PRODUCT MONOGRAPH

PrREMSIMA™
(infliximab)

Powder for Solution, Sterile, Lyophilized, 100 mg/vial

Professed Standard

Biological Response Modifier

REMSIMA™ should be used by physicians who have sufficient knowledge of rheumatoid arthritis and/or ankylosing spondylitis and/or Crohn's disease and/or ulcerative colitis and/or psoriatic arthritis and/or plaque psoriasis and who have fully familiarized themselves with the efficacy/safety profile of REMSIMA™.

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PrREMSIMA™
(infliximab)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous Infusion	Powder for Solution /100 mg/vial	*For a complete listing, see* **DOSAGE FORMS, COMPOSITION AND PACKAGING** *section*.

DESCRIPTION

REMSIMA™ (infliximab) is a subsequent entry biologic to REMICADE®. It consists of a chimeric immunoglobin G1 (IgG1) monoclonal antibody that binds with high affinity to the human tumour necrosis factor alpha (TNFα).

The REMSIMA™ drug product is formulated as a white lyophilized powder in a type I borosilicate glass vial with a 20 mm, double vent butyl rubber stopper and a 20 mm flip-off seal. The lyophilisate is reconstituted with 10 mL of sterile water for injection to yield a single dose formulation of 10 mg/mL infliximab, at pH 7.2. Each vial is designed to deliver a single dose of 100 mg infliximab active substance. The components of a single vial of the drug product REMSIMA™ are: infliximab, sucrose, sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate dehydrate, polysorbate 80.

Similarity between REMSIMA™ and REMICADE® (the reference product) was established in accordance with the *Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)*, for the authorized indications.

INDICATIONS AND CLINICAL USE

Comparability between REMSIMA™ and the reference product has been established based on comparative chemistry and manufacturing studies, comparative non-clinical studies, comparative PK studies and clinical trials, in patients with rheumatoid arthritis or ankylosing spondylitis. Indications in Crohn's disease, ulcerative colitis, psoriatic arthritis and plaque psoriasis have been granted on the basis of similarity, between REMSIMA™ and the reference product, in product quality, mechanism of action, disease pathophysiology, safety profile, dosage regimen and on clinical experience with the reference product.

REMSIMA™ (infliximab) 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.
- reduction of signs and symptoms and improvement in physical function in patients with active ankylosing spondylitis who have responded inadequately, or are intolerant to, conventional therapies.
- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing and reduction of corticosteroid use in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to a corticosteroid and/or aminosalicylate. REMSIMA™ can be used alone or in combination with conventional therapy.
- treatment of fistulising Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment.
- reduction of signs and symptoms, induction and maintenance of clinical remission and mucosal healing, and reduction or elimination of corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy (i.e., aminosalicylate and/or corticosteroid and/or an immunosuppressant).
- reduction of signs and symptoms, induction of major clinical response, and inhibition of the progression of structural damage of active arthritis, and improvement in physical function in patients with psoriatic arthritis.
- treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with chronic moderate plaque psoriasis, REMSIMA™ should be used after phototherapy has been shown to be ineffective or inappropriate. When assessing the severity of psoriasis, the physician should consider the extent of involvement, location of lesions, response to previous treatments, and impact of disease on the patient's quality of life.

REMSIMA™ should be used by physicians who have sufficient knowledge of rheumatoid arthritis and/or ankylosing spondylitis and/or Crohn's disease and/or ulcerative colitis and/or psoriatic arthritis and/or plaque psoriasis and who have fully familiarized themselves with the efficacy/safety profile of REMSIMA™.

Geriatrics (≥ 65 years of age):

Evidence from clinical studies suggests that the use in geriatric population is associated with no overall differences in safety and efficacy.

In rheumatoid arthritis clinical trials (ATTRACT) and plaque psoriasis trials, no overall differences were observed in the effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both infliximab and control groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 64.

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**).

Pediatrics:

The safety and efficacy of REMSIMA™ has not been established in pediatric patients.

CONTRAINDICATIONS

- 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 a history of hypersensitivity to infliximab, to other murine proteins, or to any of the excipients. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

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™. 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.[3] 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™ (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 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).

Pediatric Malignancy
REMSIMA™ is not indicated for use in pediatric patients. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF-blockers, including infliximab (see WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis).

In order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Risk of Inflections

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™ should not be given to patients with a clinically important active infection, including tuberculosis. Caution should be exercised when considering the use of REMSIMA™ 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™. New infections should be closely monitored. If a patient develops a serious infection, REMSIMA™ 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™ treatment should be carefully considered before initiation or continuation of REMSIMA™ therapy.

Invasive Fungal Infections

In patients treated with REMSIMA™, 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™ 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™ 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™ 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™ 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 REMSIMA™. 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™ and anakinra is not recommended.

Concurrent Administration of REMSIMA™ 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™ and abatacept is not recommended.

Concurrent Administration with other Biological Therapeutics

There is insufficient information regarding the concomitant use of REMSIMA™ with other biological therapeutics used to treat the same conditions as REMSIMA™. The concomitant use of REMSIMA™ 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

Pediatric malignancy

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤18 years of age), including

infliximab. Approximately half of these cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous post-marketing reports.

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/or 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

Rare 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 infliximab 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 REMSIMA™ 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 inflximab, 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 inflximab 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™, 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 (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for infliximab, NMSCs were more common in patients with previous phototherapy (see **ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease**).

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. Tumourigenicity studies in mice deficient in TNFα demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

Cardiovascular

Doses greater than 5 mg/kg should not be administered to patients with congestive heart failure (CHF). REMSIMA™ should be used with caution in patients with mild heart

failure (NYHA Class I/II). Patients should be closely monitored, and REMSIMA™ 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 infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg.

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™ who have a current or past history of significant cytopenias.

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™ therapy should be considered in patients with confirmed significant hematologic abnormalities.

Hepatic/Biliary/Pancreatic

Very rare cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between infliximab and these events has not been established. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations $\geq$5 times the upper limit of normal develop, REMSIMA™ 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™. 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™ therapy and monitored closely during treatment and for several months following discontinuation of therapy.

Immune

To minimize the incidence of hypersensitivity reactions, including infusion reactions and serum sickness-like reactions, REMSIMA™ should be administered as regular maintenance therapy after an induction regimen at weeks 0, 2 and 6 (see **DOSAGE AND ADMINISTRATION**).

Hypersensitivity Reactions

Infliximab has been associated with hypersensitivity reactions that vary in their time of onset. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of 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™ 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, Infusion-related Reactions**).

During clinical trials, the reference product was sometimes readministered within 14 weeks following the last infusion. After a drug free interval of 15 weeks to 2 years, the risk of delayed hypersensitivity following readministration has not been accurately determined (see **ADVERSE REACTIONS, Infusion-related Reactions**, ***Delayed Hypersensitivity/Reactions following readministration of infliximab***)

Infusion reactions following readministration of infliximab

In a rheumatoid arthritis clinical trial where subjects were receiving low dose methotrexate and in a psoriasis clinical trial, a 3-dose induction of infliximab after a period of no treatment resulted in a higher incidence of serious and severe infusion reactions during the reinduction regimen than had been observed in rheumatoid arthritis, psoriasis 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 (see **ADVERSE REACTIONS**, **Infusion-related Reactions**, ***Infusion Reactions following readministration of infliximab***).

The REMSIMA Patient Assistance Program facilitates the administration of REMSIMA™. The REMSIMA Patient Assistance Program clinics are staffed by qualified healthcare professionals specially trained in the administration of REMSIMA™ infusions and are available across Canada. Information about the REMSIMA Patient Assistance Program can be obtained by calling 1-844-466-6627.

Autoimmunity

Treatment with infliximab may result in the formation of autoantibodies and, rarely, 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**). Approximately 10% of patients were antibody positive. The majority of antibody positive patients had low titers.

In a Phase III study of Crohn's disease (SONIC) in patients who were immunomodulator-naïve, antibodies occurred at Week 30 in 14% of patients receiving infliximab monotherapy and in 1% of patients receiving infliximab in combination with azathioprine (AZA). Through Week 50, anti-infliximab antibodies occurred in 19% and 2.5% of patients, respectively. In the 20 patients on infliximab monotherapy who were positive for anti-infliximab antibodies at some point during the study through Week 50, 10 patients had an infusion reaction, one of which was serious. None of the 3 patients on infliximab in combination with AZA who were positive for anti-infliximab antibodies had an infusion reaction.

Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see **ADVERSE REACTIONS, Infusion-related Reactions**) than were patients who were antibody negative. Antibody development was lower among adult rheumatoid arthritis, Crohn's disease, and psoriatic arthritis patients receiving immunosuppressant therapies such as 6-mercaptopurine (6-MP), azathioprine (AZA), or methotrexate (MTX).

With repeated dosing of infliximab, serum concentrations of infliximab were higher in rheumatoid arthritis patients who received concomitant MTX. In the 2 Phase 3 studies of psoriasis (EXPRESS and EXPRESS II), infliximab was administered as induction followed by maintenance and without concomitant immunosuppressive therapy. In these studies, antibodies occurred in approximately 26.5% to 35.8% of patients who received 5 mg/kg every 8 week maintenance for 1 year and at higher rates (up to 1.4-fold) with other dose regimens (3 mg/kg q8 week, 3 mg/kg dosed as needed, and 5 mg/kg dosed as needed). Despite the increase in the rate of antibody formation, the infusion reaction rates in the 2 psoriasis Phase 3 studies (EXPRESS and EXPRESS II) in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year (14.1% and 23.0%, respectively) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. In the Phase 3 study of psoriatic arthritis (IMPACT 2), where patients received 5 mg/kg with and without MTX, antibodies to infliximab occurred in 15.4% of patients.

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.

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 infliximab is not recommended.

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

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

Non-Live Vaccines

It is recommended that the vaccinations of patients be brought up to date with all vaccination guidelines prior to initiating REMSIMA™ therapy.

Neurological Events

Infliximab and other agents that inhibit TNF have been associated in rare cases 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™ in patients with these neurological disorders, and should consider discontinuation of REMSIMA™ 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 REMSIMA™ should be taken in to consideration if a surgical procedure is planned. A patient who requires surgery while on REMSIMA™ should be closely monitored for infections, and appropriate actions should be taken.

Sexual Function/Reproduction

It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα.

Special Populations

Pregnant Women

Since infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab. No evidence of maternal

toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not known whether REMSIMA™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMSIMA™ should be given to a pregnant woman only if clearly needed.

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 6 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including disseminated infection that can become fatal (see **WARNINGS AND PRECAUTIONS, Live Vaccines/Therapeutic Agents** and **Non-Live Vaccines**).

Nursing Women

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

Women of Childbearing Potential

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™ treatment.

Pediatrics (6-17 years of age)

The safety and efficacy of REMSIMA™ has not been established in pediatric patients.

Geriatrics (65 years of age or older)

In rheumatoid arthritis clinical trials (ATTRACT) and in plaque psoriasis studies with infliximab, no overall differences were observed in the effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both infliximab and control groups compared to younger patients. Mean duration of infliximab treatment in this population (154) was approximately 50 weeks. In Crohn's disease, ulcerative colitis, ankylosing spondylitis, and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they responded differently from patients aged 18 to 64. There is a greater incidence of infections in the elderly population in general. The incidence of serious infections in infliximab-treated patients 65 years and older was greater than

in those under 65 years of age; therefore caution should be used in treating the elderly (see **ADVERSE REACTIONS, Infections**).

Effects on Ability to Drive and Use Machines

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

ADVERSE REACTIONS

The adverse drug reaction profiles reported in the clinical trials that compared REMSIMA™ to REMICADE® were comparable. No new adverse reactions were reported. The description of adverse reactions in this section is based on clinical experience with the reference product REMICADE®.

Adverse Drug Reaction Overview

In studies with infliximab, the most common adverse drug reactions reported from both clinical trials and post-marketing reports were 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, Neurologic Events)**, and lymphoma (see **WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis**). One of the most common reasons for discontinuing treatment in clinical trials was infusion-related reactions (dyspnea, flushing, headache and rash). (See **WARNINGS AND PRECAUTIONS, Hypersensitivity**). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and the 10 mg/kg dose in patients with Crohn's disease or ulcerative colitis and between the 3 mg/kg and 5 mg/kg dose in patients with plaque psoriasis.

Clinical Trial Adverse Drug 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Description of Data Sources

The data described herein reflect the exposure to infliximab in 5243 patients in adequate and well-controlled studies. Infliximab was studied in patients with rheumatoid arthritis (1304 patients exposed), Crohn's disease 1427 adult patients exposed), ulcerative colitis (484 adult patients exposed), plaque psoriasis (1373 patients exposed), psoriatic arthritis (293 patients exposed), ankylosing spondylitis (345 patients exposed) and other conditions (17 patients

exposed), primarily in double-blind, placebo-controlled trials. In general, integration of data in the following sections is based on clinical trials in rheumatoid arthritis and adult Crohn's disease.

Relative Frequency of Adverse Drug Reactions

Adverse events occurring at a frequency of at least 5% in infliximab-treated adult patients with rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, and ulcerative colitis are shown in **Table 1**. Adverse events occurring at a frequency of ≥1% to <5% in infliximab-treated adult patients are shown in **Table 2**.

Table 1: Number of patients with 1 or more adverse events (with frequency of ≥ 5%) by WHOART system-organ class and preferred term; treated patients ≥ 18 years of age

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Treated patients ≥ 18 years of age[a,b]	427	1304	217	1427	76	275	248	493	334	1373	98	191
Avg duration of follow-up (weeks)	52.0	59.9	29.8	44.8	25.3	87.8	31.9	40.5	18.1	41.9	20.2	42.8
Patient with 1 or more adverse events	353 (82.7%)	1198 (91.9%)	179 (82.5%)	1297 (90.9%)	57 (75.0%)	268 (97.5%)	199 (80.2%)	425 (86.2%)	210 (62.9%)	1209 (88.1%)	66 (67.3%)	162 (84.8%)
System-organ class/preferred term												
Respiratory system disorders												
Upper respiratory tract infection	22%	29%	15%	23%	14%	49%	17%	18%	16%	25%	13%	24%
Pharyngitis	7%	12%	6%	13%	5%	20%	6%	10%	4%	9%	4%	10%
Sinusitis	7%	13%	6%	9%	1%	11%	5%	9%	3%	8%	4%	11%
Coughing	7%	12%	6%	7%	3%	13%	4%	6%	1%	5%	1%	7%
Rhinitis	4%	8%	5%	6%	5%	21%	2%	4%	1%	6%	2%	4%
Bronchitis	8%	9%	3%	5%	1%	8%	3%	4%	2%	4%	3%	6%
Gastro-intestinal system disorders												
Nausea	19%	19%	25%	21%	9%	11%	9%	11%	4%	8%	6%	5%
Abdominal pain	7%	12%	17%	24%	4%	16%	13%	12%	1%	4%	2%	5%

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Diarrhea	11%	11%	7%	9%	5%	20%	5%	5%	2%	5%	3%	2%
Vomiting	6%	7%	13%	12%	4%	6%	7%	6%	1%	3%	2%	1%
Dyspepsia	6%	9%	2%	6%	4%	4%	2%	3%	1%	2%	2%	2%
Skin and appendages disorders												
Rash	5%	9%	6%	10%	7%	10%	8%	8%	1%	2%	0%	2%
Pruritus	2%	6%	3%	6%	7%	12%	4%	6%	4%	9%	3%	6%
Body as a whole general disorders												
Pain	7%	7%	6%	13%	5%	29%	12%	11%	5%	10%	1%	4%
Fatigue	6%	8%	13%	14%	4%	15%	8%	10%	2%	7%	3%	4%
Musculo skeletal system disorders												
Arthralgia	6%	7%	8%	15%	1%	8%	10%	15%	2%	10%	2%	4%
Back pain	4%	7%	6%	8%	3%	12%	8%	4%	3%	5%	6%	9%
Myalgia	3%	3%	4%	6%	3%	4%	5%	6%	1%	6%	0%	2%
Central & peripheral nervous system disorders												
Headache	12%	17%	15%	23%	11%	20%	18%	19%	8%	17%	5%	10%
Dizziness	6%	7%	6%	10%	4%	10%	5%	6%	2%	4%	4%	4%
Resistance mechanism disorders												
Fever	4%	7%	11%	11%	0%	8%	9%	10%	1%	4%	1%	2%

[a] Rheumatoid Arthritis Studies include C0168T07, C0168T09, C0168T14, C0168T15, C0168T18, C0168T22, and C0168T29. Crohn's Disease Studies include C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, and C0168T67. Ankylosing Spondylitis Studies include C0168T51. Ulcerative Colitis Studies include C0168T12, C0168T37 (through Week 54), and C0168T46 (through Week 54 including 24-week study extension). Psoriasis Studies include C0168T31, C0168T38, and C0168T44. Psoriatic Arthritis Studies include C0168T50.

[b] The adverse events included in this table are determined by the frequency of events in the combined infliximab group over all indications in this table. Percentages are rounded to an integer value after the adverse event frequency is determined.

Table 2: **Number of patients with 1 or more adverse events (with frequency of ≥ 1% to < 5%) by WHOART system-organ class and preferred term; treated patients ≥ 18 years of age**

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Treated patients ≥ 18 years of age[a,b]	427	1304	217	1427	76	275	248	493	334	1373	98	191
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System-organ class/preferred term												
Respiratory system disorders												
Dyspnea	2%	5%	1%	4%	3%	5%	2%	3%	1%	3%	1%	3%
Pneumonia	1%	4%	1%	1%	0%	1%	0%	2%	0%	1%	0%	3%
Respiratory tract allergic reaction	1%	2%	0%	1%	0%	1%	0%	1%	0%	2%	1%	2%
Epistaxis	1%	1%	0%	1%	0%	2%	0%	1%	0%	1%	0%	1%
Gastro-intestinal system disorders												
Gastroenteritis	3%	4%	6%	4%	4%	7%	2%	3%	1%	3%	3%	1%
Crohn`s disease	0%	0%	12%	13%	0%	0%	0%	0%	0%	0%	0%	0%
Stomatis ulcerative	5%	6%	1%	3%	1%	1%	1%	1%	0%	1%	1%	1%
Flatulence	1%	2%	3%	6%	0%	1%	2%	4%	0%	0%	0%	0%
Constipation	3%	2%	2%	4%	1%	3%	1%	2%	0%	1%	2%	0%
Gastro-esophageal reflux	1%	2%	0%	2%	0%	3%	2%	1%	0%	1%	1%	2%
Colitis ulcerative	0%	0%	0%	0%	0%	0%	25%	16%	0%	0%	0%	0%

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Tooth ache	0%	1%	1%	2%	0%	1%	0%	1%	1%	2%	0%	1%
Anorexia	1%	1%	2%	2%	0%	0%	1%	1%	0%	0%	0%	1%
Blood in stool	1%	1%	1%	2%	0%	1%	1%	1%	0%	0%	0%	0%
Intestinal obstruction	0%	0%	2%	4%	0%	0%	0%	0%	0%	0%	0%	0%
Skin and appendages disorders												
Urticaria	1%	4%	0%	2%	0%	2%	0%	1%	1%	4%	0%	4%
Sweating increased	0%	2%	3%	3%	5%	4%	3%	3%	0%	2%	0%	2%
Alopecia	2%	3%	2%	3%	0%	1%	1%	3%	1%	1%	2%	3%
Dermatitis	1%	2%	0%	2%	1%	7%	2%	1%	0%	2%	0%	1%
Dermatitis fungal	1%	3%	1%	1%	0%	5%	3%	1%	0%	2%	1%	2%
Psoriasis	0%	0%	1%	1%	1%	5%	1%	0%	7%	5%	2%	4%
Eczema	1%	2%	0%	3%	0%	3%	3%	1%	1%	1%	0%	1%
Acne	0%	1%	1%	3%	0%	3%	1%	2%	1%	1%	0%	0%
Skin dry	0%	1%	1%	2%	0%	7%	1%	3%	1%	1%	0%	0%
Skin wound	2%	2%	1%	1%	0%	2%	0%	1%	0%	2%	0%	1%
Erythema	0%	2%	1%	1%	0%	3%	1%	1%	0%	1%	1%	0%
Rash erythematous	1%	1%	0%	1%	1%	5%	0%	1%	0%	0%	0%	1%
Folliculitis	0%	1%	1%	1%	0%	1%	0%	1%	1%	1%	0%	0%
Body as a whole general disorders												
Chest pain	3%	4%	4%	5%	1%	6%	2%	3%	0%	4%	2%	4%
Edema peripheral	4%	4%	2%	5%	1%	4%	4%	4%	2%	3%	0%	3%
Chills	2%	3%	1%	2%	3%	3%	2%	4%	1%	3%	0%	1%
Infusion	0%	2%	0%	2%	1%	3%	0%	2%	0%	3%	0%	2%

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
syndrome												
Wound	1%	1%	0%	1%	1%	3%	0%	1%	0%	3%	1%	3%
Hot flushes	0%	2%	1%	2%	1%	3%	2%	1%	0%	1%	0%	2%
Allergic reaction	0%	1%	1%	2%	0%	5%	0%	2%	1%	1%	1%	1%
Asthenia	1%	1%	0%	3%	0%	2%	0%	1%	0%	1%	1%	1%
Reaction unevaluable	0%	1%	2%	2%	0%	2%	1%	1%	1%	1%	0%	0%
Musculo skeletal system disorders												
Arthritis	1%	1%	2%	4%	5%	14%	1%	1%	3%	7%	5%	5%
Bone fracture	3%	4%	0%	1%	0%	4%	0%	1%	1%	1%	0%	4%
Skeletal muscle strain	2%	2%	0%	1%	0%	1%	1%	0%	1%	3%	1%	2%
Tendinitis	2%	0%	0%	1%	1%	5%	1%	1%	0%	1%	2%	1%
Central & peripheral nervous system disorders												
Paresthesia	2%	3%	2%	3%	0%	7%	3%	3%	1%	3%	0%	0%
Muscle contractions involuntary	2%	4%	2%	2%	1%	3%	3%	2%	0%	2%	1%	1%
Hypesthesia	1%	2%	1%	2%	4%	3%	1%	1%	0%	2%	1%	1%
Migraine	1%	1%	1%	2%	0%	1%	0%	1%	0%	1%	0%	1%
Vertigo	2%	2%	0%	1%	3%	1%	1%	1%	0%	1%	1%	2%
Resistance mechanism disorders												
Abscess	3%	4%	4%	9%	3%	6%	3%	3%	1%	3%	2%	2%
Flu syndrome	3%	4%	1%	6%	1%	8%	2%	4%	1%	3%	0%	3%
Moniliasis	3%	5%	0%	5%	0%	5%	2%	3%	0%	1%	0%	1%
Influenza-like symptoms	0%	2%	2%	3%	1%	2%	2%	3%	1%	2%	0%	2%
Herpes simplex	1%	2%	2%	2%	0%	9%	2%	1%	1%	2%	1%	4%

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Infection	2%	3%	0%	2%	3%	4%	1%	1%	1%	2%	0%	1%
Influenza	1%	2%	2%	3%	1%	1%	2%	2%	1%	2%	0%	1%
Cellulitis	1%	2%	0%	1%	0%	2%	0%	1%	1%	1%	1%	3%
Herpes zoster	1%	1%	0%	1%	0%	0%	0%	1%	1%	1%	0%	2%
Infection bacterial	1%	1%	2%	1%	0%	1%	0%	0%	0%	1%	0%	2%
Psychiatric disorders												
Insomnia	4%	4%	3%	6%	1%	4%	2%	4%	1%	2%	1%	0%
Depression	5%	5%	2%	4%	0%	4%	2%	3%	1%	3%	2%	3%
Anxiety	1%	3%	1%	3%	1%	2%	3%	2%	0%	2%	1%	0%
Liver and biliary system disorders												
Sgpt increased	4%	5%	1%	3%	5%	12%	1%	1%	1%	4%	1%	8%
Sgot increased	2%	3%	1%	2%	3%	9%	0%	1%	1%	3%	2%	5%
Hepatic enzymes increased	3%	4%	1%	1%	0%	2%	0%	1%	0%	4%	0%	2%
Hepatic function abnormal	1%	2%	2%	1%	0%	2%	0%	0%	0%	1%	1%	2%
Vascular (extracardiac) disorders												
Flushing	0%	3%	1%	2%	3%	4%	1%	2%	0%	5%	0%	3%
Ecchymosis	2%	4%	0%	2%	0%	2%	1%	1%	0%	2%	0%	1%
Hemorrhoids	1%	1%	0%	2%	1%	3%	3%	1%	0%	0%	0%	1%
Urinary system disorders												
Urinary tract infection	5%	7%	3%	4%	0%	2%	2%	2%	1%	2%	4%	3%
Metabolic and nutritional disorders												
Hypokalemia	0%	2%	1%	4%	0%	0%	0%	1%	0%	0%	0%	1%

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
Weight increase	2%	2%	0%	0%	1%	3%	0%	0%	0%	1%	0%	0%
Cardiovascular disorders, general												
Hypertension	5%	6%	2%	3%	5%	8%	2%	2%	3%	4%	2%	3%
Hypotension	1%	2%	0%	2%	1%	3%	0%	2%	0%	1%	0%	2%
Eye and vision disorders												
Conjunctivitis	2%	4%	2%	4%	1%	4%	3%	1%	0%	1%	1%	1%
Vision abnormal	1%	2%	1%	2%	0%	4%	2%	1%	0%	1%	0%	2%
Ear and hearing disorders												
Otitis	0%	2%	1%	1%	0%	2%	1%	1%	0%	1%	0%	0%
White cell and res disorders												
Leukopenia	1%	2%	3%	2%	0%	2%	0%	2%	0%	1%	0%	1%
Lympha-denopathy	0%	1%	1%	2%	0%	2%	1%	1%	0%	1%	0%	1%
Neutropenia	0%	1%	0%	1%	0%	3%	0%	0%	0%	1%	0%	3%
Red blood cell disorders												
Anemia	4%	4%	4%	4%	1%	4%	10%	5%	0%	1%	0%	0%
Heart rate and rhythm disorders												
Tachycardia	2%	2%	0%	1%	1%	1%	2%	1%	1%	1%	1%	1%
Palpitation	1%	2%	0%	1%	0%	3%	1%	1%	0%	1%	0%	1%
Administration / application site disorders												
Injection site infiltration	3%	2%	0%	1%	0%	0%	1%	0%	0%	2%	0%	0%
Collagen												

	RA Studies		CD studies		AS studies		UC studies		Pso Studies		PsA studies	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab
disorders												
Arthritis rheumatoid	6%	7%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

[a] Rheumatoid Arthritis Studies include C0168T07, C0168T09, C0168T14, C0168T15, C0168T18, C0168T22, and C0168T29. Crohn's Disease Studies include C0168T08, C0168T11, C0168T16, C0168T20, C0168T21, C0168T26, and C0168T67. Ankylosing Spondylitis Studies include C0168T51. Ulcerative Colitis Studies include C0168T12, C0168T37 (through Week 54), and C0168T46 (through Week 54 including 24-week study extension). Psoriasis Studies include C0168T31, C0168T38, and C0168T44. Psoriatic Arthritis Studies include C0168T50.

[b] The adverse events included in this table are determined by the frequency of events in the combined infliximab group over all indications in this table. Percentages are rounded to an integer value after the adverse event frequency is determined.

Infusion-related Reactions

Acute infusion reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In Phase 3 clinical studies, 18% of infliximab-treated patients experienced an infusion reaction compared with 5% of placebo-treated patients. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period. Approximately 3% of patients discontinued infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of infusion.

In clinical trials, approximately 3% of infliximab infusions were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in less than 1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension.

Infliximab infusions beyond the initial infusion were not associated with a higher incidence of reactions. In psoriatic arthritis (IMPACT 2), infusion reactions were reported in 12% of infliximab-treated patients compared with 7% of placebo-treated patients. Among the 1376 infliximab infusions, 2% of these led to an infusion reaction. In plaque psoriasis, infusion reactions were reported in 22% of infliximab-treated patients compared with 5% of placebo-treated patients. Among the 8366 infliximab infusions, 5% of these led to an infusion reaction. In the ankylosing spondylitis study ASSERT, infusion reactions were reported in 19% of infliximab-treated patients compared with 9% of placebo-treated patients. Among the 4257 infliximab infusions, 2% of these led to an infusion reaction.

In a clinical study of patients with early rheumatoid arthritis (ASPIRE), 66% of all treated patients (686 out of 1040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1040) received at least one shortened infusion of 60 minutes or less. Of the infliximab-treated patients who received at least one shortened infusion **of 90 minutes or less** at the dose of 3 mg/kg, infusion-related reactions occurred in 19% (48/248) of patients and serious infusion reactions occurred in 0.4% (1/248) of patients. Of the infliximab-treated patients who received at least one shortened infusion **of 90 minutes or less** at the dose of 6 mg/kg, infusion-related reactions occurred in 11% (26/246) of patients and serious infusion reactions occurred in 0.4% (1/246) of patients. Shortened infusions at doses >6 mg/kg have not been studied.

In the UC studies ACT 1 and ACT 2 through Week 30, the proportion of subjects with infusion reactions was comparable in the placebo and combined infliximab treatment groups. Through Week 54, the proportion of subjects with infusion reactions rose and was greater in the combined infliximab treatment group than in the placebo treatment group (13.4% versus 9.4%, respectively). A greater proportion of subjects in the 10 mg/kg than in the 5 mg/kg infliximab treatment group (16.1% versus 10.7%) experienced an infusion reaction.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 17% of patients receiving infliximab monotherapy, 5% of patients receiving infliximab in combination with azathioprine (AZA) and 6% of patients receiving AZA monotherapy. One patient experienced a serious infusion reaction with infliximab monotherapy.

Patients who became positive for antibodies to infliximab were more likely to develop infusion reactions than were those who were negative (approximately 3-fold). Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see **WARNINGS AND PRECAUTIONS, Immunogenicity and DRUG INTERACTIONS**).

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with infliximab administration (see **WARNINGS AND PRECAUTIONS, Neurological Events**). Very rare cases of transient visual loss and myocardial ischemia/infarction occurring during or within 2 hours of infliximab infusion have been reported. Cerebrovascular accidents occurring within approximately 24 hours of initiation of infusion have also been reported.

Infusion reactions following readministration of infliximab

In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment.

In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction cycle of infliximab, 4% (8/219) of patients in the intermittent therapy arm experienced serious infusion reactions versus < 1% (1/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. Intermittent therapy in this trial was defined as the readministration of an induction cycle (maximum of four infusions at 0, 2, 6, and 14 weeks) of infliximab upon disease flare after a period of no treatment. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases, infliximab treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms (see **WARNINGS AND PRECAUTIONS, Immune, *Infusion reactions following readministration of infliximab)***.

Delayed hypersensitivity/Reactions following readministration of infliximab
In a clinical study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.
Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. Of these patients, adverse events occurred in 9 of 23 (39%) who had received liquid formulation which is no longer in use and 1 of 14 (7%) who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of

these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year.

In 3 psoriasis studies, 1% (15/1373) of patients experienced a possible delayed hypersensitivity reaction with symptoms of arthralgia, myalgia, fever, and rash, often early in the treatment course following infliximab infusions. There were no possible delayed hypersensitivity reactions identified in the psoriatic arthritis study (IMPACT 2) (see **WARNINGS AND PRECAUTIONS, Immune, Hypersensitivity Reactions**).

Infections

In infliximab clinical studies, primarily of RA and CD, treated infections were reported in 36% of infliximab-treated patients (average of 53 weeks of follow-up) and in 28% of placebo treated patients (average of 47 weeks of follow-up). In the ATTRACT I[1,] study, 60% of Infliximab-treated RA patients (average of 97 weeks of follow-up) had treated infections reported vs. 43% of placebo-treated patients (average of 75 weeks of follow-up); treated infections were more common with higher doses of infliximab. In the ASPIRE[2] study, 37% of infliximab-treated RA patients (average of 54 weeks of follow-up) had treated infections reported vs. 30% of placebo-treated patients (average of 52 weeks of follow-up). The infections most frequently reported in the RA studies were respiratory tract infections (including URI, sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis was observed with infliximab compared with placebo in the ATTRACT or ACCENT I[3] and II[4] studies. However, in the ATTRACT study, the incidence of serious events of pneumonia and lobar pneumonia combined was higher in patients receiving infliximab plus MTX vs. MTX alone (2.6% vs. 1.2%, respectively). In the ASPIRE study, the incidence of serious pneumonia was also higher in patients receiving infliximab plus MTX vs. MTX alone (2.5% vs. 0%, respectively). In other RA trials, the incidence of serious infections including pneumonia was higher in infliximab plus MTX treated patients compared with methotrexate alone, especially at higher than recommended induction regimen of infliximab 6 mg/kg or greater. Among infliximab-treated patients, serious infections included pneumonia, cellulitis, abscess and sepsis. In ATTRACT, one patient died with miliary tuberculosis, one died with disseminated coccidioidomycosis and one died due to sepsis. In the ASPIRE study, four patients were diagnosed with tuberculosis. In the ACCENT I study, one patient was diagnosed with tuberculosis. In EXPRESS II[5], two patients with psoriasis were diagnosed with tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see **WARNINGS**

[1] ATTRACT (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy)[16]
[2] ASPIRE (the Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset
[3] ACCENT I (the Anti-TNF Trial in Long-term Treatment of Moderately to Severely Active Crohn's Disease)[19,20]
[4] ACCENT II (the Anti-TNF Trial in Long-term Treatment of Fistulising Crohn's Disease)[23]
[5] EXPRESS II Evaluation of Infliximab for Psoriasis in a REMICADE Efficacy and Safety Study

AND PRECAUTIONS, Risk of Infections). In the ACCENT II study, serious infections of nocardiosis (one patient) and cytomegalovirus (one patient) were reported. Twelve percent of patients with fistulising Crohn's disease developed a new abscess 8 to 16 weeks after the last infusion of infliximab in the T20 study. In the ACCENT II study, there was no difference between the infliximab and placebo maintenance arms for proportions of patients with newly diagnosed fistula-related abscesses. In the psoriasis studies, 1.5% of patients (average of 41.9 weeks of follow up) receiving infliximab and 0.6% of patients (average of 18.1 weeks of follow up) receiving placebo developed serious infections. In EXPRESS[6], one patient died due to sepsis. In the IMPACT 2[7] study of psoriatic arthritis, 1.6% of patients (average 42.8 weeks of follow-up) receiving infliximab and 2.0% of patients (average 20.2 weeks of follow-up) receiving placebo developed serious infections.

In the infliximab clinical studies in patients with ulcerative colitis (ACT 1 and ACT 2[8]), the most frequently reported infections were upper respiratory infection (URI), sinusitis, pharyngitis, bronchitis and moniliasis. In the UC studies, infections were reported in 30.6% and 40.1% of infliximab-treated patients at Week 30 (average 26.9 weeks of follow-up) and at Week 54 (average 41.1 weeks of follow-up) and in 29.5% and 32.8% of placebo-treated patients at Week 30 (average 22.2 weeks of follow up) and at Week 54 (average 32.2 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies, and included one case of tuberculosis and a fatal case of histoplasmosis.

In post-marketing experience with infliximab, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving infliximab alone or in combination with immunosuppressive agents.

Autoantibodies/Lupus-like Syndrome

Approximately 55% of 1598 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 infliximab-treated patients compared with 0% of 422 placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

In the ATTRACT rheumatoid arthritis study through Week 102, 62% of infliximab-treated patients developed antinuclear antibodies (ANA) between screening and last evaluation, compared with 27% of placebo-treated patients. In the ASPIRE study through Week 58, 66% of 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 infliximab-treated patients, compared to none of

[6] EXPRESS European infliximab for Psoriasis (infliximab) Efficacy and Safety[32]
[7] IMPACT 2 Induction and Maintenance Psoriatic Arthritis Clinical Trial[33]
[8] ACT 1 and ACT 2 (the Anti-TNF Trials in moderately to severely active ulcerative colitis)

the placebo-treated patients. No association was seen between infliximab dose/schedule and development of ANA or anti-dsDNA antibodies.

Of Crohn's disease patients treated with 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 infliximab. The development of anti-dsDNA antibodies was not related to either the dose or duration of 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 the EXPRESS plaque psoriasis study through Week 50, 59% of infliximab-treated patients developed antinuclear antibodies following infliximab treatment compared to 2% of placebo-treated patients. Anti-dsDNA antibodies developed in 16% of infliximab-treated patients, compared to none of the placebo-treated patients. In the EXPRESS II plaque psoriasis study through Week 50, 65% of infliximab-treated patients developed antinuclear antibodies following infliximab treatment compared to 8% of placebo-treated patients. Anti-dsDNA antibodies developed in 27% of infliximab-treated patients, compared to none of the placebo-treated patients. No association was seen between infliximab dose/schedule and development of ANA or anti-dsDNA antibodies.

In the IMPACT 2 psoriatic arthritis study through Week 66, 59% of infliximab-treated patients developed antinuclear antibodies following infliximab treatment compared to 11% of placebo-treated patients. Anti-dsDNA antibodies developed in 12% of infliximab-treated patients, compared to none of the placebo-treated patients.

In the ASSERT ankylosing spondylitis study through week 102, 35% of infliximab-treated patients developed antinuclear antibodies following infliximab treatment compared to 1% of placebo-treated patients. Anti-dsDNA antibodies developed in 30% of infliximab-treated patients, compared to none of the placebo-treated patients.

In clinical studies, 22 patients were diagnosed with a possible lupus-like syndrome, four with Crohn's disease, eight patients with plaque psoriasis [seven (0.5%) patients treated with infliximab and one (0.3%) patient treated with placebo], 8 patients with ankylosing spondylitis, and two with rheumatoid arthritis. Twenty-one patients improved following discontinuation of therapy and/or appropriate medical treatment. One psoriasis patient on concomitant hydralazine had central nervous system involvement. No patients had renal involvement. No cases of lupus-like syndromes were reported in the psoriatic arthritis studies. The lupus-like syndrome in one patient with rheumatoid arthritis and one patient with ankylosing spondylitis 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, very rare cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving 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 infliximab without progression to severe hepatic injury. Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving infliximab than in controls, both when 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 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 inflximab 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 infliximab clinical trials, 5 patients developed lymphomas among 5780 patients treated with 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 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 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 infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among 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 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 infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

Among the 345 patients who received infliximab in ankylosing spondylitis trials, 3 patients developed malignancies (1 patient had a squamous cell and a basal cell carcinoma, 1 patient had a pulmonary carcinoma, and 1 patient had breast cancer). Additionally, 1 patient in ASSERT developed a nonseminoma testicular carcinoma after leaving the trial, approximately 1 year after his last dose of infliximab.

In the IMPACT 2 study of psoriatic arthritis, 2 malignancies were reported through Week 54 (Stage I Hodgkin's lymphoma in an infliximab-treated patient and basal cell carcinoma in a placebo-treated patient). No malignancies were reported through Week 50 of IMPACT. An adenocarcinoma of the pancreas was reported 2 months after completing the year 2 extension of IMPACT.

During the infliximab plaque psoriasis trials, no patients developed lymphoma. In the placebo-controlled portions of the psoriasis studies, 7 of 1123 patients who received infliximab at any dose (443 patient-years) were diagnosed with a nonmelanoma skin cancer (NMSC) compared to 0 of 334 patients who received placebo (113 patient-years). Among the 1373 patients with psoriasis who received infliximab at any dose in the controlled and uncontrolled portions of the psoriasis studies (1101 patient-years), a total of 17 were diagnosed with NMSC (12 basal cell cancers, 5 squamous cell cancers). The size of the placebo group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Patients on infliximab should be monitored for the development of NMSC. Two noncutaneous malignancies (breast cancer and adenocarcinoma) were reported during the psoriasis clinical trials.

A population-based retrospective cohort study 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.

Congestive Heart Failure

In a phase II study evaluating infliximab in NYHA Class III/IV CHF patients (left ventricular ejection fraction $\leq$35%), higher incidences of mortality and hospitalization due to worsening heart failure were seen in infliximab-treated patients, especially those treated with 10 mg/kg. One hundred and fifty patients were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 28 weeks, 4 of 101 patients treated with 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 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 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**).

Less Common Clinical Trial Adverse Drug Reactions

Other medically relevant adverse events occurring at a frequency <1% 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
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

Abnormal Hematologic and Clinical Chemistry Findings

Serious, medically relevant hematologic adverse events ≥ 0.2%, or clinically relevant hematologic adverse reactions observed in clinical trials include: pancytopenia, thrombocytopenia, anemia, hemolytic anemia, neutropenia and leukopenia.

The proportion of patients with abnormal ALT levels in response to infliximab is presented in **Table 3**.

Table 3: Proportion of patients with elevated ALT in infliximab Clinical Trials

	Proportion of patients with elevated ALT					
	≥1 to <3 X ULN		≥3 X ULN		≥5 X ULN	
	Placebo	infliximab	Placebo	infliximab	Placebo	infliximab
Rheumatoid arthritis[1]	24.0%	34.4%	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	24.1%	34.9%	2.2%	4.9%	0.0%	1.5%
Ulcerative colitis[3]	12.4%	17.4%	1.2%	2.5%	0.4%	0.6%
Psoriatic arthritis[4]	16.3%	49.5%	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis[5]	23.8%	49.4%	0.4%	7.7%	0.0%	3.4%
Ankylosing spondylitis[6]	14.5%	51.1%	0.0%	9.5%	0.0%	3.6%

[1] Note that placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate. Median follow-up was 58 weeks for placebo patients and infliximab-treated patients. RA trials include ATTRACT (T22) and ASPIRE (T29).

[2] Note that placebo patients in 2 of the 3 Phase III trials in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in this table. Median follow-up time was 54 weeks. In SONIC, placebo patients received AZA 2.5 mg/kg/day.

[3] Ulcerative colitis trials include ACT I (C0168T37) through Week 54 and ACT II (C0168T46) through Week 30; median duration of follow up was 30.8 weeks for the infliximab group and 30.1 weeks for placebo group.

[4] IMPACT 2 median duration of follow up was 39.1 weeks for the infliximab group and 18.1 weeks for placebo group.

[5] EXPRESS and EXPRESS II median duration of follow up was 16.1 weeks for placebo and 50.1 weeks for infliximab groups.

[6] Patients from the ASSERT trial (T51); median duration of follow-up was 24.1 weeks for placebo and 101.9 weeks for the infliximab group.

The difference in rates of ALT elevations ≥3 X ULN between infliximab and placebo treatment groups tended to be greater in ankylosing spondylitis, psoriasis and psoriatic arthritis clinical trials than in rheumatoid arthritis, Crohn's disease and ulcerative colitis clinical trials. See **Hepatobiliary Events**.

Post-Market Adverse Drug Reactions

Additional adverse events, some with fatal outcome, reported from worldwide post-marketing experience with infliximab are included in **Table 4** (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 infliximab exposure.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with infliximab with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, most of whom were adolescent or young adult males (see **WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis, *Hepatosplenic T-cell Lymphoma***).

Table 4: 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, very rare cases of myocardial ischemia/myocardial infarction occurring during or within 2 hours of infusion
Eye Disorders	very rare transient visual loss occurring during or within two hours of infusion
Immune System Disorders	vasculitis, sarcoidosis
Neoplasm Benign and Malignant	hepatosplenic T-cell lymphoma (the vast majority in Crohn's disease and ulcerative colitis: primarily adolescents and young adults) , 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 withing approximately 24 hours of initiation of infusion
Infections and Infestations	opportunistic infections (such as aspergillosis, atypical mycobacteria, coccidioidomycosis, cryptococcosis, candidiasis, histoplasmosis, 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 very rare 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

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

DRUG INTERACTIONS

Overview

Specific drug interaction studies have not been conducted. The majority of patients in rheumatoid arthritis, Crohn's disease or ulcerative colitis clinical trials received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-mercaptopurine/azathioprine (6-MP/AZA), methotrexate (MTX), and aminosalicylates. Patients

with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients using no immunosuppressants (see **WARNINGS AND PRECAUTIONS, Immunogenicity and ADVERSE REACTIONS, Infusion-related Reactions**).

Drug-Drug Interactions

Concurrent Use of REMSIMA™ with other Biological Therapeutics

The combination of REMSIMA™ with other biological therapeutics used to treat the same conditions as REMSIMA™, 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™ (see **WARNINGS AND PRECAUTIONS**)

It is recommended that therapeutic infectious agents not be given concurrently with REMSIMA™ (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™ 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.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dose Adjustment

For recommended infusion duration for patients with each of the indications described below, see **DOSAGE AND ADMINISTRATION, Preparation and Administration Instructions**.

Rheumatoid Arthritis
The recommended dose of REMSIMA™ (infliximab) is 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. REMSIMA™ should be given in combination with methotrexate.

Ankylosing Spondylitis
The recommended dose of REMSIMA™ is 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks thereafter.

Ulcerative Colitis
The recommended dose of REMSIMA™ is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by 5 mg/kg every 8 weeks thereafter, for the treatment of adult patients with moderately to severely active ulcerative colitis. In some adult patients, consideration may be given to adjusting the dose up to 10 mg/kg to sustain clinical response and remission. Some adult patients may not benefit from dose escalation. In addition to the physician's clinical assessment, measurement of infliximab trough levels and titers of antibodies to infliximab should be taken into account before considering dose adjustment.

Crohn's Disease
The recommended dose of REMSIMA™ is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderate to severe, active Crohn's disease. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg. Some adult patients may not benefit from dose escalation. In addition to the physician's clinical assessment, measurement of infliximab trough levels and titers of antibodies to infliximab should be taken into account before considering dose adjustment.

The recommended dose of REMSIMA™ is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of fistulising Crohn's disease. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMSIMA™ in these patients. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. In the ACCENT II clinical study, among patients who lost response at 5 mg/kg infliximab and re-established response following dose escalation to 10 mg/kg infliximab, most had done so after 1 dose and all had done so after 2 doses of 10 mg/kg.

Psoriatic Arthritis
The recommended dose of REMSIMA™ is 5 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks

thereafter. REMSIMA™ can be used with or without methotrexate. If a patient shows no response at 24 weeks, no additional treatment with REMSIMA™ should be given.

Plaque Psoriasis
The recommended dose of REMSIMA™ is 5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient does not show an adequate response at Week 14, after infusions at weeks 0, 2, and 6, no additional treatment with REMSIMA™ should be given.

The infusion solution must be administered over a period of not less than 2 hours. All patients administered REMSIMA™ should be observed for at least 1 to 2 hours post-infusion for side effects. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available (see **ADVERSE REACTIONS, Infusion-related Reactions**).

The REMSIMA Patient Assistance Program facilitates the administration of REMSIMA™. The REMSIMA Patient Assistance Program clinics are staffed by qualified healthcare professionals specially trained in the administration of REMSIMA™ infusions and are available across Canada. Information about the REMSIMA Patient Assistance Program can be obtained by calling 1-844-466-6627.

Reconstitution:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
100 mg as lyophilized powder	10 mL Sterile Water for Injection, USP The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP	250 mL	Between 0.4 mg/mL and 4 mg/mL

Since no preservative is present, it is recommended that the REMSIMA™ infusion be started within 3 hours of reconstitution and dilution.

Preparation and Administration Instructions

Use aseptic technique.
REMSIMA™ vials do not contain antibacterial preservatives. Therefore, after reconstitution, the vials should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. Since no preservative is present, it is recommended that the REMSIMA™ infusion be started within 3 hours of reconstitution and dilution.

1. Calculate the dose and the number of REMSIMA™ vials needed. Each REMSIMA™ vial contains 100 mg of infliximab. Calculate the total volume of reconstituted REMSIMA™ solution required.

2. Reconstitute each REMSIMA™ vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colourless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted REMSIMA™ solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted REMSIMA™ from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMSIMA™ solution to the 250 mL infusion bottle or bag. Gently mix.

4. For patients with Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis, the infusion solution must be administered over a period of not less than 2 hours.

   For patients with rheumatoid arthritis, the recommended infusion duration is over a period of not less than 2 hours in patients not previously treated with REMSIMA™. At the discretion of the treating physician, some patients with rheumatoid arthritis who have tolerated 3 initial 2-hour infusions of REMSIMA™ may be considered for receiving subsequent infusions at the same dose over a period of not less than 1 hour (see **CLINICAL TRIALS, Rheumatoid Arthritis and ADVERSE REACTIONS, Infusion-Related Reactions**). The safety of shortened infusions at doses >6 mg/kg has not been studied. Use only an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for reuse.

5. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If visibly opaque particles, discolouration or other foreign particulates are observed, the solution should not be used.
6. No physical biochemical compatibility studies have been conducted to evaluate the coadministration of REMSIMA™ with other agents. REMSIMA™ should not be infused concomitantly in the same intravenous line with other agents.

OVERDOSAGE

Single doses of the reference product up to 20 mg/kg 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Infliximab is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumour necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by fed-batch and is purified by a series of steps that includes measures to inactivate and remove viruses.

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[7-9] Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilises the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, and induction of acute phase reactants and other liver proteins.[10] Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* by complement or effector cells.[8] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilising human fibroblasts, endothelial cells, neutrophils,[7] B and T lymphocytes,[11,12] and epithelial cells. Anti-TNFα antibodies reduce disease activity in a cotton-top tamarin colitis model[13] and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and, when administered after disease onset, facilitates eroded joints to heal.

Pharmacodynamics

PRECLINICAL

Infliximab binds to the soluble and transmembrane forms of TNFα with high affinity and blocks the interaction of TNFα with its receptors, thereby neutralising the biological activity of TNFα.[7-8] Cells expressing transmembrane TNFα can be lysed *in vitro* by complement or effector cell-mediated mechanisms after infliximab binds.[8] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilising human fibroblasts, endothelial cells, neutrophils,[9] B and T lymphocytes,[11-12] and epithelial cells.[12]

Infliximab specifically neutralises TNFα-induced cell cytotoxicity but not lymphotoxin α.[8] Lymphotoxin α is a cytokine that shares 30% homology with TNFα and utilises the same receptors as TNFα. Species cross-reactivity of infliximab is limited to human and chimpanzee

TNFα. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity.

In a transgenic mouse (Tg197) that constitutively expresses human TNFα, infliximab administered twice weekly at 5 mg/kg or once weekly at 10 mg/kg prevents the development of polyarthritis by Week 10, demonstrating that infliximab neutralises TNFα *in vivo*.

CLINICAL

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients[15] in the joints of psoriatic arthritis patients and in the skin lesions of plaque psoriasis patients, and in the stools of Crohn's disease and ulcerative colitis patients. This correlates with elevated disease activity.[15] In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3].[15] In Crohn's disease, treatment reduces infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduces the proportion of mononuclear cells in the lamina propria able to express TNFα and interferon γ ex vivo.[15] After treatment with the reference product, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein compared to baseline. Peripheral blood lymphocytes from infliximab-treated patients showed no decrease in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with infliximab resulted in a reduction in the number of T cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. Infliximab treatment alters the histopathological features of plaque psoriasis as demonstrated in lesional skin biopsies collected at baseline, day 3 and Week 10 following initiation of treatment. Infliximab treatment reduced epidermal thickness and infiltration of inflammatory cells, downregulated the percentage of activated and cutaneous lymphocyte antigen (CLA)-positive inflammatory cells, including CD3-, CD4-, and CD8-positive lymphocytes, and upregulated the percentage of CD1a-positive epidermal Langerhans cells. In ulcerative colitis, treatment with infliximab showed changes consistent with histological healing and decreased expression of pharmacodynamic markers of tissue injury and inflammation in colonic biopsies. Treatment with infliximab also decreased serum levels of the proinflammatory molecules with statistically significant and consistent decreases observed for IL-2R, and ICAM-1. In patients with ankylosing spondylitis, infliximab was more effective at decreasing levels of serum markers of inflammation (IL-6 and VEGF) at both weeks 2 and 24 than placebo. In addition, serum levels of markers of bone formation (bone alkaline phosphatase and osteocalcin) were increased at both weeks 2 and 24 in patients with ankylosing spondylitis treated with infliximab compared with patients receiving placebo.

Pharmacokinetics

Single intravenous infusions of 1 to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the

vascular compartment. Median pharmacokinetic results for the doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the terminal half-life of infliximab is approximately 7.7 to 10 days. The terminal half-life in ulcerative colitis trials was 12.3 to 14.7 days.

	Rheumatoid Arthritis		Crohn's Disease	
Study	T09 (n=14)	T09 (n=29)	T11 (n=5)	T11 (n=5)
Dose	3 mg/kg	10 mg/kg	5 mg/kg	10 mg/kg
Cmax (µg/mL)	77.3	277	74.9	181.0
AUC (µg/day/mL)	461	2282	788	2038
CL (mL/day/kg)	6.4	4.4	6.3	4.9
Vss (mL/kg)	67.5	57.2	80	65
t1/2(day)	8	9.1	7.8	10

Absorption: Infliximab is administered intravascularly and thus has no absorption profile.

Distribution: Infliximab is primarily distributed into the blood, its apparent median steady state volume of distribution of 57.2 to 80 mL/kg estimated to 4.0 to 5.60 litres in a 70 kg individual corresponds to the total blood volume.

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.

Excretion: Infliximab as a whole molecule was not detected in the urine after its intravenous infusion.

Following an initial dose of infliximab, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals in rheumatoid arthritis patients or patients with moderate or severe Crohn's disease retreated with 4 infusions of 10 mg/kg infliximab at 8-week intervals. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 5 mg/kg at 8-week intervals in patients with psoriatic arthritis or plaque psoriasis. The proportion of patients with rheumatoid arthritis who had undetectable infliximab concentrations at 8 weeks following an infusion was approximately 25% for those receiving 3 mg/kg every 8 weeks, 15% for patients administered 3 mg/kg every 4 weeks, and 0% for patients receiving 10 mg/kg every 4 or 8 weeks. At steady state, the proportion of patients with plaque psoriasis who had undetectable infliximab concentrations at 8 weeks following an infusion ranged from 71.4% to 73.1% for patients receiving 3 mg/kg every 8 weeks (EXPRESS II), and from 25.9% to 46.4% for those administered 5 mg/kg every 8 weeks (EXPRESS and EXPRESS II). The proportion of patients with psoriatic arthritis who had undetectable infliximab concentrations was 15.8% at Week 38 when administered 5 mg/kg every 8 weeks (IMPACT 2). In IMPACT 2, approximately half of the patients received concomitant MTX.

Special populations

No major differences in clearance or volume of distribution were observed in patient subgroups defined by age. It is not known if gender differences, genetic polymorphism, renal insufficiency or hepatic insufficiency have effects on clearance or volume of distribution of infliximab.

STORAGE AND STABILITY

Store the lyophilized product under refrigeration between 2 °C and 8 °C (36 °F to 46 °F). Do not use beyond the expiration date. This product contains no preservative. Since no preservative is present, it is recommended that the administration of the infusion solution should begin within 3 hours of reconstitution and dilution.

SPECIAL HANDLING INSTRUCTIONS

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (25 °C). Diluted REMSIMA™ infusion solution is stable for 48 hours when stored between 5±3 °C and 30±2 °C/65±5% RH. If the infusion solution is not used immediately (i.e., within 3 hours of preparation), the in-use storage times and conditions prior to its use are the responsibility of the user and would not normally be longer than 24 hours between 2 °C and 8 °C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

REMSIMA™ (infliximab) is supplied as a sterile white lyophilized powder for intravenous infusion. Each vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate monohydrate and 6.1 mg dibasic sodium phosphate dihydrate. No preservatives are present.

REMSIMA™ (infliximab) lyophilized concentrate for IV injection is supplied in individually boxed single-use vials in the following strength: 100 mg infliximab.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Infliximab

Chemical name: Infliximab

Molecular mass: 149,100 daltons

Structural formula:

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

Physicochemical properties:

Infliximab drug substance is a purified, recombinant DNA-derived, chimeric human-mouse IgG monoclonal antibody (MAb) which binds to and neutralizes human tumour necrosis factor α (TNFα) with high affinity (Ka=1 X 1010 M^{-1}). 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).

CLINICAL TRIALS

REMSIMA™ is a subsequent entry biologic.

The clinical development program to show clinical comparability between REMSIMA™ and the reference product is based on

- A pivotal comparative pharmacokinetic (PK) phase 1 study (PLANETAS) in 250 patients with ankylosing spondylitis (AS) of which 128 patients received REMSIMA™.
- A pivotal comparative efficacy and safety study (PLANETRA) in 606 patients with rheumatoid arthritis (RA) of which 301 patients received REMSIMA™.

A third study (CT-P13 1.2), a small pilot study in RA patients, was performed as an initial pilot study to support initial clinical trial applications.

A summary of the design and subject demographics of the two studies is presented in **Table 5**.

Table 5: Study PLANETAS and PLANETRA patient demographics and study design

STUDY	Design	Dosage, route of administration and duration	Number of patients	Mean age (range)	Gender and Race n (%)
PLANETAS	Prospective Phase 1, randomized, double-blind, multicentre, multiple single-dose intravenous infusion, parallel-group in ankylosing spondylitis	REMSIMA™or REMICADE® 5 mg/kg bw administered as 2h intravenous infusion; at Weeks 0, 2, 6, then every 8 weeks up to 54 weeks	250	38.9 (18 to 69)	202 (80.8%) male 48 (19.2%) female 189 (75.6%) White 29 (11.6%) Asian 32 (12.8%) Other
PLANETRA	Prospective Phase 3, randomized, double blind, multicentre, multiple single dose intravenous infusion, parallel group in rheumatoid arthritis	REMSIMA™ or REMICADE® (3 mg/kg bw) administered as 2h intravenous infusion ; at Weeks 0, 2, 6, then every 8 weeks up to 54 weeks, co-administered with MTX and folic acid; 54 weeks	606	48.8 (18 to 75)	105 (17.3%) male 501 (82.7%) female 442 (72.9%) White 3 (0.5%) Black 71 (11.7%) Asian 90 (14.9%) Other
CT-P13 1.2	Prospective Phase 1, randomized double blind, parallel group, multiple single dose intravenous (i.v.) infusion, multicentre in rheumatoid arthritis	REMSIMA™ or REMICADE® (3 mg/kg bw) administered as 2h intravenous infusion, co-administered with oral MTX and folic acid; administered at Weeks 0, 2, 6 weeks, then every 8 weeks up to 102 weeks	19	REMSIMA™: 51.6 (25.0 to 69.0) REMICADE®: 47.1 (24.0 to 72.0) Patient 1016: 40	REMSIMA™: 1 (11.1%) male 8 (88.9%) female 9 (100.0%) Asian REMICADE®: 0 (0.0%) male 9 (100.0%) female 9 (100.0%) Asian Patient 1016: 0 (0.0%) male 1 (100.0%) female 1 (100.0%) Asian

Comparative Pharmacokinetic Studies

Pivotal Pharmacokinetic Study PLANETAS

PLANETAS is a randomized, double-blind, parallel-group, study in patients with AS designed to demonstrate pharmacokinetic comparability between REMSIMA™ and the reference product. The AS patients included in this PK trial were treated with the standard dose regimen as outlined in the current Canadian Product Monograph of REMICADE®. A dose of 5 mg/kg was given at an 8-week dosing interval, following the first 3 'loading' doses given at Weeks 0, 2, and 6. PK

comparability was assessed between Week 22 (dose 5) and Week 30 (dose 6). The pharmacokinetic parameters are summarized in **Table 6**. Results are presented as geometric mean for AUC_{tau} and $C_{MAX,SS}$ and as mean (%CV) for $C_{MIN,SS}$ and $T_{½}$.

Table 6: Serum Pharmacokinetic Parameters of the PK Population between Week 22 and 30 (Study PLANETAS in Ankylosing Spondylitis)

Parameter	Treatment	n	Geometric Mean	Ratio (%) of Geometric Mean	90% CI of Ratio
AUC_{tau} (µg*h/mL)	REMSIMA™ (5 mg/kg)	112	32,800	104	94.2 – 116
	REMICADE® (5 mg/kg)	110	31,400		
$C_{MAX,SS}$ (µg/mL)	REMSIMA™ (5 mg/kg)	113	147	102	94.7 – 109
	REMICADE® (5 mg/kg)	110	145		
$C_{MIN,SS}$ (µg/mL)	REMSIMA™ (5 mg/kg)	108	2.53	109	85.7 – 139
	REMICADE® (5 mg/kg)	108	2.32		
$T_{½}$ (hr)	REMSIMA™ (5 mg/kg)	102	280	97.9	90.8 – 106
	REMICADE® (5 mg/kg)	98	286		

AUC_{tau}=Area under the concentration-time curve over the dosing interval; $C_{MAX,SS}$=Maximum serum concentration at steady state; $C_{MIN,SS}$=Minimum serum concentration at steady state;$T_{1/2}$=Terminal elimination half-life; CI=Confidence interval

Note: The pharmacokinetic endpoints of the observed AUC0-tau, Cmax,ss, Cmin,ss and T1/2 between patients treated with REMSIMA™ and REMICADE® reference product at steady state were analyzed using an analysis of covariance (ANCOVA) with treatment as a fixed effect and region and baseline BASDAI score fitted as covariates. Point estimates and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

The following secondary PK endpoints were assessed up to week 54: C_{MAX}, C_{MIN} and T_{MAX}. The data is listed in **Table 7**.

Table 7: Mean (CV) Serum Pharmacokinetic Parameters of Infliximab: Pharmacokinetic Population (Study PLANETAS in Ankylosing Spondylitis)

Parameter		REMSIMA™ (N=113)		REMICADE® (N=110)
Dose 1 (Week 0)				
C_{max} *(µg/mL)*	n=109	156 (37.2)	n=107	145 (25.3)
C_{min} *(µg/mL)*	n=109	29.1 (40.1)	n=108	29.8 (40.8)
T_{max} *(h)*	n=109	2.03 (1.92, 3.20)	n=107	2.08 (1.95, 3.50)
Dose 2 (Week 2)				
C_{max} *(µg/mL)*	n=112	176 (20.9)	n=108	181 (23.8)
C_{min} *(µg/mL)*	n=110	20.1 (56.1)	n=108	22.8 (72.0)
T_{max} *(h)*	n=112	2.08 (1.75, 3.08)	n=108	2.08 (1.83, 3.17)
Dose 3 (Week 6)				
C_{max} *(µg/mL)*	n=113	172 (26.8)	n=110	166 (22.8)
C_{min} *(µg/mL)*	n=112	6.93 (80.2)	n=110	7.06 (77.6)
T_{max} *(h)*	n=113	2.05 (2.00, 3.22)	n=110	2.08 (2.00, 3.17)
Dose 4 (Week 14)				
Cmax *(µg/mL)*	n=113	158 (24.0)	n=110	154 (27.5)
Cmin *(µg/mL)*	n=112	4.50 (83.6)	n=110	4.80 (75.2)
Tmax *(h)*	n=113	3.00 (1.97, 3.32)	n=110	2.08 (1.95, 4.83)
Dose 5 (Week 22)				
C_{max} *(µg/mL)*	n=113	154 (27.4)	n=110	150 (26.9)
C_{min} *(µg/mL)*	n=108	4.23 (140)	n=108	3.59 (88.1)
T_{max} *(h)*	n=113	3.00 (2.00, 359)	n=110	3.00 (1.98, 168)
Dose 6 (Week 30)				
C_{max} *(µg/mL)*	n=108	153 (31.8)	n=108	148 (26.4)
C_{min} *(µg/mL)*	n=106	3.44 (91.7)	n=105	3.37 (86.5)
T_{max} *(h)*	n=108	2.08 (1.85, 3.25)	n=108	2.19 (2.00, 4.00)
Dose 7 (Week 38)				
C_{max} *(µg/mL)*	n=109	137 (25.9)	n=104	134 (21.4)
C_{min} *(µg/mL)*	n=102	3.57 (96.0)	n=103	3.59 (93.5)
T_{max} *(h)*	n=109	2.13 (2.00, 3.30)	n=104	2.08 (1.95, 3.20)
Dose 8 (Week 46)				
C_{max} *(µg/mL)*	n=103	138 (26.4)	n=102	150 (44.9)
C_{min} *(µg/mL)*	n=98	4.51 (275)	n=100	3.41 (91.0)
T_{max} *(h)*	n=103	2.08 (0.75, 3.23)	n=102	2.07 (2.00, 5.08)
Dose 9 (Week 54)				
C_{max} *(µg/mL)*	n=102	138 (29.0)	n=100	130 (24.3)
C_{min} *(µg/mL)*	n=0	N/A	n=0	N/A
T_{max} *(h)*	n=102	2.08 (1.90, 3.23)	n=100	2.16 (2.00, 3.20)

CV coefficient of variation; N/A, not applicable.
Note: T_{max} was reported as median (minimum, maximum).
C_{max} and T_{max} were set to missing if the highest concentrations in the profiles occurred at time zero.
C_{max} was set to missing if the concentration was below the lower limit of quantification or the same as other concentrations.

Supportive Pharmacokinetic Study PLANETRA

PLANETRA is a Phase 3, randomized, double-blind, multicentre, parallel-group study in patients with active RA. One of the secondary objectives is to evaluate the long-term pharmacokinetics of REMSIMA™ in comparison with REMICADE® reference product up to Week 54. In this study, patients received a 2 h intravenous infusion dose of either REMSIMA™ (3 mg/kg) or REMICADE® reference product (3 mg/kg) at Weeks 0, 2, and 6 and then every 8 weeks for all subsequent cycles. REMSIMA™ and REMICADE® were co-administered with methotrexate between 12.5 and 25 mg/week, oral or parenteral dose (dose and route had to be maintained from beginning to end of study) and folic acid ≥5 mg/week, oral dose.

The PK population consisted of all patients who received either REMSIMA™ or REMICADE® reference product during the 30 week blinded study period and had at least 1 PK concentration data value. Serum blood samples were obtained before each dosing (immediately prior to the beginning of the study treatment infusion), at the end of each treatment infusion, and 1 h after the end of each treatment infusion at Weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54. All samples were collected into serum sample tubes (3 mL) and obtained as close as possible to the scheduled time point.

Table 8: Geometric mean (%CV) of Infliximab at Week 30 (PK population) – Study PLANETRA in Rheumatoid Arthritis

Parameter	REMSIMA™ (3 mg/kg) (n=290)	REMICADE® (3 mg/kg) (n=288)
C_{MAX} (µg/mL)	83.5 (38.1) (n=241)	83.8 (34.9) (n=244)
T_{MAX} (h)	2.08 (2.00, 3.50) (n=241)	2.22 (0.10, 3.33) (n=244)

$C_{MAX,SS}$=Maximum serum concentration at steady state; $C_{MIN,SS}$=Minimum serum concentration at steady state; T_{MAX}=Time to reach C_{MAX}; CI=Confidence interval

Table 9: Geometric mean (%CV) of Infliximab at Week 54 (PK population) – Study PLANETRA in Rheumatoid Arthritis

Parameter	REMSIMA™ (3 mg/kg) (n=290)	REMICADE® (3 mg/kg) (n=288)
C_{MAX} (µg/mL)	75.3 (37.6) (n=221)	69.2 (32.5) (n=208)
T_{MAX} (h)*	2.12 (2.00, 3.18) (n=221)	2.08 (1.92, 3.32) (n=208)

$C_{MAX,SS}$=Maximum serum concentration at steady state; T_{MAX}=Time to reach
*T_{max} was reported as median (minimum, maximum)

Study PLANETAS showed that REMSIMA™ could not be distinguished from the reference product REMICADE® when considering seven PK parameters, estimated at steady-state using a non-compartmental analysis (AUC, Cmax, Cmin, Half-life, CL, Vss, and Fluctuation). On the basis of a predictive equation devised by a Discriminant Analysis, the classification accuracy was slightly less than 14% over what would be expected if the observations were randomly classified into the Test or Reference categories.

Comparative Clinical Efficacy and Safety Studies

Efficacy (RA)

The pivotal efficacy and safety comparability trial comparing REMSIMA™ and the reference product was a randomized, double-blind, multicentre, parallel-group, prospective Phase III study in adult patients with active RA not receiving adequate response with methotrexate alone.

The primary efficacy endpoint (the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 is summarized for the all-randomized population in **Table 10**.

In the all-randomized population, the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 was compared between the REMSIMA™ and REMICADE® treatment groups (184 [60.9%] patients and 178 [58.6%] patients, respectively). The 95% CI for the estimate of treatment difference was entirely contained within the range -15% to 15% (95% CI: [-0.06, 0.10]) indicating therapeutic comparability between the treatment groups.

Investigations of pharmacokinetics were secondary to the primary efficacy endpoints. Refer to **Table 8** and **Table 9**.

A comparison of the Mean change from baseline for each individual ACR component is presented in **Table 11**. ACR20/50/70 responses at weeks 14, 30, and 54 are compared between REMSIMA™ and the referenced product in **Table 12**.

Table 10: Proportion of Patients Achieving Clinical Response According to ACR20 Criteria at Week 30 – Study PLANETRA in Rheumatoid Arthritis: All-Randomized Population

Treatment group	n/N (%)	Estimate of treatment difference*	95% CI of treatment difference
REMSIMA™	184/302 (60.9)	0.02	-0.06, 0.10
REMICADE®	178/304 (58.6)		

ACR20=20% improvement according to the ACR criteria, CI=Confidence interval, n=Number of patients with an assessment; N=Number of all patients in this group, P value: logistic regressions analysis
*= $\Delta\% * 10^{-2}$ REMSIMA™ and REMICADE®.

Table 11: Mean Change ± SD from Baseline in the ACR Components at Week 54 – Study PLANETRA (All-Randomized Population)

ACR component	n/N (%)		REMSIMA™	REMICADE®
	REMSIMA™	*REMICADE®*		
Tender joints	235/302 (77.8)	226/304 (74.3)	-16.7±12.08	-15.4±12.30
Swollen joints	235/302 (77.8)	226/304 (74.3)	-12.3±8.69	-12.0±8.85
VAS scores for the patient assessment of pain	235/302 (77.8)	226/304 (74.3)	-30.6±23.86	-28.7±26.89
VAS scores for the patient global assessment of disease activity	234/302 (84.4)	226/304 (74.3)	-30.6±24.41	-26.8±27.76
VAS scores for the physician global assessment of disease activity	235/302 (77.8)	226/304 (74.3)	-37.3±21.52	-35.9±22.51
Scores for the health assessment questionnaire	235/302 (77.8)	226/304 (74.3)	-0.61±0.61	-0.53±0.60
CRP (mg/dl)	233/302 (77.2)	224/304 (73.9)	-0.68±2.18	-0.64±2.63
ESR (mm/h)	233/302 (77.2)	225/304 (74.0)	-12.0±22.00	-15.1±21.71

ACR=American College of Rheumatology; n=Number of patients for this evaluation; N=Number of all patients in this group; SD=Standard deviation

Table 12: Proportion of Patients Achieving Clinical Response According to ACR20 at Weeks 14, 30 and 54, as well as ACR50, and ACR70 Criteria at Weeks 14, 30 and 54 (Exact Binomial method) – Study PLANETRA (All-Randomized Population)

ACR scores	n/N (%)		Estimate of treatment difference [1]	95% CI of treatment difference
	REMSIMA™	*REMICADE®*		
ACR20 at Week 14	192/302 (63.6)	175/304 (57.6)	0.06	-0.02, 0.14
ACR20 at Week 30	184/302 (60.9)	178/304 (58.6)	0.02	-0.06, 0.10
ACR20 at Week 54	172/302 (57.0)	158/304 (52.0)	0.05	-0.03, 0.13
ACR50 at Week 14	100/302 (33.1)	91/304 (29.9)	0.03	-0.04, 0.11
ACR50 at Week 30	107/302 (35.4)	103/304 (33.9)	0.02	-0.06, 0.09
ACR50 at Week 54	100/302 (33.1)	96/304 (31.6)	0.02	-0.06, 0.09
ACR70 at Week 14	42/302 (13.9)	37/304 (12.2)	0.02	-0.04, 0.07
ACR70 at Week 30	50/302 (16.6)	47/304 (15.5)	0.01	-0.05, 0.07
ACR70 at Week 54	49/302 (16.2)	46/304 (15.1)	0.01	-0.05, 0.07

ACR20=20% improvement according to the ACR criteria; ACR50=50% improvement according to the ACR criteria; ACR70=70% improvement according to the ACR criteria; CI=Confidence interval; n=Number of patients with an assessment; N=Number of all patients in this group
[1] Estimate of the difference in proportions between the two treatment groups (REMSIMATM – REMICADE®) using the exact binomial test.

In Study PLANETRA, TEAEs occurred in 212 (70.2%) patients treated with REMSIMA™ compared to 211 (70.3%) patients treated with REMICADE®. The most frequently reported TEAEs were latent tuberculosis (8.9% vs. 8.3% patients, respectively), anemia (3.3% vs. 4.0%), nasopharyngitis (7.9% vs. 5.7%), hypertension (5.0% vs. 3.3%), urinary tract infection (6.0% vs. 7.0%), rheumatoid arthritis (5.0% vs. 3.7%), upper respiratory tract infection (8.9% vs. 5.3%), alanine aminotransferase (ALT) increased (5.0% vs. 5.7%), headache (4.3% vs. 5.3%), and bronchitis (4.3% vs. 5.7%). TEAEs due to infusion-related reactions were reported for 10 (3.3%) patients and 11 (3.7%) patients in the REMSIMA™ and REMICADE® treatment groups, respectively. Infusion-related reactions that were considered serious occurred in 5 (1.7%) REMSIMA™ patients and in 4 (1.3%) REMICADE® patients.

The safety analyses included all patients who received at least one (full or partial) dose of either of the study treatments during any dosing period. The safety population for each treatment arm is as follows: REMSIMA™ N=302, REMICADE® N=300.

Efficacy (AS)

A randomized, double-blind, multicenter, parallel-group, study designed to assess PK comparability, also compared the efficacy and safety of REMSIMA™ to REMICADE® in patients with active AS. Investigations of efficacy and safety were secondary to the primary pharmacokinetic endpoints. The study was unblinded at Week 30 for reporting; however, the study remained blinded to the investigators and patients until the end of the study (54 weeks) to reduce bias. No clinically meaningful differences were suggested when the proportions of patients achieving clinical response, according to the ASAS20 and ASAS40 criteria at weeks 14, 30 and 54 were compared between treatment groups. See **Table 13**.

Table 13: Proportion of Patients Achieving Clinical Response According to the ASAS20 and ASAS40 Criteria (Weeks 14, 30, and 54): All-Randomized Population – Study PLANETAS in Ankylosing Spondylitis

ASAS scores	n/N (%)		Estimate of treatment difference	95% CI of treatment difference
	REMSIMA™	*REMICADE®*		
ASAS20 at Week 14	72/125 (57.6)	79/125 (63.2)	-0.06	(-0.18, 0.07)
ASAS20 at Week 30	79/125 (63.2)	84/125 (67.2)	-0.04	(-0.16, 0.08)
ASAS20 at Week 54	71/125 (56.8)	75/125 (60.0)	-0.03	(-0.15, 0.09)
ASAS40 at Week 14	48/125 (38.4)	56/125 (44.8)	-0.06	(-0.19, 0.06)
ASAS40 at Week 30	58/125 (46.4)	55/125 (44.0)	0.02	(-0.10, 0.15)

ASAS scores	n/N (%)		Estimate of treatment difference	95% CI of treatment difference
	REMSIMA™	*REMICADE®*		
ASAS40 at Week 54	58/125 (46.4)	53/125 (42.4)	0.04	(-0.08, 0.16)

ASAS: Ankylosing Spondylitis Assessment

Note: n = the number of subjects with the event. N = the number of subjects with an assessment. (%) = n/N'*100.

[1] Estimate of the difference in proportions between the two treatment groups (REMSIMA™ - REMICADE®) using the exact binomial test.

In PLANETAS (ankylosing spondylitis) study, treatment emergent adverse events (TEAEs) occurred in 93 (72.7%) patients treated with REMSIMA™ compared to 82 (67.2%) patients treated with REMICADE®. The most frequently reported TEAEs were neutropenia (3.1% vs 4.1% patients, respectively), diarrhea (4.7% vs 0.8%), influenza (1.6%, 4.9%), latent tuberculosis (6.3% vs 4.1%), nasopharyngitis (9.4 vs 8.2), pharyngitis (3.1% vs 5.7%), upper respiratory tract infection (7.8% vs 10.7%), urinary tract infection (6.3% vs 0.8%), alanine aminotransferase (ALT) increased (14.8% vs 15.6%), AST (12.5% vs 10.7%), Blood creatine phosphokinase (CPK) increased (6.3% vs 4.1%), gamma glutamyltransferase (GGT) increased (3.1% vs 5.7%), headache (7.8% vs 5.7%), rash (0.8% vs 4.1%).

The safety analyses included all patients who received at least one (full or partial) dose of either of the study treatments during any dosing period. The safety population for each treatment arm is as follows: REMSIMA™ N=128, REMICADE® N=122.

Immunogenicity (AS & RA)

In clinical studies comparing REMSIMA™ with REMICADE®, the number of patients who developed antibodies to REMSIMA™ or to the reference product, REMICADE® was comparable at Screening and at end of study visit.

In the study with ankylosing spondylitis patients, antibodies to infliximab were detected in 41 patients (32.0%) in the REMSIMA™ group, compared to 35 patients (28.7%) in the reference group at the end of the study.
In the study with rheumatoid arthritis patients, antibodies to infliximab were detected in 157 patients (52.0%) in the REMSIMA™ group, compared to 150 patients (50.0%) in the reference group at the end of the study. In both studies, samples that were positive for ADA were tested for neutralizing capacity.

A summary of the Immunogenicity Testing of the two studies is presented in **Table 14** and **Table 15**. The number of patients with positive immunogenicity test results was examined in each treatment group at each time point in the two studies.

Table 14: Summary of Immunogenicity Testing: Safety Population - PLANETAS in Ankylosing Spondylitis

	REMSIMATM 5mg/kg (N=128) n (%)	REMICADE® 5mg/kg (N=122) n (%)	Total (N=250) n (%)
Screening			
ADA Positive	2 (1.6)	1 (0.8)	3 (1.2)
NAb Positive (as % of ADA positive)	1 (50.0)	0	1 (33.3)
ADA Negative	125 (97.7)	119 (97.5)	244 (97.6)
Week 14			
ADA Positive	11 (8.6)	13 (10.7)	24 (9.6)
NAb Positive (as % of ADA positive)	10 (90.9)	12 (92.3)	22 (91.7)
ADA Negative	110 (85.9)	105 (86.1)	215 (86.0)
Week 30			
ADA Positive	32 (25.0)	25 (20.5)	57 (22.8)
NAb Positive (% of as ADA positive)	31 (96.9)	25 (100)	56 (98.2)
ADA Negative	85 (66.4)	86 (70.5)	171 (68.4)
Week 54			
ADA Positive	25 (19.5)	27 (22.1)	52 (20.8)
NAb Positive (% of as ADA positive)	25 (100)	27 (100)	52 (100)
ADA Negative	84 (65.6)	78 (63.9)	162 (64.8)
EoS			
ADA Positive	41 (32.0)	35 (28.7)	76 (30.4)
NAb Positive (% of as ADA positive)	39 (95.1)	35 (100)	74 (97.4)
ADA Negative	81 (63.3)	78 (63.9)	159 (63.6)

ADA=Anti-drug antibody; N=Number of all patients in this group; NAb=Neutralizing antibody
Note: The immunogenicity ADA test involved both a screening and confirmatory assay to confirm positive results.
Samples that were positive in the screening assay were spiked with excess drug to determine if they are a true positive. Percentages for the Neutralizing antibody result are based on the number of positive ADA results at that visit.

Table 15: Summary of Immunogenicity Testing - Safety Population - PLANETRA

	REMSIMA™ 3 mg/kg (N=302) n (%)	REMICADE® 3 mg/kg (N=300) n (%)	Total (N=602) n (%)
Screening			
ADA Positive	9 (3.0)	6 (2.0)	15 (2.5)
NAb Positive (as % of ADA positive)	4 (44.4)	2 (33.3)	6 (40.0)
ADA Negative	292 (96.7)	292 (97.3)	584 (97.0)
Week 14			
ADA Positive	68 (22.5)	70 (23.3)	138 (22.9)
NAb Positive (as % of ADA positive)	68 (100.0)	67 (95.7)	135 (97.8)
ADA Negative	204 (67.5)	201 (67.0)	405 (67.3)
Week 30			
ADA Positive	123 (40.7)	119 (39.7)	242 (40.2)
NAb Positive (as % of ADA positive)	120 (97.6)	115 (96.6)	235 (97.1)
ADA Negative	129 (42.7)	134 (44.7)	263 (43.7)
Week 54			
ADA Positive	123 (40.7)	107 (35.7)	230 (38.2)
NAb Positive (as % of ADA positive)	122 (99.2)	103 (96.3)	225 (97.8)
ADA Negative	114 (37.7)	111 (37.0)	225 (37.4)
EoS			
ADA Positive	157 (52.0)	150 (50.0)	307 (51.0)
NAb Positive (as % of ADA positive) ,	155 (98.7)	147 (98.0)	302 (98.4)
ADA Negative	112 (37.1)	119 (39.7)	231 (38.4)

ADA=Anti-drug antibodies; N=Number of all patients in this group; NAb=Neutralizing antibody

ADA titres were measured for samples taken up to and including the Week 30 study visit. The antibody titre results for ADA by visit and treatment, with cut-point based on normal serum, are presented in the tables below. Titre was evaluated using the end-point titration method, whereby all confirmed positive samples were titrated by performing sufficient serial dilutions to produce at least one dilution with a mean response below the screening cut point. The titres obtained are presented as the log transformed data ($[\log_2(x/5)]+1$ transformation).

ADA titre data are presented for ankylosing spondylitis (AS) patients receiving 5 mg/kg REMSIMA™ or REMICADE® (Study PLANETAS) in **Table 16**. ADA titre data for rheumatoid arthritis (RA) patients receiving the 3 mg/kg dose of REMSIMA™ or REMICADE® (Study PLANETRA) are provided in **Table 17**.

Table 16: Descriptive Statistics of Anti-Drug Antibody (ADA) Titre in Study PLANETAS (Safety Population)

Visit	Statistic	REMSIMA™ 5 mg/kg (N=128)	REMICADE® 5 mg/kg (N=122)	Total (N=250)
Screening	n	2	2	4
	Mean	3.5	5.0	4.3
	SD	0.71	2.83	1.89
	Minimum	3	3	3
	Median	3.5	5.0	3.5
	Maximum	4	7	7
Week 14	n	10	13	23
	Mean	8.6	8.9	8.8
	SD	3.20	2.36	2.70
	Minimum	5	5	5
	Median	9.0	9.0	9.0
	Maximum	13	14	14
Week 30	n	31	24	55
	Mean	8.5	8.5	8.5
	SD	2.97	1.82	2.51
	Minimum	3	6	3
	Median	8.0	8.0	8.0
	Maximum	17	12	17

Note: The CT-P13 tag was used for this summary. Statistics displayed are those of the transformed values of the titre results. The transformation [log2(x/5)]+1 was used.

Table 17: Descriptive Statistics of Anti-Drug Antibody (ADA) Titre in Study PLANETRA (Safety Population)

Visit	Statistic	REMSIMA™ 3 mg/kg (N=302)	REMICADE® 3 mg/kg (N=300)	Total (N=602)
Screening	n	12	7	19
	Mean	3.4	4.0	3.6
	SD	1.00	1.91	1.38
	Minimum	3	3	3
	Median	3.0	3.0	3.0
	Maximum	6	8	8
Week 14	n	72	70	142
	Mean	6.9	6.6	6.8
	SD	2.40	2.31	2.35

Visit	Statistic	REMSIMA™ 3 mg/kg (N=302)	REMICADE® 3 mg/kg (N=300)	Total (N=602)
	Minimum	3	3	3
	Median	7.0	6.5	7.0
	Maximum	13	14	14
Week 30	n	126	120	246
	Mean	8.0	8.4	8.2
	SD	2.90	3.06	2.98
	Minimum	3	3	3
	Median	8.0	8.0	8.0
	Maximum	15	18	18

Note: The REMSIMA™ tag was used for this summary. Statistics displayed are those of the transformed values of the titre results. The transformation [log2(x/5)]+1 was used.

In the Study PLANETAS and Study PLANETRA, the mean titre was comparable for ADA positive patients receiving REMSIMA™ (mean titre 8.6) and REMICADE® (mean titre 8.9) up to Week 30.

A further analysis of these titre data obtained using tagged REMSIMA™ has been performed by ADA titre subgroup, defined using a categorised titre system (Negative, Low, Medium and High). The data were ordered in ascending sequence based on titre value:

- Negative titre is all patients with a 'Negative' test result from the ADA REMSIMA™ tag assessment at that study visit.
- Low titre is defined as a titre value which is between zero and the first tertile of the data.
- Medium titre is defined as a titre value which is greater than or equal to the first tertile of the data, and is less than the second tertile of the data.
- High titre is defined as a titre value which is greater than or equal to the second tertile of the data.

The data for ADA titre by category are provided in **Table 18** for Study PLANETAS. For Study PLANETRA, the data for ADA titre by category are provided in **Table 19**.

Table 18: Distribution of Patients per ADA Titre Category Administered either 5 mg/kg REMSIMA™ or REMICADE® in Study PLANETAS (Safety Population)

Visit	ADA Titre Category	REMSIMA™ 5 mg/kg (N=128)	REMICADE® 5 mg/kg (N=122)	Total (N=250)
Screening	Negative	125 (97.7%)	118 (96.7%)	243 (97.2%)
	Low	2 (1.6%)	1 (0.8%)	3 (1.2%)
	Medium	0	1 (0.8%)	1 (0.4%)
	High	0	0	0
Week 14	Negative	111 (86.7%)	105 (86.1%)	216 (86.4%)
	Low	4 (3.1%)	2 (1.6%)	6 (2.4%)

Visit	ADA Titre Category	REMSIMA™ 5 mg/kg (N=128)	REMICADE® 5 mg/kg (N=122)	Total (N=250)
	Medium	2 (1.6%)	7 (5.7%)	9 (3.6%)
	High	4 (3.1%)	4 (3.3%)	8 (3.2%)
Week 30	Negative	86 (67.2%)	87 (71.3%)	173 (69.2%)
	Low	7 (5.5%)	2 (1.6%)	9 (3.6%)
	Medium	14 (10.9%)	16 (13.1%)	30 (12.0%)
	High	10 (7.8%)	6 (4.9%)	16 (6.4%)

Note: The REMSIMA™ tag was used for this summary.

Table 19: Distribution of Patients per Anti-Drug Antibody (ADA) Titre Category Administered either 3 mg/kg REMSIMA™ or REMICADE® in Study PLANETRA (Safety Population)

Visit	ADA Titre Category	REMSIMA™ 3 mg/kg (N=302)	REMICADE® 3 mg/kg (N=300)	Total (N=602)
Screening	Negative	289 (95.7%)	291 (97.0%)	580 (96.3%)
	Low	11 (3.6%)	6 (2.0%)	17 (2.8%)
	Medium	1 (0.3%)	1 (0.3%)	2 (0.3%)
	High	0	0	0
Week 14	Negative	199 (65.9%)	200 (66.7%)	399 (66.3%)
	Low	21 (7.0%)	26 (8.7%)	47 (7.8%)
	Medium	34 (11.3%)	28 (9.3%)	62 (10.3%)
	High	17 (5.6%)	16 (5.3%)	33 (5.5%)
Week 30	Negative	126 (41.7%)	133 (44.3%)	259 (43.0%)
	Low	27 (8.9%)	28 (9.3%)	55 (9.1%)
	Medium	50 (16.6%)	36 (12.0%)	86 (14.3%)
	High	49 (16.2%)	56 (18.7%)	105 (17.4%)

Note: The CT-P13 tag was used for this summary.

These results therefore support those demonstrating similar frequency of antibody responses to REMSIMA™ and REMICADE®, and indicate that the intensity of the immune response to REMSIMA™ and the reference medicinal product can be regarded as comparable.

Psoriatic Arthritis, Plaque Psoriasis, Crohn's Disease and Ulcerative Colitis

Randomized clinical trials have not been conducted to compare REMSIMA™ and REMICADE® in psoriatic arthritis, plaque psoriasis, Crohn's disease or ulcerative colitis. Clinical efficacy and safety have been conducted in selected indications (RA and AS) to demonstrate clinical comparability between REMSIMA™ and REMICADE®. The extrapolation of these data to support uses of REMSIMA™ in psoriatic arthritis, plaque psoriasis, Crohn's disease and ulcerative colitis is based on the demonstrated comparability, in terms of product quality, non-clinical, human pharmacokinetic, and clinical characteristics.

DETAILED PHARMACOLOGY

Since REMSIMA™ is a Subsequent Entry Biologic, where the pharmacodynamic and pharmacokinetic properties of infliximab have already been described for the reference biologic drug REMICADE®, this section summarizes the extensive comparative studies that were conducted to compare the pharmacology of REMSIMA™ to REMICADE®.

Pharmacodynamics

The biological activity of infliximab can be categorized into two parts. The [F(ab')2] end related primary mechanism of action involves the TNFα neutralization by binding to TNFα and inhibition of cell signaling for proliferation. Assays for this include in vitro TNFα neutralization activity, apoptosis, TNFα binding affinity (Surface Plasmon Resonance (SPR)), TNFα binding affinity (ELISA) for potency measurements, and cell-based TNFα binding affinity. The secondary mechanism of action (through the Fc end of the molecule, alone or in combination with the F(ab')2 end) involves activation of the immune responses which includes ADCC, CDC, FcγR family binding affinity (SPR), FcRn binding affinity (SPR) and C1q binding affinity (ELISA).

Primary PD consisted of 33 in vitro studies assessing the binding affinity of REMSIMA™ and REMICADE® to soluble (from different species) and transmembrane form of human TNFα, TNFβ, FcγRI, FcγRIIa, FcγRIIIa, FcRn and C1q; the TNFα neutralization activity; the CDC, ADCC, apoptotic effects; and the cross-reactivity with various human tissues. REMICADE® was included as reference product in all of these studies. The type, test method used and key findings of these studies are summarized below (**Table 20**).

Table 20: Summary of Studies Comparing in vitro Activity between REMSIMA™ and REMICADE®

Test Method	Key Findings
F(ab')2 related	
Comparative binding of REMSIMA™ and REMICADE® to hTNFα using ELISA	The relative binding affinities of REMSIMA™ and REMICADE® were shown to be comparable. REMSIMA™ and REMICADE® demonstrated comparable binding activity to both monomeric and trimeric hTNFα.
Comparative binding of REMSIMA™ and REMICADE® to hTNFα using Surface Plasmon Resonance [SPR]	Similar equilibrium binding affinities (K_D) toward the intact trimeric form of hTNFα. The binding affinity of REMSIMA™ and REMICADE® to monomeric and trimeric hTNFα was comparable. The relative binding affinities of REMSIMA™ and REMICADE® were shown to be comparable. REMSIMA™ and REMICADE® demonstrated comparable binding activity to both monomeric and trimeric hTNFα.
Comparative transmembrane (tm) hTNFα binding affinity of REMSIMA™ and REMICADE® using cell-based ELISA	The relative binding affinities of REMSIMA™ and REMICADE® were shown to be comparable.
The human TNFβ binding specificities of REMSIMA™ and REMICADE®	Neither REMSIMA™ nor REMICADE® had binding affinity for hTNFβ.

Test Method		Key Findings
Human tissue cross-reactivity of REMSIMA™ and REMICADE® using immunohistochemistry		The tissue cross-reactivity of biotinylated REMSIMA™ and biotinylated REMICADE® were shown to be comparable using a panel of human tissues.
Comparative TNFα binding affinity from different species of REMSIMA™ and REMICADE® using SPR		For REMSIMA™ and REMICADE®, neither product displayed binding affinity for mouse, rat, canine, porcine, or rhesus monkey TNFα.
Comparative hTNFα neutralization assay of REMSIMA™ and REMICADE®		The neutralizing activities of REMSIMA™ and REMICADE® on a TNF sensitive cell line were shown to be dose dependent and comparable and within ≤15% of assay variance.
Comparative apoptosis of REMSIMA™ and REMICADE®		The apoptotic effects by reverse signalling through tmhTNFα for REMSIMA™ and REMICADE® were comparable. No statistically significant differences were detected at any time point.
Comparative Reverse signalling		Blockade of pro-inflammatory cytokine production by reverse signalling through tmhTNFα for REMSIMA™ and REMICADE® were comparable using peripheral mononuclear blood cells (PBMC) from either healthy donors or CD patients.
Effect of blocking soluble TNFα *in vitro* IBD model	Suppression of cytokine secretion in epithelial cell line by blocking soluble TNFα	Suppression of pro-inflammatory cytokine (IL-6 and IL-8) secretion from co-stimulated epithelial cell line was shown to be comparable and dose dependent for REMSIMA™ and REMICADE®. No statistical difference in pro-inflammatory cytokine suppression was found.
	Suppression of apoptosis in epithelial cell line cells by blocking soluble TNFα	Suppression of epithelial cell line apoptosis was shown to be comparable for REMSIMA™ and REMICADE®.
Fc Receptor related		
Comparative binding to Fcγ receptors: FcγRI, FcγRIIa, FcγRIIb, and FcRn using Surface Plasmon Resonance [SPR]		The relative binding affinities of REMSIMA™ and REMICADE® to Fcγ receptors (FcγRI, FcγRIIa, FcγRIIb and FcRn) are comparable.
Comparative binding to Fcγ receptors: FcγRIIIa (V and F hemizygotes) and FcγRIIIb using SPR		Differences in the relative binding affinity of REMSIMA™ and REMICADE® were detected; reduced binding to FcγRIIIa (V and F hemizygotes) and FcγRIIIb was detected in REMSIMA™ lots.
Comparative binding to Fcγ receptors: *Ex vivo* assay using NK cells and neutrophils to assess FcγRIIIa and FcγRIIIb binding, respectively		There was a difference in mean relative binding affinities to isolated NK cells of healthy donors and Crohn's disease (CD) patients (between REMSIMA™ and REMICADE®, which was shown to be FcγRIII genotype dependent (V/V and V/F genotypes, respectively). No differences were shown with F/F genotype. In the presence of diluted CD patient serum, the observed differences in binding for REMSIMA™ and REMICADE® lots binding were not evident
		The mean relative binding affinities of REMSIMA™ and REMICADE® to isolated neutrophils (*ex vivo*) from a healthy donor or CD patient were shown to be comparable. (genotype was not determined)
Fc-F(ab')2 related		
Comparative C1q binding affinity of REMSIMA™ and REMICADE® using ELISA		The relative binding affinities of REMSIMA™ and REMICADE® were shown to be comparable;
Comparative complement-dependent cytotoxicity (CDC) of REMSIMA™ and REMICADE®		CDC effects of REMSIMA™ and REMICADE® against tmhTNFα-Jurkat cells by lysis were comparable. No statistically significant differences were detected.
Comparative Antibody-de-pendent cell-mediated	Using tmhTNFα-Jurkat cells as target cells and human PBMC as effector cells	REMSIMA™ and REMICADE® had comparable ADCC activity. No statistically significant differences were detected. (genotype was not determined)

Test Method		Key Findings
cytotoxicity (ADCC) of REMSIMA™ and REMICADE®	Using tmhTNFα-Jurkat cells as target cells and NK cells from healthy donor as effector cells	Comparable ADCC for REMSIMA™ and REMICADE® when NK cells from a healthy donor (genotype V/F) were used as effector cells.No statistically significant difference were detected.
	Using tmhTNFα-Jurkat cells as target cells and NK cells from a RA patient as effector cells	No significant cytotoxicity was observed, it is likely that RA patient have an impaired ADCC response
	Using transfected Jurkat cells as target cells and either PBMCs or NK cells from CD patients as effector cells	No differences in ADCC activity were detected using PBMC from CD patients (V/F or F/F genotype). Differences in ADCC with REMSIMA™ and REMICADE® were seen when NK cells from CD patients were used as effector cells. Effect was FcγRIIIa genotype specific; differences were observed with V/V and V/F, but not F/F genotypes.
	Using transfected Jurkat cells as target cells and whole blood from healthy donor or CD patients as effector cells	No differences in ADCC were seen between various batches of REMSIMA™ and REMICADE®.
	Using LPS-stimulated monocytes from healthy donor or CD patient as target cells and PBMC as effector cells	No ADCC activity was seen with REMSIMA™ and REMICADE® when PBMCs from a healthy donor (V/F) or a CD patient (V/F) were used as effector cells and LPS-stimulated monocytes were used as target cells.
Evaluation of Regulatory Macrophage Function	Suppression of T cell proliferation by induced regulatory macrophages in mixed lymphocyte reaction (MLR) assay	Inhibition of T cell proliferation of PBMCs from healthy donors and CD patients was shown to be comparable and dose dependent for REMSIMA™ and REMICADE®.
	Quantitation of the induced regulatory macrophages by FACS analysis	Induction of regulatory macrophages in a 2-way allogenenic MLR using FcγRIIIa genotype matched PBMCs, from either healthy donors or CD patients, was shown to be comparable for REMSIMA™ and REMICADE®.
	Induced regulatory macrophage-mediated wound healing of colorectal epithelium cells	Promotion of *in vitro* wound healing of colorectal epithelial cells by regulatory macrophages from healthy donors and CD patients (induced by REMSIMA™ or REMICADE®) in the MLR assay was comparable.

TOXICOLOGY

REMSIMA™ is a SEB where the animal toxicology properties of infliximab have already been characterized for the reference biologic drug REMICADE®. This section summarizes the comparative toxicity studies conducted to compare REMSIMA™ to REMICADE®, followed by the REMICADE® Comparative toxicity studies.

Three repeat-dose toxicity studies in rats were performed to evaluate the safety of REMSIMA™ (**Table 21**). Due to the lack of cross-reactivity of infliximab with any species other than chimpanzee or human, these studies were performed to compare general off-target product toxicity (including immunogenicity) of REMSIMA™ with REMICADE®. Studies in species other than chimpanzee are not capable of identifying target-related toxicity. Two 2-weeks repeat dose toxicity studies in rats were performed to compare off-target toxicity profiles of REMSIMA™ and REMICADE®. Initially, an exploratory dose-finding study was also performed with REMICADE® in rats to confirm dose selection of the comparative studies.

Table 21: Summary of repeat-dose toxicity studies performed with REMSIMA™and REMICADE®

Study ID	Species/Sex/ Number/Group	Dose (mg/kg) / Route	Duration	NOAEL (mg/kg/day)	Major findings
8214167*	Rat / M&F / 5	0, 10, 40 IV REMICADE®	2 doses 1 week apart	40 mg/kg	No major toxicity
8214158	Rat / M&F / 10	0, 10, 40 IV REMSIMA™ & REMICADE®	2 doses 1 week apart	40 mg/kg	No major toxicity; the two drugs are comparable
G09197	Rat / M&F / 10	0, 10, 50 IV REMSIMA™& REMICADE®	2 doses 1 week apart	50 mg/kg	No major toxicity; the two drugs are comparable

* No claim of GLP compliance is made for this study. IV= intravenous, M=male, F=female, NOAEL=no observed adverse effect level

Study 8214167 was a pilot exploratory dose-finding study performed with REMICADE® in rats which confirmed that a dose level up to 40 mg/kg given intravenous on two occasions one week apart did not reveal any significant adverse effects, and therefore, would be suitable for further testing. The study was not comparative in nature and did not involve REMSIMA™. Two GLP-compliant repeat dose toxicity studies, 8214158 and G09197, were then performed in rats dosed intravenously with either REMSIMA™ or REMICADE® at 0, 10 or 40 mg/kg (study 8214158) and at 0, 10 or 50 mg/kg (study G09197). In both studies, two doses were given one week apart. No significant test-article related findings were noted in any of the studies. In the first study, minimally higher absolute reticulocyte count in males and mildly higher platelet count in males and females at 40 mg/kg/dose REMSIMA™ or REMICADE®, as well as minimal Kupffer cell hyperplasia in livers at 10 and 40 mg/kg/dose REMSIMA™ or REMICADE®, were observed. However, the changes were of similar magnitude for both test articles. The NOAELs for REMSIMA™ and REMICADE® were both 40 mg/kg/dose infliximab. In the second study, subdued behavior, decreases in food consumption, changes in creatine kinase and albumin/globulin ratio, and increases in platelets and reticulocytes (%), total protein and female liver weights were observed. The findings were comparable for REMSIMA™ and REMICADE®. The NOAELs for both products were the same 50 mg/kg/dose. In terms of off-

target toxicity, REMSIMA™ can be considered biosimilar to REMICADE®. However, due to the lack of primary pharmacodynamic activity in rats, toxicity testing conducted was not relevant to judging comparability between REMSIMA™ and REMICADE® or to predicting safety in humans. Immunogenicity analysis from study 8214158 showed that none of the serum samples from treated animals were positive with antibodies to REMSIMA™ or REMICADE®. TK results from the study indicated that animals were almost continuously exposed to REMSIMA™ or REMICADE® throughout the study. Exposure to REMSIMA™ and REMICADE® increased with the increase in dose level from 10 to 40 mg/kg/dose. Increases in C0, Cmax, and AUC0-168 after dosing with REMSIMA™ or REMICADE® were generally dose proportional and sex differences were less than 2-fold.

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PART III: CONSUMER INFORMATION

PrREMSIMA™
(infliximab)

REMSIMA™ is a subsequent entry biologic (SEB) to REMICADE®. An SEB is a biologic drug product that is authorized based on its likeness to a biologic drug product already authorized for sale in Canada. This leaflet is a summary and will not tell you everything about REMSIMA™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

REMSIMA™ (pronounced) <<Rem-see-mah>> is a medicine that is used in people with moderate to severe rheumatoid arthritis (in combination with methotrexate) and ankylosing spondylitis. Your doctor has chosen to treat your rheutamoid arthritis with **REMSIMA™** because you have moderately to severely active rheumatoid arthritis. Your doctor has chosen to treat your ankylosing spondylitis with **REMSIMA™** because you have had inadequate response to other treatment or because you cannot tolerate other treatments.

REMSIMA™ is also used in people with moderate to severe plaque psoriasis. Your doctor has chosen to treat your plaque psoriasis with **REMSIMA™** because your disease is still active even though you have tried other treatments.

REMSIMA™ is also used in people with active psoriatic arthritis. Your doctor has chosen to treat your psoriatic arthritis with REMSIMA™ because your disease is still active even though you have tried other treatments.

REMSIMA™ is also used in adult patients with moderate to severe Crohn's disease or with moderate to severe ulcerative colitis. Your doctor has chosen to treat your Crohn's disease or ulcerative colitis with **REMSIMA™** because your disease is still active even though you have tried other treatments.

What it does:

Research has shown that in these diseases the body overproduces a substance known as tumour necrosis factor alpha (TNF alpha). The active ingredient in **REMSIMA™** is called infliximab. Infliximab is a monoclonal antibody, a type of protein that recognises and binds to other unique proteins. Infliximab binds to and neutralizes TNF alpha. **REMSIMA™** is made from mouse and human proteins. **REMSIMA™** is a medicine that affects your immune system. REMSIMA™ can lower the ability of your immune system to fight infections.

When it should not be used:

Do not use **REMSIMA™** if you have:

• severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis or other serious infection.

• heart failure that is moderate or severe.

• an allergy to infliximab or any ingredient in REMSIMA™ (polysorbate 80, sodium phosphate and sucrose), or if you have a history of allergies to mouse proteins.

What the medicinal ingredient is:

Infliximab

What the important nonmedicinal ingredients are:

Dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, polysorbate and sucrose. No preservatives are present.

What dosage forms it comes in:

REMSIMA™ is an injectable medicine. It is supplied as a lyophilized concentrate for intravenous infusion in individually-boxed single-use vials of 100 mg infliximab.

Where I may receive the infusion:

Your doctor will decide where you will receive the infusion. The REMSIMA Patient Assistance Program facilitates the administration of **REMSIMA™**. The REMSIMA Patient Assistance Program clinics are staffed by qualified healthcare professionals specially trained in the administration of **REMSIMA™** infusions and are available across Canada. Information about the REMSIMA Patient Assistance Program can be obtained by calling 1-844-466-6627.

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

WARNINGS AND PRECAUTIONS

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, 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™** you should tell your doctor if you have a chronic infection, a history of recurrent infection, or if you have lived in or traveled to an area where infections called histoplasmosis, coccidioidomycosis or blastomycosis are common.These infections are caused by fungus that can affect the lungs or other parts of your body.Ask your doctor if you don't know if these infections are common in the area in which you have lived or traveled. If you develop an infection during treatment with **REMSIMA™**, you should tell your doctor right away.

• Prior to treatment with **REMSIMA™,** you should tell your doctor if you have had tuberculosis, or if you have been exposed recently to anyone who might have tuberculosis, or if you have any other reason to believe you may be at risk for tuberculosis. Your doctor will evaluate you for tuberculosis and may begin treatment for tuberculosis before you are treated **REMSIMA™**.

• Treatment with **REMSIMA™** must be interrupted if you develop a serious infection or sepsis.Tell your doctor if you have any symptoms of an infection (for example, fever, fatigue, cough, flu-like symptoms, or pain) while you are taking **REMSIMA™** and for 6 months after you receive the medicine.

• If you need surgery, tell your doctor that you have taken **REMSIMA™**.

• Lymphoma and other cancers, which may result in death, have been reported in children and teenage patients taking TNF- blockers, including infliximab. Some patients who have received TNF-blockers, including infliximab have developed a rare type of cancer called hepatosplenic T-cell lymphoma. Of these patients, most were teenage or young adult males and most had either Crohn's disease or ulcerative colitis. This type of cancer often results in death. Almost all patients had also received drugs known as azathioprine or 6-mercaptopurine in addition to TNF-blockers. You should also tell your doctor if you have had or develop lymphoma or other cancers while you are taking **REMSIMA™**.

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

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

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

Patients with a lung disease called COPD (Chronic Obstructive Pulmonary Disease) may be at increased risk for cancer with **REMSIMA™** treatment. Tell your doctor if you have COPD.

BEFORE you start taking REMSIMA™, you should tell your doctor if you have any of the following:

• Congestive heart failure: If you have mild heart failure and you are being treated with **REMSIMA™**.you must be closely monitored by your doctor. Tell your doctor immediately if you develop new or worsening symptoms of heart failure (such as shortness of breath or swelling of your feet).
• Immediate allergic reactions: Some patients who have received **REMSIMA™.**have developed allergic reactions, including anaphylaxis. Some reactions can happen while you are getting your infusion or shortly afterwards. Some of these reactions have been serious. The symptoms include hives, difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop **REMSIMA™** treatment for severe reactions. Your doctor can prescribe medicines to treat these effects.
• Delayed allergic reactions: Some allergic reactions can occur 3 to 12 days after **REMSIMA™** retreatment. The symptoms of this type of delayed reaction include muscle or joint pain with fever or rash. Tell your doctor if you notice any of these symptoms.
• Nervous system diseases: Tell your doctor if you have a disease that affects your nervous system, like multiple sclerosis, neuropathies, Guillain-Barré syndrome, or seizures, or you have been diagnosed with optic neuritis, or if you experience any numbness, tingling, or visual disturbances. These symptoms may worsen after receiving **REMSIMA™**.
• Autoimmune disease: Some patients treated with **REMSIMA™.**have developed symptoms that suggest an autoimmune disease called lupus-like syndrome. Tell your doctor if you notice symptoms of lupus-like syndrome, such as, prolonged chest discomfort or pain, shortness of breath, joint pain, or sun-sensitive rash on the cheeks or arms. Your doctor will evaluate your condition and may decide to stop your treatment with **REMSIMA™**.
• Liver injury: There have been very rare cases where people taking **REMSIMA™** have developed liver problems. Signs that you could be having a problem include: jaundice (skin and eyes turning yellow), dark brown-colored urine, rightsided abdominal pain, fever, and severe fatigue (tiredness). You should contact your doctor immediately if you develop any of these symptoms.

• Previous phototherapy: Tell your doctor if you have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine to make your skin sensitive to light) for psoriasis. In clinical trials, skin cancers were more common in patients who received prior phototherapy.
• Blood problems: In some instances, patients treated with TNF blocking agents may develop low blood counts, including a severely decreased number of white blood cells. If you develop symptoms such as persistent fever or infections, bleeding, or bruising, you should contact your doctor right away.
• Stroke: On rare occasions, patients have experienced a stroke within approximately 24 hours of their infusion of **REMSIMA™**. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.
• Hepatitis B: Treatment with TNF-blocking agents such as **REMSIMA™** may result in a reactivation of the hepatitis B virus in people who carry this virus. If you have or have had hepatitis B infection or know or suspect you may be a carrier of hepatitis B virus, be sure to tell your doctor about this as this may impact the decision to start or continue treatment with **REMSIMA™**. Your doctor should do a blood test for hepatitis B virus before you start treatment with **REMSIMA™**.
• Vaccination: Tell your doctor that you have received **REMSIMA™** if you need to get a vaccination. It is not known if medicines like **REMSIMA™** can interfere with vaccinations. You should not receive live vaccines while you are taking **REMSIMA™**. It is recommended that the vaccinations of patients be brought up to date with all vaccinations guidelines prior to starting **REMSIMA™**.
• Therapeutic infectious agents: Tell your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).
• Pregnancy, breast-feeding and ability to have children:
If you have a baby and you were using **REMSIMA™** during your pregnancy, it is important to tell your baby's doctor and other healthcare professionals about your **REMSIMA™** use so they can decide when your baby should receive their vaccinations, including live vaccines, such as BCG (used to prevent tuberculosis). If you received **REMSIMA™** while you were pregnant, your baby may be at higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your **REMSIMA™** use before the baby receives any vaccine. Administration of BCG vaccine within 6 months after birth to the baby whose mother received **REMSIMA™** while pregnant may result in infection in the newborn with severe complications, including death. For other types of vaccines, discuss with your doctor. Breast feeding is not recommended during treatment and for 6 months after the last dose of **REMSIMA™**. Your doctor will help you decide whether or not to use **REMSIMA™**. Severely decreased numbers of white blood cells have also been reported in infants born to women treated with **REMSIMA™** during pregnancy. If your baby has continual fevers or infections, contact your baby's doctor immediately. It is not known if **REMSIMA™** can affect your ability to have children in the future.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all medicines that you have recently taken or are taking during your treatment with **REMSIMA™**. These include any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis. Drugs that may interact with **REMSIMA™** 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™**. In studies of infliximab patients were also taking antibiotics, antivirals, corticosteroids, mercaptopurine (6MP), azathioprine (AZA), methotrexate (MTX), and aminosalicylates along with infliximab. Patients who took immunosuppressants, such as methotrexate, corticosteroids, mercaptopurine, azathioprine, had a lower risk of allergic reactions during infusion.

Especially, tell your doctor if you take KINERET® (anakinra) or ORENCIA® (abatacept). **REMSIMA™** should not be taken together with anakinra or abatacept.

If you have a baby while you are using **REMSIMA™**, tell your baby's doctor about your **REMSIMA™** use before the baby receives any live vaccines.

PROPER USE OF THIS MEDICATION

Usual dose:

Rheumatoid Arthritis:
The recommended dose of **REMSIMA™** is 3 mg/kg given as an intravenous infusion followed by additional 3 mg/kg doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. **REMSIMA™** should be given in combination with methotrexate.

Ankylosing Spondylitis:
The recommended dose of **REMSIMA™** is one initial infusion of 5 mg/kg followed by infusions of 5 mg/kg at 2 and 6 weeks after the first dose. Then you will receive an infusion every 6 to 8 weeks thereafter.

Crohn's Disease and Fistulising Crohn's Disease:
The recommended dose of **REMSIMA™** is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderate to severe activeCrohn's disease. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg.

Ulcerative Colitis:
If you are receiving **REMSIMA™** for ulcerative colitis, you will receive your first 5 mg/kg dose followed by additional 5 mg/kg doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks thereafter. Your doctor will monitor your response to **REMSIMA™** and may change your dose. Your doctor may consider doing a blood test (therapeutic drug monitoring) to determine how much infliximab is in your bloodstream in order to optimize your dose of **REMSIMA™.**

Psoriatic Arthritis
The recommended dose of **REMSIMA™** is 5 mg/kg as an intravenous infusion followed with additional doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. If you show no response at 24 weeks, no additional treatment with **REMSIMA™** should be given.

Plaque Psoriasis:
The recommended dose of **REMSIMA™** is 5 mg/kg as an intravenous infusion followed with additional doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. If you do not show an adequate response at Week 14, after infusions at Weeks 0, 2, and 6, no additional treatment with **REMSIMA™** should be given.

Overdose:

Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate treatment instituted immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

How to give this medication:

REMSIMA™ will be given to you by a healthcare professional. The medicine will be given to you through a needle placed in a vein in your arm. This is called an infusion. For Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, or plaque psoriasis, the infusion will take about 2 hours. For rheumatoid arthritis, the first 3 infusions will be given to you over a period of about 2 hours, after the third infusion your doctor may decide to give you the infusion over a 1 hour period. During the infusion you will be monitored for side effects. You must stay for 1 to 2 hours after the infusion so that you can continue to be watched for any reactions to the medicine.
Your doctor may ask you to take other medicines along with **REMSIMA™.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some patients had side effects that caused them to stop **REMSIMA™** 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™ may have a minor influence on the ability to drive and use of machines. Dizziness may occur after receiving REMSIMA™.

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Serious infections: symptoms of fever, feel very tired, have a cough or have flu-like symptoms		✓	
	Allergic reactions: Symptoms while you are getting your **REMSIMA™** during infusion or shortly afterwards, of hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure (or symptoms 3 to 12 days after receiving **REMSIMA™** 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 abdominal pain, fever and severe fatigue (tiredness).		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Heart failure: If you have been told that you have a heart problem called congestive heart failure, you will need to be closely monitored by your doctor. New or worse symptoms that are related to your heart condition, including shortness of breath or swelling of your ankles or feet.		✓	
	Blood problems: symptoms of fever that doesn't go away, bruising or bleeding very easily or looking very pale.		✓	
	Nervous system disorders: signs include changes in your vision, 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™.**		✓	
	Lupus-like syndrome: 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.		✓	

*This is not a complete list of side effects. For any unexpected effects while taking **REMSIMA™**, contact your doctor or pharmacist.*

HOW TO STORE IT

REMSIMA™ must be stored in the original package in the refrigerator before use. It must be kept out of the reach and sight of children. The vial must be kept sealed. Only a healthcare professional should prepare the medicine before use and administer it to you. It should not be used beyond the expiration date.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Hospira Healthcare Corporation, at: **1-866-488-6088, Option 4**.

The REMSIMA Patient Assistance Program facilitates the administration of REMSIMA™. The REMSIMA Patient Assistance Program clinics are staffed by qualified healthcare professionals specially trained in the administration of **REMSIMA™** infusions and are available across Canada. Information about the REMSIMA Patient Assistance Program can be obtained by calling 1-844-466-6627.

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