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.
- maintenance treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response or were intolerant to conventional therapy. Remsima SC should only be used as maintenance therapy after the completion of an induction period with intravenous infliximab.
- maintenance treatment of adults with moderately to severely active ulcerative colitis who have had an inadequate response or were intolerant to conventional therapy. Remsima SC should only be used as maintenance therapy after the completion of an induction period with intravenous infliximab.

REMSIMA SC should be used by health professionals who have sufficient knowledge of rheumatoid arthritis, Crohn's disease and/or ulcerative colitis, and who have fully familiarized themselves with the efficacy/safety profile of REMSIMA SC.

Remsima SC is not intended for use as an induction regimen in patients with Crohn's disease or ulcerative colitis.

1.1 Pediatrics

No data on the safety and efficacy of Remsima SC 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

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. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see **ADVERSE REACTIONS, Infections**).

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, 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 with loading doses of infliximab which may be intravenous or subcutaneous. When subcutaneous loading is used, Remsima 120 mg

should be given as a subcutaneous injection followed by additional subcutaneous injections at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter. If intravenous loading doses of infliximab are given to initiate treatment, 2 intravenous infusions of infliximab 3 mg/kg should be given 2 weeks apart. The first treatment with Remsima SC should be initiated as maintenance therapy 4 weeks after the second intravenous administration, see **4.3 Administration**. The recommended maintenance dose for Remsima SC is 120 mg once every 2 weeks. Remsima SC should be given in combination with methotrexate.

Crohn's Disease and Ulcerative Colitis

For patients who have completed an induction regimen with intravenously administered infliximab:

The recommended maintenance dosing regimen of Remsima SC is 120 mg (given as one subcutaneous injection) once every 2 weeks, starting 4 weeks following completion of an induction regimen.

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 the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease or ulcerative colitis every 8 weeks to Remsima SC.

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**).

4.4 Administration

Remsima SC 120 mg solution for subcutaneous injection is provided with a pre-filled syringe (with or without needle guard) 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:

Rheumatoid Arthritis

For patients beginning infliximab therapy initial induction doses may be given intravenously or subcutaneously. When subcutaneous loading is used, Remsima SC 120 mg should be given as a subcutaneous injection followed by additional subcutaneous injections at 1, 2, 3 and 4 weeks after the first injection. If intravenous loading doses of infliximab are given to initiate treatment, 2 intravenous infusions of infliximab 3 mg/kg should be given 2 weeks apart. See detailed instructions in the appropriate labelling for the selected intravenous infliximab preparation.

Ulcerative Colitis and Crohn's Disease

For patients beginning infliximab therapy, induction doses should be given intravenously. See detailed instructions in the appropriate labelling for the selected intravenous infliximab preparation.

Remsima SC maintenance therapy:

Rheumatoid Arthritis, Ulcerative Colitis, and Crohn's Disease

- The first maintenance dose of Remsima SC may be administered under the supervision of the health professional 4 weeks after last IV induction dose (i.e. at Week 6 following two IV infusion doses at Weeks 0 & 2 for rheumatoid arthritis; at Week 10 following three IV infusion doses at Weeks 0, 2 & 6 for ulcerative colitis or Crohn's disease) or 2 weeks after five SC injection doses at Weeks 0, 1, 2, 3 & 4 for rheumatoid arthritis.

- The first maintenance dose of Remsima SC may also be administered under the supervision of a health professional 8 weeks after the most recent IV infusion for patients already receiving infliximab maintenance therapy.

- The health professional 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 to 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**).

4.5 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

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
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

Remsima SC (infliximab injection) consists of a chimeric immunoglobin G1 (IgG1) monoclonal antibody that binds with high affinity to the human tumor necrosis factor alpha (TNFα).

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.

7 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 TNFα-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 TNFα-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 and Crohn's disease, 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. Before initiating or continuing Remsima SC therapy in a patient who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, carefully assess the need for continuing the immunosuppressant therapy in

light of the potential risks of concomitant treatment. 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 TNFα 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. In clinical trials of Crohn's disease and ulcerative colitis patients, three patients treated with Remsima SC had drug induced livery injury based on hepatic transaminase elevations, including one subject with accompanying bilirubin elevation (**See ADVERSE REACTIONS,** Hepatobiliary Events). Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥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 reinstituted 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.

In Phase III ulcerative colitis (CT-P13 3.7), 62.7% subjects treated with Remsima SC developed anti-drug antibodies to subcutaneous infliximab, and in Phase III Crohn's disease clinical study (CT-P13 3.8), 65.1% subjects treated with Remsima SC developed anti-drug antibodies to subcutaneous infliximab.

Patients with rheumatoid arthritis, ulcerative colitis and Crohn's disease 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.

Infant exposure in utero

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. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. Administration of the live vaccine prior to 12 months of age might be considered if infliximab exposure was limited to the first trimester of pregnancy, or if infant infliximab serum levels are undetectable, or if there is a clear clinical benefit for the individual infant (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women**).

Infant exposure via breast milk

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see **WARNINGS AND PRECAUTIONS, Special Populations, Breast-feeding**).

Therapeutic Infectious Agents

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.

Reproductive Health: Female and Male Potential

- **Fertility**

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.

It is not known whether infliximab can affect reproductive potential.

7.1 Special Populations

7.1.1 Pregnant Women

It is not known whether Remsima SC can cause fetal harm when administered to a pregnant woman. As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 12 months following birth. The clinical significance of low serum levels of infliximab on the immune status in infants is unknown. 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**).

7.1.2 Breast-feeding

Infliximab has been detected at low levels in human milk and in infant serum via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Limited data from published literature reported that infants exposed to infliximab through breast milk had no increase in rates of infections and developed normally. The consideration of Remsima SC use during breast-feeding should take into account the importance of the drug to the mother and health benefits of breast-feeding for the infant.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

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.

8 ADVERSE REACTIONS

8.1 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**).

8.2 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.

The safety profile of subcutaneous infliximab was evaluated in a Phase I/III parallel group study in patients with active rheumatoid arthritis and Phase III placebo-controlled studies in patients with active ulcerative colitis and Crohn's disease. The safety population consisted of 168 patients in the subcutaneous infliximab group and 175 patients in the intravenous infliximab group for rheumatoid arthritis; 296 patients in the subcutaneous infliximab group for ulcerative colitis and 238 patients in the subcutaneous infliximab group for Crohn's disease. For study details, see **PART II, Clinical Trials**.

Rheumatoid Arthritis

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[a] (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)

	Week 6 to < Week 30		Week 6 to Week 64	
	Intravenous Infliximab (N=175)	Subcutaneous Infliximab (N=168)	Intravenous Infliximab[a] (N=175)	Subcutaneous Infliximab (N=168)
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)
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				

	Week 6 to < Week 30		Week 6 to Week 64	
	Intravenous Infliximab (N=175)	Subcutaneous Infliximab (N=168)	Intravenous Infliximab[a] (N=175)	Subcutaneous Infliximab (N=168)
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 infliximab and intravenous infliximab, while data from Weeks 6 to 64 provide the overall safety picture of subcutaneous infliximab or intravenous to subcutaneous maintenance therapy.

[a] Intravenous infliximab was switched to subcutaneous infliximab at Week 30

Ulcerative Colitis

In UC, TEAEs were reported in 67.6% of subcutaneous infliximab-treated patients and 59.3% of placebo-treated patients. Treatment-emergent serious adverse events (TESAEs) were reported in 6.4% of subcutaneous infliximab-treated patients vs 2.9% of placebo-treated patients.

Table 2: Number of UC Patients with 1 or More Treatment-Emergent Adverse Events (Frequency of at least 2% of subcutaneous infliximab treated patients and at a higher rate than placebo) during the Maintenance Phase of UC trial (Study CT-P13 3.7)

System Organ Class Preferred Term	Subcutaneous Infliximab (N=296)	Placebo (N=140)
Blood and lymphatic system disorders		
Anaemia[a]	16 (5.4)	5 (3.6)
Thrombocytosis	6 (2.0)	2 (1.4)
Gastrointestinal disorders		
Abdominal pain[b]	8 (2.7)	2 (1.4)
General disorders and administration site conditions		
Injection site reaction	10 (3.4)	3 (2.1)
Pyrexia	8 (2.7)	3 (2.1)
Infections and infestations		
COVID-19[c]	32 (10.8)	9 (6.4)
Pharyngitis	6 (2.0)	0
Upper respiratory tract infection	9 (3.0)	3 (2.1)
Urinary tract infection[d]	6 (2.0)	2 (1.4)
Injury, poisoning and procedural complications		
Injection related reaction	12 (4.1)	4 (2.9)
Investigations		
Alanine aminotransferase increased	10 (3.4)	2 (1.4)
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (4.4)	2 (1.4)
Nervous system disorders		
Headache	17 (5.7)	7 (5)
Vascular disorders		
Hypertension[e]	9 (3.0)	2 (1.4)

[a] Anaemia: includes anaemia and iron deficiency anaemia

[b] Abdominal pain: includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort

[c] COVID-19: includes COVID-19 and COVID-19 pneumonia

[d] Urinary tract infection: includes urinary tract infection and pyelonephritis

[e] Hypertension: includes hypertension and essential hypertension

Crohn's Disease

In CD, TEAEs were reported in 72.3%% of subcutaneous infliximab-treated patients and 61.9% of placebo-treated patients. Treatment-emergent serious adverse events (TESAEs) were

reported in 6.7% of subcutaneous infliximab-treated patients vs 7.6% of placebo-treated patients.

Table 3. Number of CD Patients with 1 or More Treatment-Emergent Adverse Events (Frequency of at least 2% of subcutaneous infliximab treated patients and at a higher rate than placebo) during the Maintenance Phase of CD trial (Study CT-P13 3.8)

System Organ Class Preferred Term	Subcutaneous Infliximab (N=238)	Placebo (N=105)
Blood and lymphatic system disorders		
Anaemia[a]	15 (6.3)	6 (5.7)
Leukopenia	6 (2.5)	0
Neutropenia	8 (3.4)	0
Gastrointestinal disorders		
Abdominal pain	11 (4.6)	4 (3.8)
Diarrhoea	11 (4.6)	2 (1.9)
General disorders and administration site conditions		
Injection site reaction	14 (5.9)	1 (1.0)
Infections and infestations		
COVID-19[b]	27 (11.3)	5 (4.8)
Oral herpes	6 (2.5)	1 (1.0)
Upper respiratory tract infections[c]	20 (8.4)	6 (5.7)
Urinary tract infection[d]	7 (2.9)	2 (1.9)
Investigations		
Alanine aminotransferase increased	9 (3.8)	1 (1.0)
Blood creatine phosphokinase increased	9 (3.8)	2 (1.9)
Metabolism and nutrition disorders		
Hypertriglyceridaemia	5 (2.1)	1 (1.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	9 (3.8)	3 (2.9)
Nervous system disorders		
Dizziness	6 (2.5)	0
Headache	18 (7.6)	5 (4.8)
Vascular disorders		
Hypertension[e]	8 (3.4)	2 (1.9)

[a] Anaemia: includes anaemia and iron deficiency anaemia
[b] COVID-19: includes COVID-19 and COVID-19 pneumonia
[c] Upper respiratory tract infection: includes upper respiratory tract infection, respiratory infection, respiratory tract infection viral, viral upper respiratory tract infection, acute sinusitis, chronic sinusitis, influenza, nasopharyngitis, pharyngitis, pharyngitis streptococcal, rhinitis, rhinorrhoea, rhinovirus infection, sinusitis, tonsillitis
[d] Urinary tract infection: includes urinary tract infection and pyelonephritis
[e] Hypertension: includes hypertension and essential hypertension

Subcutaneous Infliximab

Hypersensitivity Reactions

Systemic Injection Reaction/ Localized Injection Site Reaction

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

administration (from Week 30) for rheumatoid arthritis; and 5.20 per 100 patient-years in the subcutaneous infliximab group (from Week 10) and 5.34 per 100 patient-years in the placebo group (from Week 10) for UC; and 1.57 per 100 patient-years in the subcutaneous infliximab group (from Week 10) and 1.69 per 100 patient-years in the placebo group (from Week 10) for CD. Most 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 infliximab group (from Week 6) and 21.4 per 100 patient-years in those who switched to subcutaneous infliximab administration (from Week 30) for rheumatoid arthritis; and 4.33 per 100 patient-years in the subcutaneous infliximab group (from Week 10) and 4.0 per 100 patient-years in the placebo group (from Week 10) for UC; and 7.31 per 100 patient-years in the subcutaneous infliximab group (from Week 10) and 1.69 per 100 patient-years in the placebo-group (from Week 10) for CD. Most of these reactions were mild to moderate.

Infections

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

In the maintenance period of 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 the maintenance period of Studies CT-P13 3.7, 28.0% of subcutaneous infliximab-treated UC patients had infections reported vs. 25.7% of placebo-controlled UC patients. The infections most frequently reported in the UC study were COVID-19, upper respiratory tract infection, nasopharyngitis, urinary tract infection, pharyngitis and oral herpes.

In the maintenance period of Studies CT-P13 3.8, 31.1% of subcutaneous infliximab-treated CD patients had infections reported vs. 18.1% of placebo-controlled CD patients. The infections most frequently reported in the CD study were COVID-19, urinary tract infection, oral herpes, and nasopharyngitis .

In subcutaneous infliximab studies, latent tuberculosis was reported in 4% of RA patients,0.7% of UC patients, and none of CD 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 RA study; and in 1.7% of subcutaneous infliximab-treated patients and in 0.7% in placebo-treated patients in UC; and in 2.9% of subcutaneous infliximab-treated patients and in 1.9% in placebo-treated patients in CD studies.

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).

In Studies CT-P13 3.7 and CT-P13 3.8, abnormal hepatic function, cholelithiasis, hepatic steatosis, hepatitis, hepatotoxicity, hyperbilirubinemia and non-alcoholic fatty liver were reported in subcutaneous infliximab-treated UC or CD patients.

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. However, three cases of drug induced liver injury were noted in Remsima SC-treated patients that led to study drug discontinuation.

- In two patients in Study CT-P13 3.7, ALT and AST levels started rising 7 to 12 months after starting Remsima SC, reaching peak values of 4 to 11 x ULN for ALT, and 2 to 7x ULN for AST. In both patients, total bilirubin levels remained below 2 x ULN
- In one patient in Study CT-P13 3.8, ALT and AST started rising within a month after starting Remsima SC, reaching peak values of 18 x ULN for ALT and 14 x ULN for AST. At approximately 5 months, total bilirubin levels also increased to a peak value of 2.5 x ULN.

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; and one IBD patient developed prostate cancer amongst 534 IBD patients administered with subcutaneous infliximab, which is at a rate of 0.27 per 100 patient-years. In another clinical trial in patients with CD, one malignancy (non-small cell lung cancer) was reported in a Remsima-SC treated patient.

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 ≤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.

8.3 Less Common Clinical Trial Adverse Drug Reactions

Subcutaneous Infliximab

Other medically relevant adverse events occurring in less than 2% patients overall in patients treated with Remsima SC for any indication (RA, UC, CD) were as follows, presented by body system:

Blood and lymphatic system disorders: eosinophilia, haemorrhagic anaemia, hypereosinophilic syndrome, iron deficiency anaemia, leukocytosis, leukopenia, lymphadenopathy, lymphadenopathy mediastinal, lymphopenia, monocytosis, polycythaemia, thrombocytopenia, thrombocytosis
Cardiac disorders: aortic valve incompetence, arrhythmia, atrial fibrillation, atrioventricular block second degree, bundle branch block right, cardiac arrest, cardiac failure, left atrial enlargement, left ventricular hypertrophy, mitral valve incompetence, myocardial infarction, palpitations, subendocardial ischaemia, supraventricular tachycardia, tachycardia, tricuspid valve incompetence, ventricular extrasystoles
Congenital, familial and genetic disorders: hereditary haemochromatosis
Ear and labyrinth disorders: ear pain, tinnitus, vertigo, vertigo positional
Endocrine disorders: cushingoid
Eye disorders: chalazion, conjunctival haemorrhage, eye pain, eye pruritus, swelling of eyelid, xerophthalmia
Gastrointestinal disorders: abdominal distension, abdominal pain lower, abdominal pain upper, anal fissure, anal ulcer, aphthous ulcer, chronic gastritis, colitis, constipation, dry mouth, duodenal ulcer haemorrhage, duodenal ulcer perforation, dyspepsia, flatulence, food poisoning, frequent bowel movements, gastrointestinal inflammation, gastrooesophageal reflux disease, gingival bleeding, glossodynia, haematochezia, haemorrhoidal haemorrhage, haemorrhoids, inguinal hernia, intestinal metaplasia, large intestinal stenosis, large intestine polyp, lip pruritus, lower gastrointestinal haemorrhage, nausea, peritoneal adhesions, proctalgia, pseudopolyposis, rectal haemorrhage, subileus, toothache, vomiting
General disorders and administration site conditions: accidental death, adverse drug reaction, asthenia, chest discomfort, chest pain, chills, cyst, enanthema, fatigue, hyperthermia, inflammation, injection site pain, injection site paraesthesia, malaise, mucosal inflammation, non-cardiac chest pain, oedema, oedema peripheral, peripheral swelling, pyrexia, soft tissue inflammation, sudden death, swelling face, vaccination site pain
Hepatobiliary disorders: cholecystitis chronic, cholelithiasis, chronic hepatitis, hepatic function abnormal, hepatic steatosis, hepatitis, hepatomegaly, hepatotoxicity, hyperbilirubinaemia, liver disorder, non-alcoholic fatty liver
Immune system disorders: infusion related hypersensitivity reaction
Infections and infestations: abscess intestinal, abscess limb, abscess rupture, acute sinusitis, adenoviral upper respiratory infection, anal abscess, appendicitis, arthritis bacterial, ascariasis,

asymptomatic bacteriuria, bartholinitis, bronchiolitis, bronchitis, bronchitis haemophilus, COVID-19 pneumonia, candida infection, cellulitis, chronic sinusitis, conjunctivitis, conjunctivitis bacterial, cystitis, ear infection, folliculitis, furuncle, gastroenteritis, gastroenteritis viral, gastrointestinal viral infection, gingivitis, herpes dermatitis, herpes simplex, herpes zoster, impetigo, infected fistula, influenza, latent tuberculosis, lower respiratory tract infection, nasal herpes, nasopharyngitis, onychomycosis, oral bacterial infection, oral candidiasis, orchitis, otitis externa, otitis media, paronychia, periodontitis, peritonitis, pertussis, pharyngitis, pharyngitis streptococcal, pharyngotonsillitis, pilonidal disease, pneumonia, pulpitis dental, pustule, pyelonephritis, pyelonephritis chronic, pyoderma, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, salpingitis, salpingo-oophoritis, sinusitis, skin bacterial infection, streptococcal impetigo, tinea versicolour, tonsillitis, tooth infection, tracheobronchitis, vaginal infection, varicella, viral upper respiratory tract infection

Injury, poisoning and procedural complications: administration related reaction, animal bite, bone contusion, burns second degree, clavicle fracture, contusion, fall, foot fracture, gastrointestinal stoma complication, heat stroke, hip fracture, joint injury, ligament sprain, skin laceration, sunburn, synovial rupture, thermal burn, wrong technique in product usage process

Investigations: aspartate aminotransferase increased, bilirubin conjugated increased, blood alkaline phosphatase increased, blood bilirubin increased, blood creatine phosphokinase MB increased, blood lactate dehydrogenase increased, blood pressure abnormal, blood pressure increased, blood triglycerides increased, blood urea increased, body temperature increased, c-reactive protein increased, coronavirus test positive, creatinine renal clearance decreased, creatinine renal clearance increased, faecal calprotectin increased, gamma-glutamyltransferase increased, haemoglobin decreased, heart rate increased, hepatic enzyme increased, interferon gamma release assay positive, liver function test increased, mycobacterium tuberculosis complex test positive, neutrophil count decreased, platelet count increased, transaminases increased, weight decreased, weight increased, white blood cell count decreased, white blood cells urine positive

Metabolism and nutrition disorders: diabetes mellitus, glucose tolerance impaired, gout, hypercholesterolaemia, hyperkalaemia, hyperlipidaemia, hyperphosphataemia, hypertriglyceridaemia, hyperalbuminaemia, hypoferritinaemia, hypokalemia, hypophosphataemia, iron deficiency, type 2 diabetes mellitus, vitamin D deficiency

Musculoskeletal and connective tissue disorders: arthritis, arthritis enteropathic, arthropathy, back pain, bursitis, connective tissue inflammation, costochondritis, exostosis, fistula, intervertebral disc compression, intervertebral disc degeneration, intervertebral disc disorder, intervertebral disc protrusion, joint swelling, musculoskeletal pain, myalgia, osteoporosis, pain in extremity, rheumatoid arthritis, rotator cuff syndrome, scleroderma, spinal osteoarthritis, spinal pain, spondyloarthropathy, tenosynovitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): colorectal adenoma, haemangioma, large intestine benign neoplasm, malignant ovarian cyst, prostate cancer, skin papilloma, uterine leiomyoma

Nervous system disorders: altered state of consciousness, autonomic nervous system imbalance, carotid artery stenosis, cerebral infarction, dementia Alzheimer's type, dizziness, hypoaesthesia, neurovascular conflict, paresthesia, parosmia, sciatica, somnolence, syncope, vertebrobasilar insufficiency

Product issues: device loosening

Psychiatric disorders: anxiety, depression, irritability, mixed anxiety and depressive disorder, stress

Renal and urinary disorders: calculus urinary, chronic kidney disease, dysuria, haematuria, leukocyturia, nephrolithiasis, proteinuria, renal amyloidosis, renal colic, urinary incontinence, urinary tract pain, urine odour abnormal

Reproductive system and breast disorders: amenorrhoea, balanoposthitis, benign prostatic hyperplasia, breast pain, dysmenorrhoea, endometrial hyperplasia, gynaecomastia, menstruation delayed, nipple pain, prostatitis, uterine haemorrhage, vulvovaginal inflammation
Respiratory, thoracic and mediastinal disorders: acute respiratory failure, asthma, bronchiectasis, cough, dyspnoea, epistaxis, haemoptysis, hiccups, increased bronchial secretion, nasal congestion, nasal dryness, oropharyngeal pain, productive cough, pulmonary mass, rhinorrhoea
Skin and subcutaneous tissue disorders: acne, acne fulminanas, alopecia, alopecia areata, angioedema, blister, cutaneous vasculitis, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug eruption, dry skin, ecchymosis, eczema, erythema, hyperhidrosis, intertrigo, night sweats, pruritus, psoriasis, pustular psoriasis, rash, rash erythematous, rash papular, seborrhoeic dermatitis, skin discolouration, skin disorder, skin exfoliation, skin lesion, skin lesion inflammation, target skin lesion, urticaria
Surgical and medical procedures: tooth extraction
Vascular disorders: deep vein thrombosis, flushing, haematoma, hot flush, hypotension, phlebitis, 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, fascitis
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

8.4 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, leukocytosis, leukopenia, lymphadenopathy, lymphopenia, neutropenia, thrombocytopenia, thrombocytosis.

The proportion of patients with abnormal ALT levels in response to infliximab is presented in **Table 4** for RA, UC and CD patients.

Table 4: 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	
	Control[1]	Subcutaneous Infliximab	Control[a]	Subcutaneous Infliximab	Control[a]	Subcutaneous Infliximab
RA[b]	28.0%	46.4%	5.1%	2.4%	1.1%	0.0%
UC[c]	18.6%	24.3%	2.9%	1.7%	0.0%	1.0%
CD[c]	21.9%	30.7%	1.9%	2.1%	0.0%	1.3%

[a] Control group was intravenous infliximab for RA, and placebo for UC and CD.
[b] 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.
[c] All patients in the UC and CD trial received intravenous induction dosing 5 mg/kg at Weeks 0, 2, and 6. And, Week 10 onwards patients were randomized to receive either placebo or subcutaneous infliximab 120 mg every 2 weeks.

8.5 Post-Market Adverse Reactions

<u>Subcutaneous Infliximab</u>

The following adverse reactions have been identified during post-approval use of Remsima SC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Remsima SC exposure.

- *Infections and infestations*: cellulitis, disseminated tuberculosis, lower respiratory tract

infection, pneumonia, sepsis

- *Neoplasms benign, malignant and unspecified*: breast cancer, gastric cancer, lung cancer
- *Nervous system disorders*: multiple sclerosis
- *General disorders and administration site conditions*: fatigue, malaise

Intravenous Infliximab

Additional adverse events, some with fatal outcome, reported from worldwide post-marketing experience with intravenous infliximab are included in Table 5 (see **ADVERSE REACTIONS**, **Infections** and **Infusion-related Reactions**). Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to intravenous infliximab exposure.

Table 5. POST-MARKETING REPORTS	
Blood and Lymphatic System Disorders	Agranulocytosis (including infants exposed *in utero* to infliximab), idiopathic thrombocytopenic purpura, hemolytic anemia, pancytopenia, thrombotic thrombocytopenic purpura
General Disorders and Administration Site Conditions	anaphylactic reactions, anaphylactic shock, infusion-related reactions, serum sickness
Cardiac Disorders	pericardial effusion, myocardial ischemia/myocardial infarction (within 24 hours of initiation of infusion), arrhythmia (within 24 hours of initiation of infusion)
Eye Disorders	Transient visual loss occurring during or within 2 hours of infusion
Immune System Disorders	Vasculitis, sarcoidosis, hemophagocytic lymphohistiocytosis (HLH)
Neoplasm Benign and Malignant	hepatosplenic T-cell lymphoma (the vast majority in Crohn's disease and ulcerative colitis: primarily adolescents and young adults), pediatric malignancy, leukemia, melanoma, Merkel cell carcinoma, cervical cancer
Hepatobiliary System Disorders	hepatocellular damage, hepatitis, jaundice, autoimmune hepatitis, liver failure
Nervous System Disorders	central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, numbness, seizure, tingling, transverse myelitis, cerebrovascular accidents occurring within approximately 24 hours of initiation of infusion, orbital apex syndrome
Infections and Infestations	opportunistic infections (such as aspergillosis, atypical mycobacteria, coccidioidomycosis, cryptococcosis, candidiasis, histoplasmosis, legionellosis, listeriosis, pneumocystosis), salmonellosis, sepsis, tuberculosis, protozoal infections, hepatitis B reactivation and vaccine breakthrough infection (after *in utero* exposure to infliximab)*
Respiratory, Thoracic and Mediastinal Disorders	interstitial lung disease, including pulmonary fibrosis/interstitial pneumonitis, and rapidly progressive disease
Skin and Subcutaneous Tissue Disorders	vasculitis (primarily cutaneous), psoriasis including new onset and pustular (primarily palmar/plantar), erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, linear IgA bullous dermatosis (LABD), acute generalized exanthematous pustulosis (AGEP), lichenoid reactions

*including bovine tuberculosis (disseminated BCG infection), see **WARNINGS AND PRECAUTIONS**, **Live Vaccines/Therapeutic Infectious Agents**)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

9.4 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 12 months following birth, unless infliximab exposure was limited to the first trimester or if infant infliximab serum levels are undetectable. Administration of a live vaccine prior to 12 months of age might be considered if the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infants (see **WARNINGS AND PRECAUTIONS**).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (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., TNFα, 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Infliximab is a chimeric IgG1κ monoclonal antibody that binds specifically to human TNFα. Infliximab binds to the soluble and transmembrane forms of TNFα with high affinity, thereby neutralizing the biological activity of TNFα. Infliximab was also shown to bind to Fcγ receptors [FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa (V and F) and FcγRIIIb], FcRn, and C1q. Following binding, cells expressing transmembrane TNFα can be lysed in vitro by complement or effector cell-mediated mechanisms. Infliximab was shown to inhibit the functional activity of TNFα 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 TNFα-dependent apoptosis, suppression of pro-inflammatory cytokine secretion [interleukin 6 (IL-6) and IL-8], and induction of regulatory macrophages.

10.2 Pharmacodynamics

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

10.3 Pharmacokinetics

Table 6: Summary of Infliximab Pharmacokinetic Parameters in RA, UC and CD Populations at Steady State

Indication	Treatment	C_{trough} (mcg/mL)	C_{max} (mcg/mL)	AUC (hr*mcg/mL)
RA	Subcutaneous Infliximab (120 mg Q2W)	12.22 ± 6.60	17.78 ± 7.241	20974.1 ± 9479.62
	Intravenous Infliximab (3 mg/kg Q8W)	1.51 ± 2.50	71.88 ± 12.185	14302.3 ± 6603.79
UC	Subcutaneous Infliximab (120 mg Q2W)	18.97 ± 7.924	31.57 ± 7.244	36623.5 ± 12886.66
CD	Subcutaneous Infliximab (120 mg Q2W)	18.18 ± 5.661	26.62 ± 9.015	33829.2 ± 10671.48

Absorption: Single subcutaneous injections of 120, 180 and 240 mg of infliximab yielded approximately dose proportional increases in the maximum serum concentration (C_{max}) 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 mcg/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 for RA; and from Week 10 after 3 doses of intravenous infliximab at Weeks 0, 2 and 6 for IBD), the median (CV%) C_{trough} level at Week 22 was 12.8 mcg/mL (80.1%), 17.5 mcg/mL (45.9%) and 20.4 mcg/mL (46.5%) at steady state for RA, UC and CD, respectively.

Estimated by a population PK model, the bioavailability of subcutaneous infliximab was 64.5% (95% CI: 62.5% - 66.4%).

There are no clinical trials with Remsima SC 120 mg without intravenous loading doses of infliximab in patients with rheumatoid arthritis. However, population pharmacokinetic and pharmacokinetics/pharmacodynamics modelling and simulation predicted comparable infliximab exposure (AUC over 8 weeks) and efficacy (DAS28 and ACR20 response) in rheumatoid arthritis patients treated with Remsima SC 120 mg given at Weeks 0, 1, 2, 3 and 4 when compared with Remsima 3 mg/kg given intravenously for the induction phase only or for both the induction and maintenance phases (Remsima 3 mg/kg given intravenously at Weeks 0, 2 and 6, and then every 8 weeks thereafter.

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 (± SD) apparent clearance of infliximab 120 mg administered subcutaneously was 19.3 ± 6.9 mL/hr.

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

In the ulcerative colitis and Crohn's disease patients, the mean (± SD) clearance of infliximab 120 mg subcutaneous at Week 22 was 20.3 ± 8.3 mL/hr and 17.2 ± 7.1 mL/hr at steady state, respectively.

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.

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2 to 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.

12 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

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Infliximab

Chemical name: Infliximab

Molecular mass: 145,878 daltons

Structural formula: The infliximab molecule consists of 2 identical heavy chains and 2 identical light chains. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteine residues in the heavy and light chains are involved in either intra- or inter-disulfide bonding. C-terminal lysine variation is a feature of infliximab drug substance. The oligosaccharide is bound exclusively to Asn_{300} in the CH_2 domian of each heavy chain.

Physicochemical properties: Inflixmab drug substance 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 α (TNFα) with high affinity. Infliximab contains murine heavy (H) and light (L) chain variable regions (VH and VL, respectively) derived from the murine anti-TNFα MAb, A2, and genomic DNA-derived human H and L chain constant regions (C_H and C_L, respectively).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Rheumatoid Arthritis

Table 7: Summary of trial design and patient demographics for RA

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 study in rheumatoid arthritis	**<Dose-loading phase> - Week 0 to 6** Two doses of intravenous infliximab 3 mg/kg at Weeks 0 and 2 for all patients **<Maintenance phase> - Week 6 to 64** • 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. • 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.	343	51.4 (18 to 74)	74 (21.6%) male 269 (78.4%) female

The efficacy and safety 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 8: Mean (SD) Actual Values of DAS28 (CRP and ESR)

	Subcutaneous Infliximab (N=165)	Intravenous Infliximab[b] (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)[a]	3.5 (1.2)[a]
Week 54	2.8 (1.1)	2.9 (1.2)[b]

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.
[a] 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
[b] 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 9: Proportions of Patients Achieving Clinical Response According to the ACR Criteria

	Subcutaneous Infliximab (N=165)	Intravenous Infliximab[a] (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%)[a]
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%)[a]
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%)[a]

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.
[a] Intravenous infliximab was switched to subcutaneous infliximab at Week 30

Ulcerative Colitis

Table 10: Summary of trial design and patient demographics for UC

Study	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)

CT-P13 3.7	Phase 3, randomized, placebo-controlled, double-blind, multicentre, parallel-group study in ulcerative colitis	**<Induction phase> - Week 0 to 10** Three doses of CT-P13 IV 5 mg/kg at Weeks 0, 2 and 6 for all patients **<Maintenance phase> - Week 10 to 54** • SC Arm: CT-P13 SC 120 mg via PFS at Week 10 and then every 2 weeks up to Week 54 • Placebo Arm: Placebo SC 120 mg via PFS at Week 10 and then every 2 weeks up to Week 54	438	38.9 (18 to 75)	246 (56.2%) male 192 (43.8%) female

Maintenance Phase Study: CP-P13 3.7

The efficacy and safety of REMSIMA SC were assessed in a randomized, double-blind, placebo-controlled clinical study in subjects with moderately to severely active UC (defined as a modified Mayo score [mMs] of 5 to 9, including an endoscopy subscore [ES] of 2 or 3). Subjects had previously demonstrated an inadequate response, loss or response, or intolerance to conventional therapy (i.e., corticosteroids alone or in combination with 6-mercaptopurine or azathioprine). Concomitant treatment with stable doses of aminosalicylates, corticosteroids, UC-related antibiotics, and/or immunomodulatory agents were permitted. Corticosteroid taper was permitted after Week 10.

A total of 548 subjects received open-label infliximab 5 mg/kg administered intravenously as induction dosing at Weeks 0, 2, and 6. A total of 438 subjects achieved clinical response at Week 10 and were randomized (2:1) in a double-blind fashion to receive REMSIMA SC 120 mg or placebo SC administered subcutaneously every 2 weeks (Q2W) via pre-filled syringe (PFS) from Week 10 through Week 54. Randomization was stratified by previous exposure to UC-related biologic agent and/or JAK inhibitors (used or not used), use of UC-related oral corticosteroids at Week 0 (used or not used), and clinical remission at Week 10 (remitter or non-remitter). Clinical response was defined as a decrease from baseline in the mMs of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

At the time of randomization into the double-blind phase (Week 10), 92% of subjects were receiving concomitant aminosalicylates, 41% were receiving UC-related oral corticosteroids, and 22% were receiving UC-related immunomodulators. A total of 10% of randomized subjects had prior exposure to a UC-related biological or JAK inhibitor.

Subjects had a median mMs of 7.0 and 55.3% had severely active disease (mMs ≥7).

The primary endpoint was the proportion of subjects in clinical remission at Week 54.
The key secondary endpoints were the proportion of subjects achieving clinical response, endoscopic-histologic mucosal improvement, and corticosteroid-free remission at Week 54.

Study Results

The results of primary and key secondary endpoints are provided in Table 11.

Table 11: Results of Key Efficacy Endpoints at Week 54 in Subjects with Ulcerative Colitis in Study CT-P13 3.7

	Remsima SC[e] (N=294)	Placebo[e] (N=144)	Treatment Difference and 95% CI[f]
Primary endpoint			
Clinical Remission[a]	43.2%	20.8%	21.1% (11.8, 29.3)[g]
Key secondary endpoints			
Clinical Response[b]	53.7%	31.3%	21.1% (11.2, 30.1)[g]
Endoscopic-histologic Mucosal Improvement [c]	35.7%	16.7%	18.0% (9.1, 25.7)[g]
Corticosteroid-free Remission [d]	36.7% (44/120)	18.0% (11/61)	17.3% (3.1, 28.9)[g]

Abbreviations: CI = confidence intervals

a Defined as stool frequency subscore of 0 or 1 point; rectal bleeding subscore of 0 point; and endoscopic subscore of 0 or 1 point.

b Defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

c Defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute Robarts Histopathology Index (RHI) score of 3 points or less with an accompanying lamina propria neutrophils and neutrophils in epithelium subscore of 0 point.

d Defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline.

e This is a randomized withdrawal study. All subjects received three intravenous induction doses of 5 mg/kg infliximab at Weeks 0, 2, and 6. The Remsima SC arm includes those subjects who achieved a clinical response at Week 10 and were randomized to receive a subcutaneous injection of 120 mg Remsima SC q2w as maintenance treatment; the placebo arm includes those subjects who achieved a clinical response at Week 10 and were randomized to receive placebo q2w as maintenance treatment.

f Based on Cochran-Mantel-Haenszel (CMH) method adjusted for randomization stratification factors (previous exposure to biological product and/or JAK inhibitor, use of treatment with oral corticosteroids at Week 0, and clinical remission status at Week 10).

g Statistically significant under multiplicity control for Remsima SC vs placebo comparison ($p<0.05$).

Crohn's Disease

Table 12: Summary of trial design and patient demographics for CD

Study	Trial Design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex n (%)
CT-P13 3.8	Phase 3, randomized, placebo-controlled, double-blind, multicentre, parallel-group study in Crohn's disease	**<Induction phase> - Week 0 to 10** Three doses of CT-P13 IV (5 mg/kg) at Weeks 0, 2 and 6 for all patients **<Maintenance phase> - Week 10 to 54** • SC Arm: CT-P13 SC 120 mg via PFS every 2 weeks from Week 10 to Week 54 • Placebo Arm: Placebo SC (matching volume to CT-P13 SC 120 mg) via PFS every 2 weeks from Week 10 to Week 54	343	34.8 (18 to 75)	203 (59.2%) male 140 (40.8%) female

Maintenance Phase Study: CT-P13 3.8

The efficacy and safety of Remsima SC were assessed in a randomized, double-blind, placebo-controlled clinical study in subjects with moderately to severely active Crohn's Disease (CD). Enrolled subjects had a Crohn's Disease Activity Index (CDAI) of 220 to 450 points, an average daily stool frequency (SF) ≥4 points and/or average worst daily abdominal pain (AP) score ≥2 points, and a Simplified Endoscopic Activity Score for CD (SES-CD) of ≥6 for ileal-colonic CD (or ≥4 points for isolated ileal/colonic CD). Subjects had previously demonstrated an inadequate response or intolerance to conventional therapies (corticosteroids and/or immunosuppressants). Concomitant treatment with stable doses of aminosalicylates, corticosteroids, CD-related antibiotics and/or immunomodulatory agents were permitted. Corticosteroid dose was tapered after Week 10.

A total of 396 subjects received open-label infliximab 5 mg/kg administered intravenously as induction dosing at Weeks 0, 2, and 6. A total of 343 subjects achieved clinical response at Week 10 and were randomized (2:1) in a double-blind fashion to receive Remsima SC 120 mg or placebo SC administered subcutaneously every 2 weeks (Q2W) via pre-filled syringe (PFS) from Week 10 through Week 54. Randomization was stratified by previous exposure to a biologic agent and/or JAK inhibitor (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used), and clinical remission at Week 10 (remitter or non-remitter). Clinical response was defined as a decrease from baseline in CDAI of at least 100 points (i.e., CDAI-100 responders).

At baseline, 63.0% subjects, 30.7% subjects and 40.8% subjects received aminosalicylates, immunomodulators and oral corticosteroids, respectively, in the Remsima SC group, and 57.1% subjects, 35.2% subjects and 37.1% subjects received aminosalicylates, immunomodulators and oral corticosteroids, respectively, in the Placebo SC group.

At baseline, 11.3% subjects were exposed to biologic agent and/or JAK inhibitors in Remsima SC group, and 8.0% subjects were exposed to biological agent and/or JAK inhibitors in Placebo SC group.

The co-primary endpoints were the proportion of subjects in clinical remission (based on CDAI) and the proportion of subjects achieving endoscopic response at Week 54. The key secondary endpoints were the proportion of subjects achieving CDAI-100 response, clinical remission (based on abdominal pain [AP] and stool frequency [SF]), endoscopic remission and corticosteroid-free remission at Week 54.

Study Results

The results of primary and key secondary endpoints are provided in Table 9.

Table 13: Results of Key Efficacy Endpoints at Week 54 in Subjects with Crohn's Disease in Study CT-P13 3.8

Endpoint	Remsima SC[g] (N=231)	Placebo[g] (N=112)	Treatment Difference and 95% CI[h]
Co-primary endpoints			
Clinical remission (based on CDAI)[a]	62.3%	32.1%	32.1% (20.9, 42.1)[i]
Endoscopic response[b]	51.1%	17.9%	34.7% (24.2, 43.5)[i]
Key secondary endpoints			
CDAI-100 response[c]	65.8%	38.4%	29.0% (17.7, 39.3)[i]
Clinical remission (based on AP and SF)[d]	56.7%	31.3%	27.0% (15.8, 37.1)[i]
Endoscopic remission[e]	34.6%	10.7%	24.9% (15.4, 32.8)[i]
Corticosteroid-free remission[f]	39.8% (39/98)	22.7% (10/44)	17.1% (-0.4, 31.5)

Abbreviations: CI = confidence intervals

a Defined as an absolute CDAI score of <150 points.

b Defined as a >50% decrease in SES-CD score from the baseline value.

c Defined as a decrease in CDAI score of 100 points or more from the baseline value.

d Defined as average worst daily abdominal pain (AP) score of ≤1 (using 4-point scale) and an average daily loose/watery stool frequency (SF) score of ≤3 (of Type 6 or Type 7 on BSFS) with no worsening in either average score compared with the baseline value.

e Defined as an absolute SES-CD score of ≤4 and at least 2-point reduction from the baseline value with no sub-score of >1.

f Defined as being in clinical remission in addition to not receiving any corticosteroid for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at baseline.

g This is a randomized withdrawal study. All subjects received three intravenous induction doses of 5 mg/kg infliximab at Weeks 0, 2, and 6. The Remsima SC arm includes those subjects who achieved a clinical response at Week 10 and were randomized to receive a subcutaneous injection of 120 mg Remsima SC q2w as maintenance treatment; the placebo arm includes those subjects who achieved a clinical response at Week 10 and were randomized to receive placebo q2w as maintenance treatment.

h Based on Cochran-Mantel-Haenszel (CMH) method adjusted for randomization stratification factors (previous exposure to biological product and/or JAK inhibitor, use of treatment with oral corticosteroids at Week 0, and clinical remission status at Week 10).

i Statistically significant under multiplicity control for Remsima SC vs placebo comparison ($p<0.05$).

14.4 Immunogenicity

Rheumatoid Arthritis

In Study CT-P13 3.5 Part 2, samples that were positive for 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.

Ulcerative Colitis and Crohn's Disease

Approximately 62.7% of subjects with ulcerative colitis and 65.1% of subjects with Crohn's disease, treated with Remsima SC developed ADA to infliximab following induction treatment with intravenous infliximab and maintenance treatment with Remsima SC by Week 54. ADA to subcutaneous infliximab were associated with reduced or undetectable serum infliximab concentrations. The steady-state serum infliximab concentration was 11.7 mcg/mL and 17.0 mcg/mL in ADA-positive and ADA-negative patients in the UC study, respectively, and 10.9 mcg/mL and 18.0 mcg/mL in ADA-positive and ADA-negative patients in the CD study, respectively. Among ADA positive patients, 92.2% had neutralizing antibodies [160/180 (88.9%) subjects with UC and 149/151 (98.7%) subjects with CD].

15 MICROBIOLOGY

No microbiological information is required for this drug product.

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 healthcare professional 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 healthcare professional 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 healthcare professional right away.
- Prior to treatment with **Remsima SC,** you should tell your healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 moderately to severely active rheumatoid arthritis (in combination with methotrexate), ulcerative colitis and Crohn's disease. Your healthcare professional has chosen to treat your rheumatoid arthritis, ulcerative colitis or Crohn's disease with **Remsima SC** because you have moderately to severely active rheumatoid arthritis, ulcerative colitis or Crohn's disease.
- For people with moderately to severely active ulcerative colitis or Crohn's disease, Remsima SC should only be used as maintenance therapy after the completion of an induction period with intravenous infliximab.
- Remsima SC is not intended for use as an induction regimen in patients with ulcerative colitis or

Crohn's disease.

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 healthcare professional. Tell your healthcare professional 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 healthcare professional 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 healthcare professional may decide to stop **Remsima SC** treatment for severe reactions. Your healthcare professional 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 healthcare professional if you notice any of these symptoms.
- Nervous system diseases: Tell your healthcare professional 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 painful and limited eye movements, loss

of feeling in the forehead or vision loss (orbital apex syndrome); or 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional right away.
- Stroke: Some patients have experienced a stroke within approximately 24 hours of receiving infliximab**.** Tell your healthcare professional 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 healthcare professional about this as this may impact the decision to start or continue treatment with **Remsima SC**. Your healthcare professional should do a blood test for hepatitis B virus before you start treatment with **Remsima SC**.
- Vaccination: Tell your healthcare professional 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 healthcare professional 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 healthcare professional if you think you may be pregnant, are breastfeeding, or planning to conceive a child. Your healthcare professional 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 healthcare professional 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), rotavirus vaccine or any other live vaccines. 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 healthcare professionals and other health care professionals about your **Remsima SC** use before the baby receives any vaccine, including live vaccines, such as BCG (used to prevent tuberculosis), rotavirus vaccine or any other live vaccines. Administration of BCG vaccine within 12 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 healthcare professional. If you are breast-feeding, it is important to tell your baby's healthcare professionals and other healthcare professionals about your Remsima SC use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's healthcare professional recommends otherwise. 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 healthcare professional 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 healthcare professional.

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 healthcare professional 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 healthcare professional 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 healthcare professional 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, ulcerative colitis or Crohn's disease. Drugs that may interact with **Remsima SC** include: prescription and non-prescription medicines, vitamins, and herbal supplements.
- Patients with rheumatoid arthritis or Crohn's disease 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 healthcare professional 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 healthcare professional 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 (RA) or three (UC, CD) infusions of intravenous infliximab. The initial two (RA) or three (UC, CD) intravenous infusions will be given to you by your healthcare professional or nurse. The first **Remsima SC** injection will be given 4 weeks after the last intravenous infusion followed by Remsima SC injections given every 2 weeks.
- For patients with rheumatoid arthritis, your healthcare professional may start your **Remsima SC** treatment with or without two intravenous infliximab infusion doses. If **Remsima SC** treatment is initiated without two intravenous infliximab infusion doses, the table below shows how often you will usually have this medicine after your first dose.

2nd dose	1 week after your 1st dose
3rd dose	2 weeks after your 1st dose

4th dose	3 weeks after your 1st dose
5th dose	4 weeks after your 1st dose
Further doses	6 weeks after your 1st dose and every 2 weeks thereafter

- The first dose of **Remsima SC** will be administered under the supervision of your healthcare professional.
- After proper training, if you feel you are well-trained and confident to inject **Remsima SC** yourself, your healthcare professional may allow you to inject subsequent doses of **Remsima SC** yourself at home.
- Talk to your healthcare professional 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 healthcare professionals involved in your care that you take Remsima SC.

Usual dose:

Rheumatoid Arthritis:

Your healthcare professional will start your treatment with or without 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). If intravenous infliximab infusion doses are given to start the treatment, 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.

Ulcerative Colitis and Crohn's Disease

Your healthcare professional will start your treatment with three intravenous infliximab infusion doses of 5 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). Intravenous infliximab infusion doses are administered at 0, 2 and 6 weeks 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 maintenance 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 then follow the original dosing schedule.

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 then follow the original dosing schedule.

If you are not sure when to inject **Remsima SC**, call your healthcare professional.

If you have any further questions on the use of this medicine, ask your healthcare professional, 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 healthcare professional if you experience any of the effects listed in this leaflet or any other side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
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 **Remsima SC** 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 **Remsima SC** including fever, rash, headache and muscle or joint pain.		✓	
UNCOMMON			
Liver injury: signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-coloured urine, right sided		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
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 healthcare professional. 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 **Remsima SC**.		✓	
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.		✓	
RARE			
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) 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 to 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).

This leaflet was prepared by:
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Republic of Korea

Last Revised:

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*):

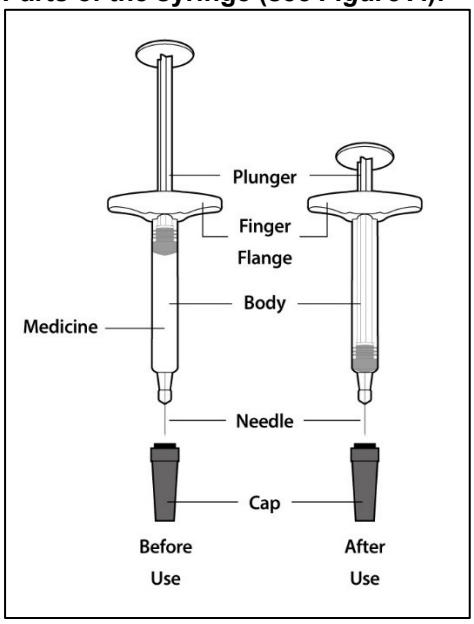

Figure A

- **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*).
The liquid should be clear and colourless to pale brown.
Do not use the syringe if the liquid is cloudy, discoloured or contains particles in it.
Note: You may see air bubbles in the liquid. This is normal.

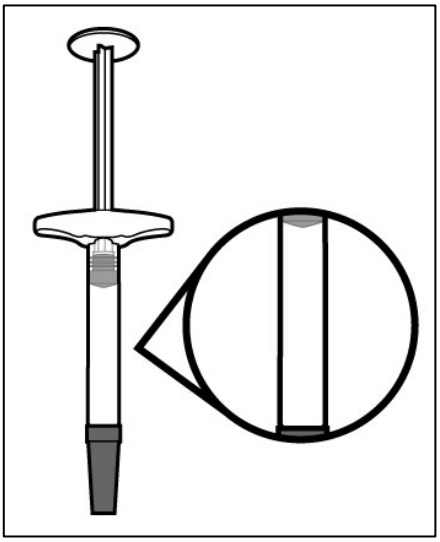

Figure B

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.

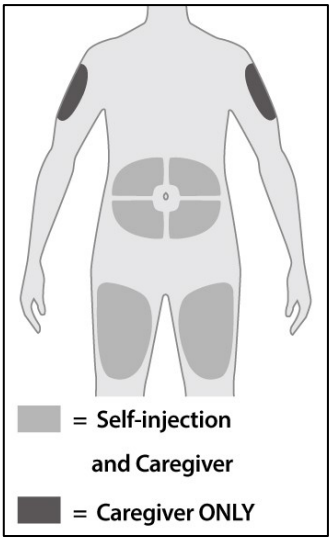

Figure C

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.

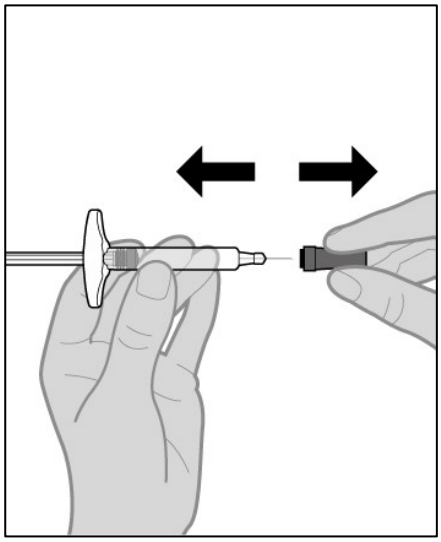

Figure D

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.

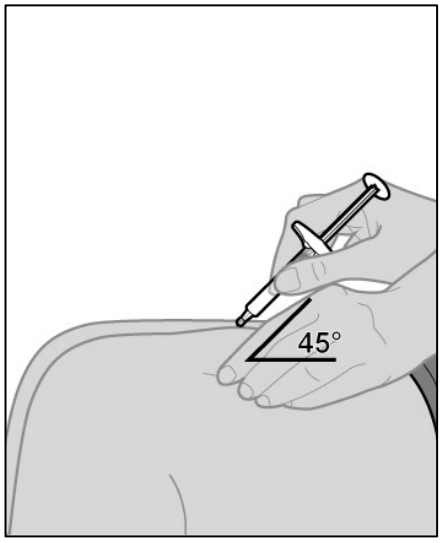

Figure E

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.

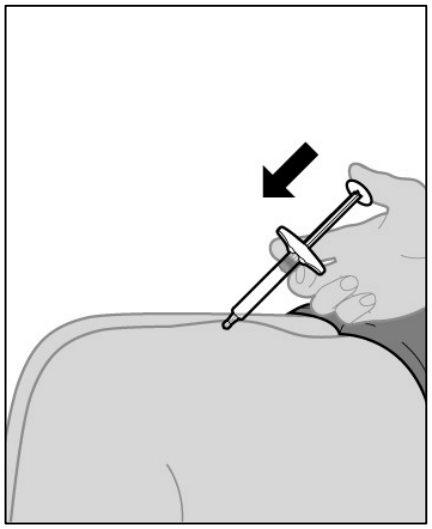

Figure F

11. Remove the 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.

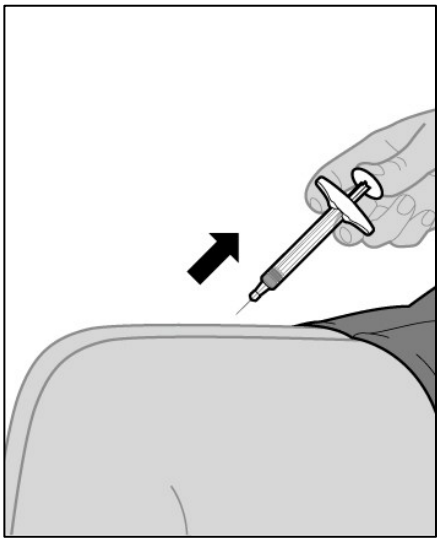

Figure G

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 healthcare professional 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 healthcare professional 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 healthcare professional right away.
- Prior to treatment with **Remsima SC,** you should tell your healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 moderately to severely active rheumatoid arthritis (in combination with methotrexate), ulcerative colitis and Crohn's disease. Your healthcare professional has chosen to treat your rheumatoid arthritis, ulcerative colitis or Crohn's disease with **Remsima SC** because you have moderately to severely active rheumatoid arthritis, ulcerative colitis or Crohn's disease.
- For people with moderately to severely active ulcerative colitis or Crohn's disease, Remsima SC should only be used as maintenance therapy after the completion of an induction period with intravenous infliximab.
- Remsima SC is not intended for use as an induction regimen in patients with ulcerative colitis or

Crohn's disease.

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 healthcare professional. Tell your healthcare professional 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 healthcare professional 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 healthcare professional may decide to stop **Remsima SC** treatment for severe reactions. Your healthcare professional 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 healthcare professional if you notice any of these symptoms.
- Nervous system diseases: Tell your healthcare professional 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 painful and limited eye movements, loss

of feeling in the forehead or vision loss (orbital apex syndrome); or 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional right away.
- Stroke: Some patients have experienced a stroke within approximately 24 hours of receiving infliximab**.** Tell your healthcare professional 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 healthcare professional about this as this may impact the decision to start or continue treatment with **Remsima SC**. Your healthcare professional should do a blood test for hepatitis B virus before you start treatment with **Remsima SC**.
- Vaccination: Tell your healthcare professional 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 healthcare professional 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 healthcare professional if you think you may be pregnant, are breastfeeding, or planning to conceive a child. Your healthcare professional 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 healthcare professional 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), rotavirus vaccine or any other live vaccines. 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 healthcare professionals and other health care professionals about your **Remsima SC** use before the baby receives any vaccine, including live vaccines such as BCG vaccine (used to prevent tuberculosis), rotavirus vaccine or any other live vaccines. Administration of BCG vaccine within 12 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 healthcare professional. If you are breast-feeding, it is important to tell your baby's healthcare professionals and other healthcare professionals about your Remsima SC use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's healthcare professional recommends otherwise. 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 healthcare professional 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 healthcare professional.

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 healthcare professional 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 healthcare professional 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 healthcare professional 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, ulcerative colitis or Crohn's disease. Drugs that may interact with **Remsima SC** include: prescription and non-prescription medicines, vitamins, and herbal supplements.
- Patients with rheumatoid arthritis or Crohn's disease 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 healthcare professional 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 healthcare professional 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 (RA) or three (UC, CD) infusions of intravenous infliximab. The initial two (RA) or three (UC, CD) intravenous infusions will be given to you by your healthcare professional or nurse. The first **Remsima SC** injection will be given 4 weeks after the last intravenous infusion followed by **Remsima SC** injections given every 2 weeks
- For patients with rheumatoid arthritis, your healthcare professional may start your **Remsima SC** treatment with or without two intravenous infliximab infusion doses.If **Remsima SC** treatment is initiated without two intravenous infliximab infusion doses, the table below shows how often you will usually have this medicine after your first dose.

2nd dose	1 week after your 1st dose
3rd dose	2 weeks after your 1st dose

4th dose	3 weeks after your 1st dose
5th dose	4 weeks after your 1st dose
Further doses	6 weeks after your 1st dose and every 2 weeks thereafter

- The first dose of **Remsima SC** will be administered under the supervision of your healthcare professional.
- After proper training, if you feel you are well-trained and confident to inject **Remsima SC** yourself, your healthcare professional may allow you to inject subsequent doses of **Remsima SC** yourself at home.
- Talk to your healthcare professional 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 healthcare professionals involved in your care that you take Remsima SC.

Usual dose:

Rheumatoid Arthritis:

Your healthcare professional will start your treatment with or without 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). If intravenous infliximab infusion doses are given to start the treatment, 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.

Ulcerative Colitis and Crohn's Disease

Your healthcare professional will start your treatment with three intravenous infliximab infusion doses of 5 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). Intravenous infliximab infusion doses are administered at 0, 2 and 6 weeks 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 maintenance 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 then follow the original dosing schedule.

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 then follow the original dosing schedule.

If you are not sure when to inject **Remsima SC**, call your healthcare professional.

If you have any further questions on the use of this medicine, ask your healthcare professional, 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 healthcare professional if you experience any of the effects listed in this leaflet or any other side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
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 **Remsima SC** 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 **Remsima SC** including fever, rash, headache and muscle or joint pain.		✓	
UNCOMMON			
Liver injury: signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-coloured urine, right sided		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
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 healthcare professional. 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 **Remsima SC**.		✓	
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.		✓	
RARE			
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) 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 to 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).

This leaflet was prepared by:
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Last Revised:

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*):

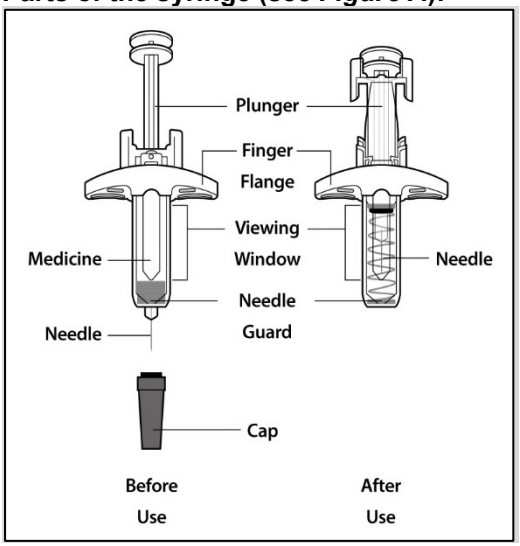

Figure A

- **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*).
The liquid should be clear and colourless to pale brown.
Do not use the syringe if the liquid is cloudy, discoloured or contains particles in it.
Note: You may see air bubbles in the liquid. This is normal.

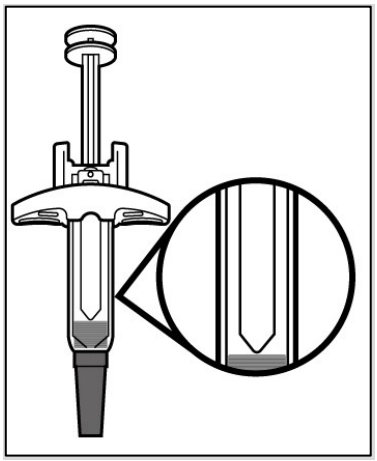

Figure B

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.

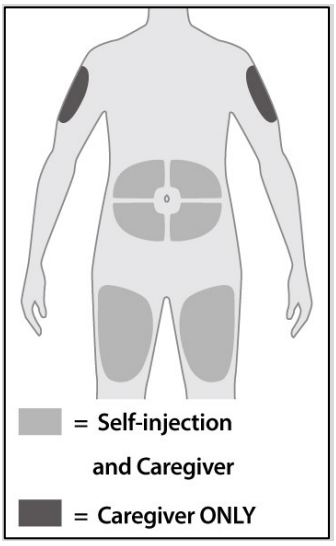

Figure C

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.

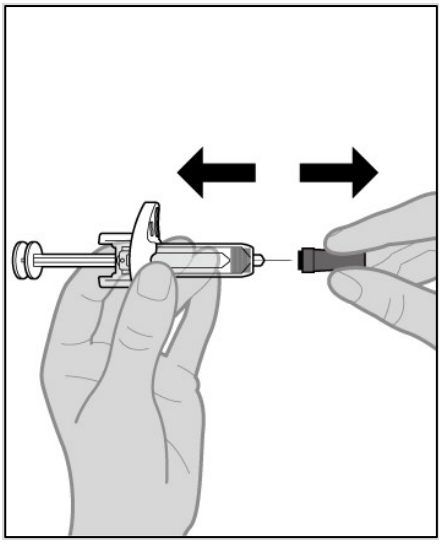

Figure D

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.

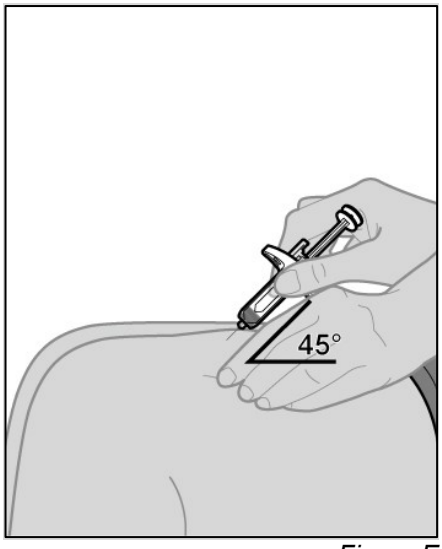

Figure E

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.

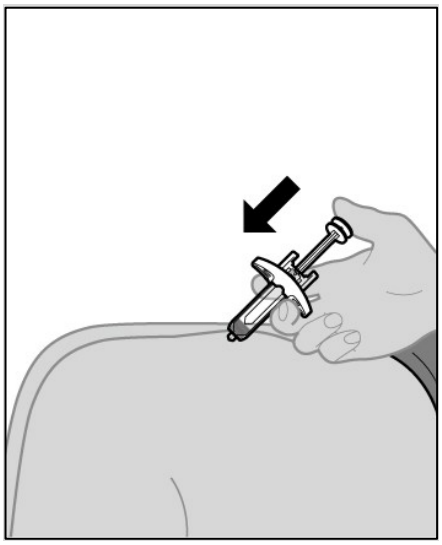

Figure F

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.

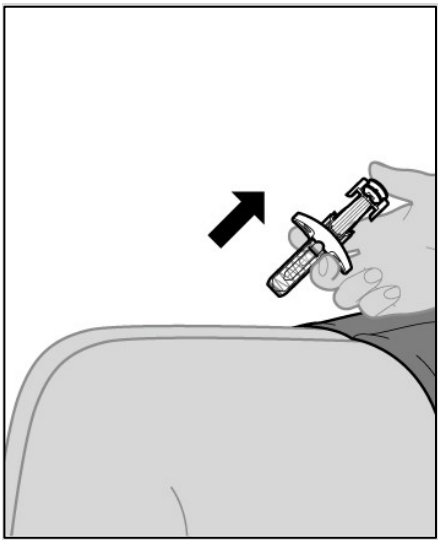

Figure G

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.

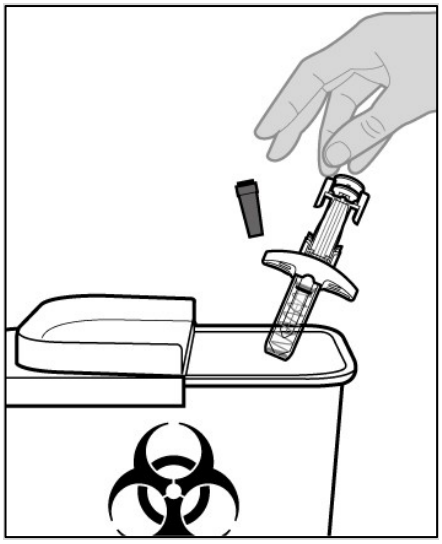

Figure H

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 healthcare professional 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 healthcare professional 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 healthcare professional right away.
- Prior to treatment with **Remsima SC,** you should tell your healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 moderately to severely active rheumatoid arthritis (in combination with methotrexate), ulcerative colitis and Crohn's disease. Your healthcare professional has chosen to treat your rheumatoid arthritis, ulcerative colitis or Crohn's disease with **Remsima SC** because you have moderately to severely active rheumatoid arthritis, ulcerative colitis or Crohn's disease.
- Remsima SC is a medicine that is used in maintenance treatment of adults with moderately to severely For people with moderately to severely active ulcerative colitis or Crohn's disease, Remsima SC should only be used as maintenance therapy after the completion of an induction period with intravenous infliximab.

- Remsima SC is not intended for use as an induction regimen in patients with ulcerative colitis or Crohn's disease.

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 healthcare professional. Tell your healthcare professional 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 healthcare professional 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 healthcare professional may decide to stop **Remsima SC** treatment for severe reactions. Your healthcare professional 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 healthcare professional if you notice any of these symptoms.
- Nervous system diseases: Tell your healthcare professional 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 painful and limited eye movements, loss of feeling in the forehead or vision loss (orbital apex syndrome); or 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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional right away.
- Stroke: Some patients have experienced a stroke within approximately 24 hours of receiving infliximab**.** Tell your healthcare professional 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 healthcare professional about this as this may impact the decision to start or continue treatment with **Remsima SC**. Your healthcare professional should do a blood test for hepatitis B virus before you start treatment with **Remsima SC**.
- Vaccination: Tell your healthcare professional 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 healthcare professional 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 healthcare professional if you think you may be pregnant, are breastfeeding, or planning to conceive a child. Your healthcare professional 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 healthcare professional 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), rotavirus vaccine or any other live vaccines. 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 healthcare professionals and other health care professionals about your **Remsima SC** use before the baby receives any vaccine, including live vaccines such as BCG vaccine (used to prevent tuberculosis), rotavirus vaccine or any other live vaccines. Administration of BCG vaccine within 12 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 healthcare professional. If you are breast-feeding, it is important to tell your baby's healthcare professionals and other healthcare professionals about your Remsima SC use before your baby is given any vaccine. Live vaccines should not be given to your baby while you are breast-feeding unless your baby's healthcare professional recommends otherwise. 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 healthcare professional 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 healthcare professional.

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 healthcare professional 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 healthcare professional 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 healthcare professional 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, ulcerative colitis or Crohn's disease. Drugs that may interact with **Remsima SC** include: prescription and non-prescription medicines, vitamins, and herbal supplements.
- Patients with rheumatoid arthritis or Crohn's disease 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 healthcare professional 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 healthcare professional 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 (RA) or three (UC, CD) infusions of intravenous infliximab. The initial two (RA) or three (UC, CD) intravenous infusions will be given to you by your healthcare professional or nurse. The first **Remsima SC** injection will be given 4 weeks after the last intravenous infusion followed by **Remsima SC** injections given every 2 weeks.
- For patients with rheumatoid arthritis, your healthcare professional may start your **Remsima SC** treatment with or without two intravenous infliximab infusion doses. If **Remsima SC** treatment is initiated without two intravenous infliximab infusion doses, the table below shows how often you will usually have this medicine after your first dose.

2nd dose	1 week after your 1st dose

3rd dose	2 weeks after your 1st dose
4th dose	3 weeks after your 1st dose
5th dose	4 weeks after your 1st dose
Further doses	6 weeks after your 1st dose and every 2 weeks thereafter

- The first dose of **Remsima SC** will be administered under the supervision of your healthcare professional.
- After proper training, if you feel you are well-trained and confident to inject **Remsima SC** yourself, your healthcare professional may allow you to inject subsequent doses of **Remsima SC** yourself at home.
- Talk to your healthcare professional 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 healthcare professionals involved in your care that you take Remsima SC.

Usual dose:

Rheumatoid Arthritis:

Your healthcare professional will start your treatment with or without 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). If intravenous infliximab infusion doses are given to start the treatment, 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.

Ulcerative Colitis and Crohn's Disease

Your healthcare professional will start your treatment with three intravenous infliximab infusion doses of 5 mg for every kg of body weight (given to you into a vein, usually in your arm, over a period of 2 hours). Intravenous infliximab infusion doses are administered at 0, 2 and 6 weeks 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 maintenance 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 then follow the original dosing schedule.

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 then follow the original dosing schedule.

If you are not sure when to inject **Remsima SC**, call your healthcare professional.

If you have any further questions on the use of this medicine, ask your healthcare professional, 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 healthcare professional if you experience any of the effects listed in this leaflet or any other side effects.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
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 **Remsima SC** 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 **Remsima SC** including fever, rash, headache and muscle or joint pain.		✓	
UNCOMMON			
Liver injury: signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-coloured urine, right sided		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
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 healthcare professional. 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 **Remsima SC**.		✓	
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.		✓	
RARE			
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) 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 to 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).

This leaflet was prepared by:
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Republic of Korea

Last Revised:

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*):

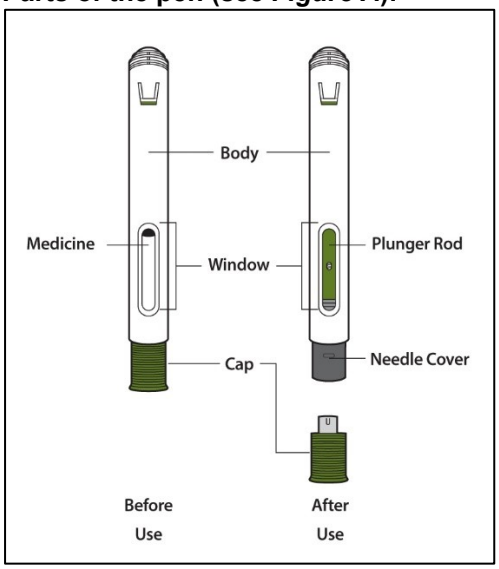

Figure A

- **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*).
The liquid should be clear and colourless to pale brown.
Do not use the pen if the liquid is cloudy, discoloured or contains particles in it.
Note: You may see air bubbles in the liquid. This is normal.

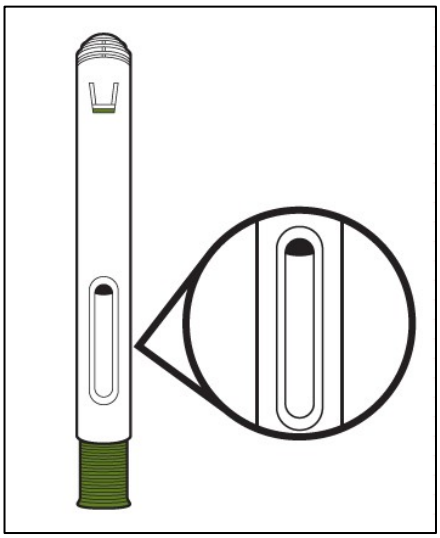

Figure B

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.

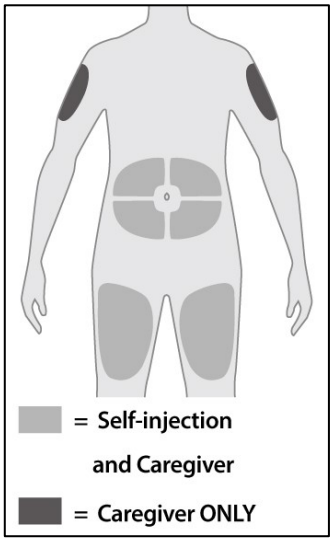

Figure C

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.

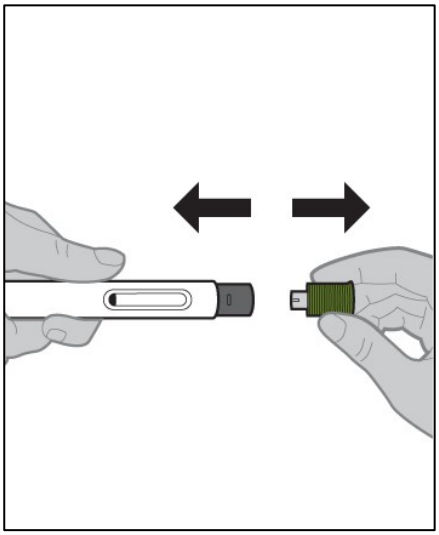

Figure D

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.

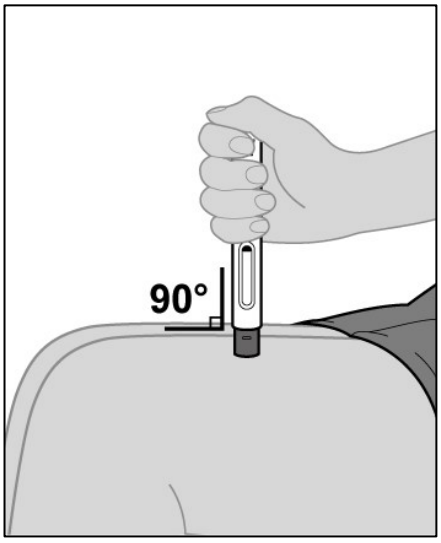

Figure E

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

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

Note: When the injection starts you will hear the 1st 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 2nd loud "click."

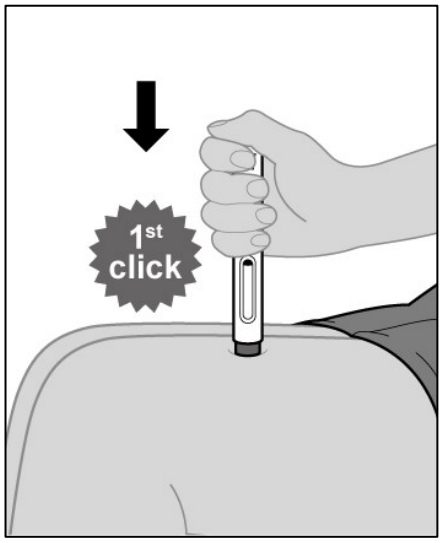

Figure F

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

a. After you hear the 2nd 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.

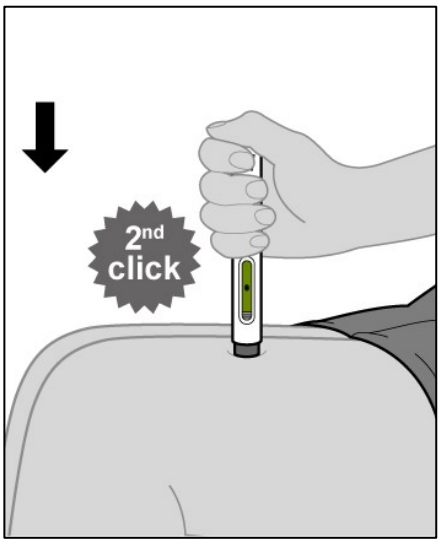

Figure G

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.

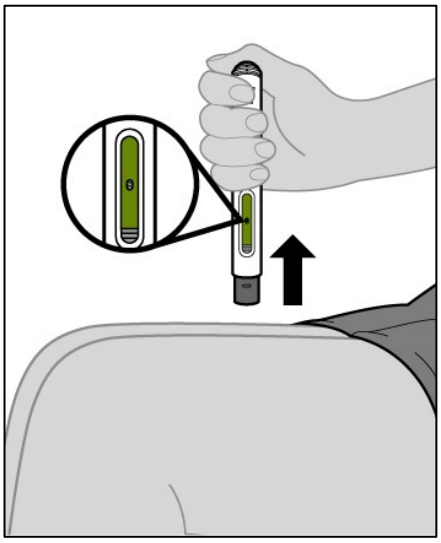

Figure H

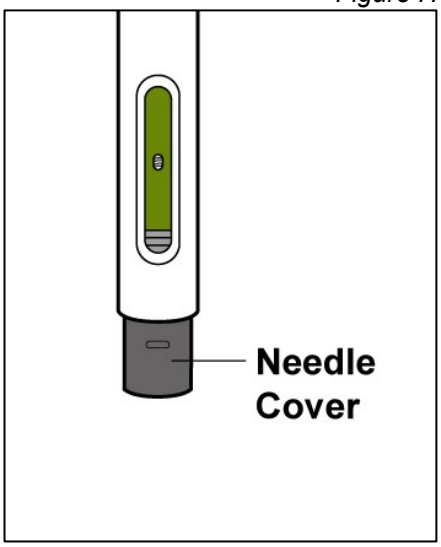

Figure I

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