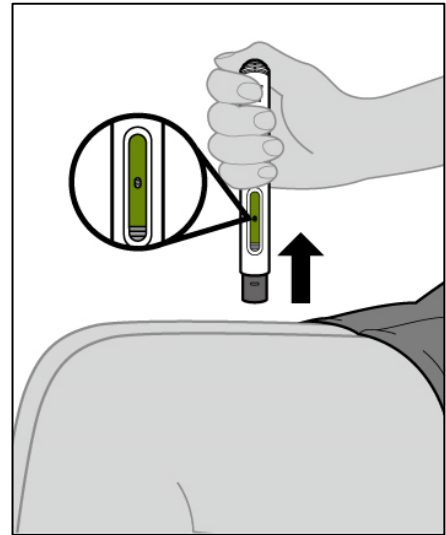
**12. Remove the pen from the injection site.**

- a. Look at the pen and confirm that the olive green plunger rod is filling the window completely.
- b. Lift the pen from the injection site (see *Figure H*).
- c. Gently press a cotton ball or gauze over the injection site and apply an adhesive bandage, if necessary.

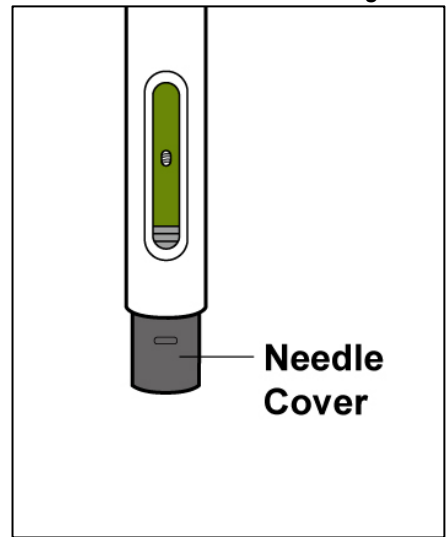
**Do not** rub the injection site.

*Note: After you remove the pen from the injection site, the needle will be automatically covered (see *Figure I*).*

*Note: If the olive green plunger rod does not fill the window completely, you did not receive your full dose. Do not reuse the pen in this case. Call your healthcare provider immediately.*



*Figure H*



*Figure I*

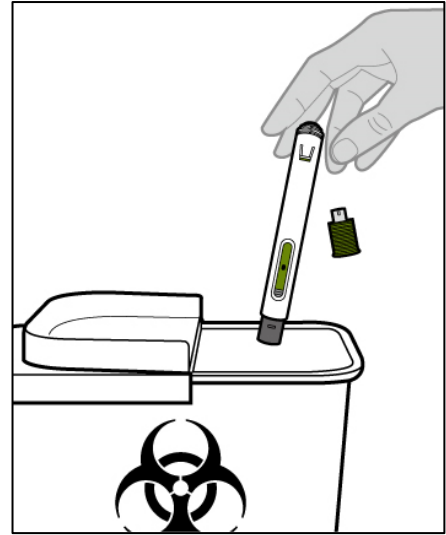
## After the injection

### 13. Dispose of the pen (see *Figure J*).

- a. Put the used pen in an approved sharps disposal container immediately after use.
- b. If you do not have an approved sharps disposal container, you may use a household container that is:
  - made of a heavy-duty plastic;
  - able to close with a tight-fitting, puncture-resistant lid, without sharps being able to come out;
  - upright and stable during use;
  - leak-resistant; and
  - properly labelled to warn of hazardous waste inside the container.
- c. When your sharps disposal container is almost full, it should be disposed of in accordance with local requirements.

**Do not** recap the pen.

*Note: Keep the pen and sharps disposal container out of the sight and reach of children.*



*Figure J*