PRODUCT NAME

REMSIMA® 100 mg/vial powder for concentrate for solution for infusion.

DOSAGE FORMS AND STRENGTHS

Each vial of REMSIMA® contains 100 mg of infliximab a chimeric lgG1 monoclonal antibody manufactured from a recombinant cell line cultured by continuous perfusion. Upon reconstitution each ml contains 10 mg of infliximab. For excipients, see *List of Excipients*.

Powder for concentrate for solution for infusion.
The powder is a freeze-dried white pellet.

CLINICAL INFORMATION

Indications

Rheumatoid Arthritis

REMSIMA®, in combination with methotrexate (MTX), is indicated for:
The reduction of signs and symptoms as well as the improvement in physical function in

- patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate.
- patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by x-ray, has been demonstrated (see *Pharmacodynamic Properties*).

Crohn's Disease

REMSIMA® is indicated for:

- Treatment of moderately to severely, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and an immunosuppressant: or who are intolerant to or have medical contraindications for such therapies.
- Treatment of fistulising Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Paediatric Crohn's Disease

REMSIMA® is indicated for:
Treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. REMSIMA® has been studied only in combination with conventional immunosuppressive therapy.

Ulcerative Colitis

REMSIMA® is indicated for:

Treatment of moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Paediatric Ulcerative Colitis

REMSIMA® is indicated for: Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Ankylosing Spondylitis

REMSIMA® is indicated for:

Treatment of ankylosing spondylitis, in patients who have severe axial symptoms, elevated serological markers of inflammatory activity and who have responded inadequately to conventional therapy.

Psoriatic Arthritis

REMSIMA®, in combination with methotrexate, is indicated for:

Treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying anti-rheumatoid drugs.

Psoriasis

REMSIMA® is indicated for:

Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultraviolet A (PUVA) (see *Pharmacodynamic Properties*)

Dosage and Administration

REMSIMA® treatment is to be administered under the supervision and monitoring of specialized physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, ankylosing spondylitis, psoriatic arthritis or psoriasis. REMSIMA® should be administered intravenously.

During REMSIMA® treatment, other concomitant therapies, e.g., corticosteroids and immunosuppressants should be optimized.

Adults (≥ 18 years)

Rheumatoid Arthritis

3 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

REMSIMA® must be given concomitantly with methotrexate.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Moderately to Severely, Active Crohn's Disease

5 mg/kg given as an intravenous infusion over a 2-hour period. Available data do not support further infliximab treatment, in patients not responding within 2 weeks to the initial infusion. In responding patients, the strategy for continued treatment is.

- Maintenance: Additional infusions of 5 mg/kg at 2 and 6 weeks after the initial dose, followed by infusions every eight weeks.

Fistulising Crohn's Disease

An initial 5 mg/kg infusion given over a 2-hour period is to be followed with additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion. If a patient does not respond after these 3 doses, no additional treatment with infliximab should be given.

In responding patients, the strategies for continued treatment are:

- Additional infusions of 5 mg/kg every 8 weeks or
- Readministration if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks (see *Readministration* below and *Warnings and Precautions*).

Ulcerative Colitis

5mg/kg given as intravenous infusion over a 2 hour period followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Ankylosing Spondylitis

5 mg/kg given as an intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e. after 2 doses), no additional treatment with infliximab should be given.

Psoriatic Arthritis

5 mg/kg given as intravenous infusion over a 2-hour period followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Efficacy and safety have been demonstrated in combination with methotrexate.

Psoriasis

5mg/kg given as intravenous over a 2-hour period followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

Readministration for Crohn's Disease and Rheumatoid Arthritis

If the signs and symptoms of disease recur, REMSIMA® can be readministered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after drug free intervals of less than 1 year (see *Warnings and Precautions* and *Adverse Reactions: Delayed Hypersensitivity*). After a drug free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following readministration is not known. Therefore, after a drug free interval of 16 weeks, readministration is not recommended.

Readministration for Ulcerative Colitis

The safety and efficacy of readministration, other than every 8 weeks, has not been established. (see *Warnings and Precautions* and *Adverse Reactions*).

Readministration for Ankylosing Spondylitis

The safety and efficacy of readministration, other than every 6 to 8 weeks, has not been established. (see *Warnings and Precautions* and *Adverse Reactions*).

Readministration for Psoriatic Arthritis

The safety and efficacy of readministration, other than every 8 weeks, has not been established. (see *Warnings and Precautions* and *Adverse Reactions*).

Readministration for Psoriasis

Limited experience from retreatment with one single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen (see *Pharmacodynamic Properties*).

Pediatrics

Crohn's Disease (6 to 17 years)

5mg/kg given as intravenous infusion over a 2-hour period followed by additional 5mg/kg infusion

doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. For some patients a longer dosing interval may be sufficient. Available data do not support further infliximab treatment in paediatric patients not responding within the first 10 weeks of treatment.

Pediatric Crohn's disease patients who have had their dose adjusted to greater than 5 mg/kg every 8 weeks, may be at greater risk for adverse reactions. Continued therapy with the adjusted dose should be carefully considered in patients who show no evidence of additional therapeutic benefit after dose adjustment.

Ulcerative Colitis (6 to 17 years)

5mg/kg given as intravenous infusion over a 2 hour period followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Administration

REMSIMA® should be administered intravenously over a 2 hour period. All patients administered REMSIMA® are to be observed for at least 1-2 hours post-infusion for acute infusion-related reactions. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pre-treated with e.g., an antihistamine hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion-related reactions especially if infusion-related reactions have occurred previously (see *Warnings and Precautions*).

Shortened Infusions Across Adult Indications

In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of REMSIMA® (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses >6mg/kg have not been studied.

For preparation and administration instructions, see *Instructions for Use and Handling and Disposal.*

Contraindications

REMSIMA® is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see *Warnings and Precautions*).

REMSIMA® is contraindicated in patients with moderate or severe heart failure (NYHA class III/IV) (see *Warnings and Precautions* and *Adverse Reactions*).

REMSIMA® must not be given to patients with a history of hypersensitivity to infliximab (see *Adverse Reactions*), to other murine proteins, or to any of the excipients.

Warnings and Precautions

REMSIMA® is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding its interchangeability.

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.

REMSIMA® is contraindicated in patients with tuberculosis. Before starting treatment with REMSIMA®, patients must be evaluated for both active and inactive ('latent') tuberculosis (see *Infections*).

REMSIMA® is contraindicated in patients with moderate or severe heart failure (NYHA Class III/IV), and it should be used with caution in patients with mild heart failure (NYHA Class I/II) (see *Heart failure*).

Infusion reactions and hypersensitivity
Infliximab has been associated with acute infusion-related reactions, including, anaphylactic shock, and delayed hypersensitivity reactions (see *Adverse Reactions*)

Acute infusion reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pretreated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions were serious allergic reactions. In Crohn's disease patients, an association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during infliximab treatment are at greater risk of developing these antibodies. Antibodies to infliximab cannot always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further

REMSIMA® infusions must not be administered (see *Adverse Reactions: "Immunogenicity"*).

In clinical trials, delayed hypersensitivity reaction has been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing drug free interval. Advise patients to seek immediate medical advice if they experience any delayed adverse event (see *Adverse Reactions: "Delayed hypersensitivity"*). If patients are retreated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infusion reactions following re-administration of infliximab: In a psoriasis clinical trial, a 3-dose re-induction of infliximab after a period of no treatment resulted in a higher incidence of serious infusion reactions during the re-induction regimen (see *Adverse Reactions)* 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 re-induction. In general, the benefit-risk of re-administration of infliximab after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2, and 6 should be carefully considered.

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with REMSIMA®. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with REMSIMA® must not be given if a patient develops a serious infection or sepsis.

Caution should be exercised when considering the use of REMSIMA® in patients with chronic infection or a history of recurrent infections, including use of concomitant immunosuppressive medications. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Tumour necrosis factor alpha (TNFα) mediates inflammation and modulates cellular immune responses. Experimental data show that TNFα is essential for the clearing of intracellular infections. Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab.

It should be noted that suppression of TNFα may also mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections is critical in order to minimize delays in diagnosis and treatment.

Tuberculosis, viral infections, bacterial infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal.

Cases of active tuberculosis have occurred in patients treated with infliximab during and after treatment for latent tuberculosis. Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported in patients treated with infliximab.

Opportunistic infections reported in patients on infliximab have included, but are not limited to pneumocystosis, histoplasmosis, cytomegalovirus infection, atypical mycobacterial infections listeriosis and aspergillosis. The most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis.

Patients who develop a new infection while undergoing treatment with Remsima, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Remsima should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial and antifungal therapy should be initiated until the infection is controlled.

In clinical trials, infections have been reported more frequently in paediatric patient populations than in adult populations (see *Adverse Reactions*).

Before starting treatment with REMSIMA®, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal 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, should be performed in all patients (local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, REMSIMA® therapy must not be initiated (see *Contraindications*).

If inactive ('latent') tuberculosis is diagnosed, prophylactic anti-tuberculosis therapy must be started before the initiation of REMSIMA®, and in accordance with local recommendations. In this situation, the benefit/risk balance of REMSIMA® therapy should be very carefully considered.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of REMSIMA®. Use of anti-tuberculosis therapy should also be considered before the initiation of REMSIMA® in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Use of anti-tuberculosis therapy should be considered before the initiation of REMSIMA® in patients

who have several of 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.

For patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of REMSIMA® treatment should be carefully considered before initiation or continuation of REMSIMA® therapy.

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 systematic illness, and a physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients.

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 taking into account both the risk for severe fungal infection and the risks of antifungal therapy.

Patients with fistulising Crohn's disease with acute suppurative fistulas must not initiate REMSIMA® therapy until a source for possible infection, specifically abscess, has been excluded (see *Contraindications*).

All patients should be informed to seek medical advice if signs / symptoms suggestive of tuberculosis (e.g. persistent cough, wasting / weight loss, low-grade fever) appear during or after REMSIMA® treatment.

Concurrent Administration of TNF-alpha Inhibitor and Anakinra

Concurrent administration of etanercept (another agent that inhibits TNFα) and anakinra (a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, an increased risk of neutropenia and no additional benefit compared to these medicinal products alone.

The safety and efficacy of anakinra used in combination with infliximab has not been established. Therefore, combination of REMSIMA® and anakinra is not recommended.

Concurrent Administration of TNF-alpha Inhibitor and Abatacept

In clinical studies, concurrent administration of TNF-blocking agents and abatacept have 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 infliximab with other biological therapeutics used to treat the same conditions as infliximab. The concomitant use of infliximab with these biologics is not recommended because of the possibility of an increased risk of infection and other potential pharmacological interactions.

Switching Between Biological DMARDS

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

Vaccinations

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently. Use of live vaccines could result in clinical infections, including disseminated infections.

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

Infant exposure *in utero*

In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see *FERTILITY, PREGNANCY and LACTATION* section).

Infant exposure via breast milk

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see *FERTILITY, PREGNANCY and LACTATION*).

Therapeutic infectious agents

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

Autoimmune Processes

The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMSIMA® and is positive for antibodies against double-stranded DNA, further treatment with REMSIMA® must not be given (see *Adverse Reactions, Anti-nuclear antibodies (ANA)/Double-stranded DNA (dsDNA) antibodies*).

Neurological Events

Infliximab and other agents that inhibit TNFα have been associated seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders, including Guillian–Barre syndrome (see *Adverse Reactions*). In patients with pre-existing or recent onset of central nervous system demyelinating disorders, the benefits and risks of REMSIMA® treatment should be carefully considered before initiation of REMSIMA® therapy and should consider discontinuation of REMSIMA® if these disorders develop.

Malignancies and Lymphoproliferative Disorders

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical trials of infliximab across all approved indications, the incidence of lymphoma in infliximab-treated subjects was higher than expected in the general population, but the occurrence of lymphoma was rare. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long standing, highly active, inflammatory disease, which

complicates the risk estimation.

In an exploratory clinical trial evaluation the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Caution should be exercised in considering treatment of patients with increased risk of malignancy due to heavy smoking. With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded (see *Adverse Reactions*). Caution should be exercised when considering TNF-blocking therapy for patients with history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.

Psoriasis patients should be monitored for non-melanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment.

Pediatric Malignancy

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) who received TNF-blocking agents (initiation of therapy ≤ 18 years of age), including infliximab, to treat Juvenile Idiopathic Arthritis (JIA). Crohn's disease or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine or 6-mercaptopurine. The role of TNF blockers in the development of malignancies in children and adolescents remains unclear.

Hepatosplenic T-cell Lymphoma

Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents 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 patients 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, the need for continuing the immunosuppressant therapy should be carefully

assessed in light of the potential risks of concomitant therapy. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see *Dosage and Administration* and *Adverse Reactions*).

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before the therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. With current data it is not known if infliximab treatment influences the risk for developing dysplasia or colon cancer (see *Adverse Reactions*).

Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with REMSIMA® is not established, the risk and benefits to the individual patients must be carefully reviewed and consideration should be given to discontinuation of therapy.

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.

Skin Cancers

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

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 infliximab, including those over 60 years of age.

Heart Failure

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*).

Hepatobiliary Events

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported in post-marketing data in patients receiving infliximab. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of infliximab; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or sign of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (i.e. ≥ 5 times the upper limit of normal) develops, REMSIMA® should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab without progression to severe hepatic injury.

Hepatitis B Reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including infliximab, who are chronic carriers of this virus. Some cases have had fatal outcome. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating REMSIMA® therapy. Carriers of HBV who require treatment with REMSIMA® should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, REMSIMA® should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. Patients should be tested for Hepatitis B Virus (HBV) infection before initiating treatment with immunosuppressants, including infliximab. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Haematologic Events

Cases of leukopenia, neutropenia, thombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab. The causal relationship to infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMSIMA® who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g. persistent fever) while on REMSIMA®. Discontinuation of REMSIMA® therapy should be considered in patients who develop significant hematologic abnormalities.

Pediatrics

REMSIMA® has not been studied in patients with Crohn's disease or ulcerative colitis below the age

of 6 years.

Others

The pharmacokinetics of infliximab in elderly patients has not been studied. The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general, therefore, caution should be used in treating the elderly. Studies have not been performed in patients with liver or renal disease (see *Pharmacokinetic Properties*).

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see *Preclinical Safety Data*).

There is limited safety experience of surgical procedures in infliximab treated patients. The long half-life of infliximab should be taken into 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.

There is limited safety experience of infliximab treatment in patients who have undergone arthroplasty.

Treatment of patients with intestinal stricture due to Crohn's disease is not recommended since the risk/benefit relationship in this patient population has not been established.

Interactions

Specific drug interaction studies have not been conducted with infliximab.

In rheumatoid arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.

Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent.

The combination of REMSIMA® with other biological therapeutics used to treat the same conditions as REMSIMA®, including anakinra and abatacept, is not recommended (see *Warnings and Precautions*).

Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with infliximab. It is also recommended

that live vaccines not be given to infants after *in utero* exposure to infliximab for 12 months following birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant (see *Warnings and Precaution*).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see *Warnings and Precautions, and FERTILITY, PREGNACNY and LACTATION sections*).

It is recommended that therapeutic infectious agents not be given concurrently with infliximab (see *Warnings and Precautions*).

FERTILITY, PREGNANCY and LACTATION

Women of childbearing potential

Women of childbearing potential should consider the used of adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last infliximab treatment.

Pregnancy

The moderate number of prospectively collected pregnancies exposed to infliximab resulting in live birth with known outcomes, including approximately 1,100 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn.

Based on an observational study from Northern Europe, an increased risk (OR, 95% CI; p-value) for C-section (1.50, 1.14-1.96; p = 0.0032), preterm birth (1.48, 1.05-2.09; p = 0.024), small for gestational age (2.79, 1.54-5.04; p = 0.0007), and low birth weight (2.03, 1.41-2.94; p = 0.0002) was observed in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids, 270 pregnancies) as compared to women exposed to immunomodulators and/or corticosteroids only (6,460 pregnancies). The potential contribution of exposure to infliximab and/or the severity of the underlying disease in these outcomes remains unclear.

Due to its inhibition of TNFα, infliximab administered during pregnancy could affect normal immune responses in the newborn. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity (see *Preclinical Safety Data* Section).

The available clinical experience is limited. Infliximab should only be used during pregnancy if clearly

needed.

Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of infection, including serious disseminated infection that can become fatal. Administration of live vaccines (e.g., BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth (see WARNINGS and PRECAUTIONS, and DRUG INTERACTIONS sections). If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. Cases of agranulocytosis have also been reported (see ADVERSE EFFECTS section).

Breast-feeding

Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding.

Fertility

There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed.

Adverse Reactions

In clinical studies with infliximab, adverse drug reactions (ADRs) were observed in approximately 60% of infliximab-treated patients and 40% of placebo-treated patients. The adverse reactions listed in **Table 1** are based on experience from clinical trials. Within the organ system classes, adverse reactions are listed under the headings of frequency using the following categories: common (>1/100, <1/10); uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000). Infusion-related reactions were the most common ADRs reported. Infusion-related reactions (dyspnea, urticaria and

headache) were the most common cause for discontinuation.

Table 1

Adverse Reactions in Clinical Studies

Infections and Infestations	
Common:	Viral infection(e.g. influenza, herpes infections)
Uncommon:	Abscess, cellulitis, moniliasis, sepsis, bacterial infection, tuberculosis, fungal infection, hordeolum
Neoplasms benign, malignant and unspecified	
Uncommon:	Basal cell carcinoma, squamous cell carcinoma
Rare:	Lymphoma
Immune system disorders	
Common:	Serum sickness-like reactions
Uncommon:	Lupus-like syndrome, respiratory tract allergic reactions, anaphylactic reactions
Blood and lymphatic disorders	
Uncommon:	Anemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropoenia, thrombocytopenia
Psychiatric disorders	
Uncommon:	Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence, insomnia
Nervous system disorders	
Common:	Headache, vertigo/dizziness
Uncommon:	Exacerbation of demyelinating disease suggestive of multiple sclerosis
Rare:	Meningitis
Eye disorders	
Uncommon:	Conjunctivitis, endophthalmitis, keratoconjunctivitis, periorbital oedema
Cardiac disorders	
Uncommon:	Syncope, bradycardia, palpitation, cyanosis, arrhythmia, worsening heart failure
Rare:	Tachycardia

Vascular disorders	
Common:	Flushing
Uncommon:	Ecchymosis/hematoma, hot flushes, hypertension, hypotension, petechia, thrombophleblitis, vasospasm, peripheral ischaemia
	Circulatory failure
Rare:	
Respiratory, thoracic and mediastinal disorders	
Common:	Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, sinusitis
Uncommon:	Epistaxis, bronchospasm, pleurisy, pulmonary oedema
Rare:	Pleural effusion
Gastro-intestinal system	
Common:	Nausea, diarrhea, abdominal pain, dyspepsia
Uncommon:	Constipation, gastroesophageal reflux, cheilitis, diverticulitis
Rare:	Intestinal perforation, intestinal stenosis, gastrointestinal hemorrhage
Hepatobiliary disorders	
Common:	Abnormal hepatic function, cholecystitis
Rare:	Hepatitis
Skin and subcutaneous tissue disorders	
Common:	Rash, pruritus, urticaria, increased sweating, dry skin
Uncommon:	Fungal dermatitis/ onychomycosis, eczema/ seborrhea, bullous eruption, furunculosis, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/coloration, alopocia
Musculoskeletal and connective tissue disorders	
Uncommon:	Myalgia, arthralgia, back pain
Renal and urinary disorders	
Uncommon:	Urinary tract infection, pyelonephritis
Reproductive system and breast disorders	
Uncommon:	Vaginitis
General disorders and administration site conditions	
Common:	Fatigue, chest pain, infusion-related reactions, fever
Uncommon:	Injection site reactions, oedema, pain, chills/rigors, impaired healing
	Granulomatous lesion
Rare:	

Investigations	
Common:	Elevated hepatic transaminases
Uncommon:	Autoantibodies, complement factor abnormality

Table 2

Adverse Reactions in Post-marketing reports

(common > 1/100, <1/10; uncommon >1/1000, < 1/100; rare >1/10,000, <1/1000, very rare <1/10,000, including isolated reports)

Nervous system disorders	
Rare:	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, tingling, seizure, cerebrovascular accidents occurring within approximately 24 hours of initiation of infusion
Very rare:	Transverse myelitis
Blood and lymphatic system disorders	
Rare:	Pancytopenia
Very rare:	Hemolytic anemia, idiopathic thrombocytopenia purpura, thrombotic thrombocytopenic purpura, agranulocytosis (including infants exposed *in utero* to infliximab)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare:	Hepatosplenic T-cell lymphoma (the vast majority in Crohn's Disease and ulcerative colitis: primarily in adolescent and young adults), lymphoma (including non-Hodgkin's lymphoma and Hodgkin's Disease), leukemia, melanoma, cervical cancer
Very Rare:	Pediatric malignancy, Merkel cell carcinoma
Immune system disorders	
Uncommon:	Anaphylactic reactions
Rare:	Anaphylactic shock, serum sickness, vasculitis, sarcoid-like reaction
Cardiac disorders	
Rare:	Worsening heart failure, new onset heart failure
Very rare:	Pericardial effusion

Infections and infestations	
Rare:	Opportunistic infections (such as tuberculosis, atypical mycobacteria, pneumocystis carinii pneumonia (PCP), pneumocystosis, histoplasmosis, coccidiodomycosis, aspergillosis, listeriosis and candidiasis, cryptococcosis)
Very rare:	Salmonellosis, hepatitis B reactivation, protozoal infection, and vaccine breakthrough infection (after *in utero* exposure to infliximab)*
Respiratory, thoracic and mediastinal disorders	
Rare:	Interstitial lung disease, including pulmonary fibrosis/ interstitial pneumonitis
Very rare:	Rapidly progressive interstitial lung disease
Gastrointestinal disorders	
Rare:	Pancreatitis
Hepatobiliary disorders	
Rare:	Hepatitis
Very rare:	Hepatocellular damage, jaundice, autoimmune hepatitis, liver failure
Skin and subcutaneous tissue disorders	
Rare:	Vasculitis (primarily cutaneous), acute generalized exanthematous pustulosis (AGEP)
Very rare:	Toxic epidermal necrolysis, Stevens-Johnson-Syndrome, erythema multiforme, psoriasis, including new onset and pustular (primarily palmar/plantar), linear IgA bullous dermatosis (LABD), lichenoid reactions
General disorders and administration site conditions	
Common:	Infusion-related reactions

* Including bovine tuberculosis (disseminated BCG infection), see *Precautions*

Transient visual loss occurring during or within 2 hours of infliximab infusion have also been reported.

Myocardial ischemia/myocardial infarction and arrhythmia within 24 hours of initiation of infusion have also been reported.

Infusion-Related Reactions

An infusion-related 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 compared with 5% of placebo-treated patients experienced an infusion-related reaction. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period, week 7 through week 54. 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 treatment due to infusion-related reactions, and all patients recovered with or without medical therapy.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), study medication was administered to each patient by infusion over 2 hours for the first 3 study infusions. For patients who did not experience a serious infusion reaction with the first 3 study infusions, subsequent infusions could be shortened to not less than 40 minutes. Sixty six percent of the 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, infusion-related reactions occurred in 15% (74/494) of patients and serious infusion reactions occurred in 0.4% (2/494) of patients. Shortened infusions at doses > 6 mg/kg have not been studied.

In Phase 3 clinical studies, in patients receiving infliximab with or without concomitant immunomodulator therapy, 13-19% of patients receiving infliximab at a low infusion rate (≤ 6 mg/kg/2-hr) experienced an infusion-related reaction, compared to 15-16% of patients receiving infliximab at a high infusion rate (> 6 mg/kg/2-hr or equivalent to >3 mg/kg/1-hr). Of patients receiving infliximab at a low infusion rate, 0.4%-0.7% experienced a serious infusion-related reaction, compared to 0.4%-0.5% of patients receiving infliximab at a high infusion rate.

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving infliximab monotherapy, 5.0% (9/179) of patients receiving infliximab in combination with azathioprine, and 5.6% (9/161) of patients receiving azathioprine monotherapy. One patient experienced a serious infusion reaction with infliximab monotherapy.

In post-marketing surveillance, reports of anaphylactic-like reactions, including laryngeal/pharyngeal edema, severe bronchospasm, and seizure have been associated with infliximab administration. Cases of transient visual loss occurring during or within 2 hours of infliximab infusion have been reported. Cerebrovascular accidents, myocardial ischemia/myocardial infarction (some fatal), and arrhythmia occurring within 24 hours of initiation of infusion have also been reported.

Infusion reactions following re-administration of infliximab: In rheumatoid arthritis, Crohn's disease

and psoriasis clinical trials, re-administration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment.

A clinical study in patients with moderate to severe psoriasis was designed to assess the efficacy and safety of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab (maximum of four infusions at 0, 2, 6 and 14 weeks) following disease flare. Patients did not receive any concomitant immunosuppressant therapy. In the re-treatment arm, 4% (8/219) of patients experienced a serious infusion reaction versus <1% (1/222) on maintenance therapy. The majority of serious infusion reactions occurred during the second infusion at Week 2. The interval between the last maintenance dose and the first re-induction dose ranged from 35-231 days. Symptoms included, but were not limited to, dyspnea, urticaria, facial oedema, and hypotension. In all cases, infliximab treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Hypersensitivity

In a clinical study of 41 patients retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. No similar set of delayed adverse events has been observed in any other clinical study involving a total of 771 patients receiving 4749 infusions with intervals predominantly of 14 weeks or less, but ranging from 1 to 55 weeks. In ongoing studies and post-marketing reports, these events have been rare and have occurred at intervals of less than 1 year.

In a 1-year trial with repeated infusions in patients with Crohn's disease (ACCENT I study), the incidence of serum sickness-like reactions was 2.4%.

Immunogenicity

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion-related reactions.

In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 140 of 980 (14%) patients with any immunosuppressant therapy, and in 92 of 383 (24%) patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 6 of 77 (8%) patients developed antibodies to infliximab. In Crohn's disease patients who received maintenance treatment, antibodies to infliximab occurred overall in 3.3% of patients receiving immunosuppressants and in 13.3% of patients not receiving immunosuppressants. The antibody

incidence was 2-3 folds higher for patients treated episodically. Due to methodological limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy (see *Warnings and Precautions: "Infusion Reactions and Hypersensitivity"*). In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab.

Infections

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal infections, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal. Opportunistic infections reported in patients on infliximab have included, but are not limited to pneumocystosis, histoplasmosis, cytomegalovirus infection, atypical mycobacterial infections, listeriosis and aspergillosis. The most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis. (see *Warnings and Precautions*)

In clinical studies 36% of infliximab-treated patients experienced infections compared with 25% of placebo-treated patients.

In RA trials, the incidence of serious infections including pneumonia was higher in infliximab plus methotrexate treated patients compared with methotrexate alone especially at doses of 6 mg/kg or greater (see *Warnings and Precautions*).

In post-marketing spontaneous reporting, infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Nearly 50% of reported deaths have been associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported (see *Warnings and Precautions*).

Malignancies and Lymphoproliferative Disorders

In clinical studies with infliximab in which 5706 patients were treated, representing 4990 patient years, 5 cases of lymphomas and 24 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non-lymphoma malignancy in 1600 placebo-treated patients representing 892 patients years.

In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6234 patients-years (3210 patients), 5 cases of lymphoma and 38 cases of non-lymphoma malignancies were reported.

From August 1998 to August 2005, 1909 cases of suspected malignancies have been reported from

post marketing, clinical trials and registries (321 in Crohn's disease patients, 1302 in rheumatoid arthritis patient and 286 in patients with other or unknown indication). Among those there were 347 lymphoma cases. During this period, the estimated exposure is 1,909,941 patient years since first exposure (see *Warning and Precautions - "Malignancies"*).

In an explanatory clinical trial involving patients with moderate to severe COPD who were either current smoker or ex-smokers, 157 patients were treated with infliximab at doses similar to those used in RA and Crohn's disease. Nine of these patients developed malignancies, including 1 lymphoma. The median duration of follow-up was 0.8 years (incidence 5.7% [95% CI 2.65%-10.6%]. There was one reported malignancy amongst 77 control patients (median duration of follow-up 0.8 years; incidence 1.3% [95% CI 0.03%-7.0%]. The majority of the malignancies developed in the lung or head and neck.

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 treated with infliximab, the majority and most of whom were adolescent or young adult males(see *Warnings and Precautions, Malignancies, Lymphoma*).

Heart failure

In a phase II study aimed at evaluating infliximab in congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure were seen in patients treated with infliximab, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this trial, 150 patients with NYHA Class Ⅲ-IV CHF (left ventricular ejection fraction ≤35%) were treated with 3 infusions of infliximab 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Antinuclear Antibodies (ANA)/Anti-Double-Stranded DNA (dsDNA) Antibodies

In clinical studies, approximately half of infliximab-treated patients who were ANA negative at baseline developed a positive ANA during the trial (compared with approximately one-fifth placebo-treated patients). Anti-dsDNA antibodies developed in approximately 17% of patients treated with infliximab (compared with 0% of placebo-treated patients). At the last evaluation, 57% infliximab-treated patients remained anti-dsDNA positive. Clinical signs consistent with a lupus-like syndrome remained uncommon.

Hepatobiliary Events

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 ALT 5 x Upper Limit of Normal (ULN) have been observed (see **Table 3**). 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.

In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see *Warnings and Precautions*).

Table 3

Proportion of patients with increased ALT activity in Clinical Trials

indication	Number of Patients[3]		Median follow-up (wks)[4]		Proportion of patients with increased ALT			
					≥3xULN		≥5xULN	
	Placebo	Infliximab	Placebo	Infliximab	Placebo	Infliximab	Placebo	infliximab
Rheumatoid arthritis[1]	375	1087	58.1	58.3	3.2%	3.9%	0.8%	0.9%
Crohn's disease[2]	324	1034	53.7	54.0	2.2%	4.9%	0.0%	1.5%
Pediatric Crohn's disease	N/A	139	N/A	53.0	N/A	4.4%	N/A	1.5%
Ulcerative colitis	242	482	30.1	30.8	1.2 %	2.5%	0.4%	0.6%
Pediatric Ulcerative colitis	N/A	60	N/A	49.4	N/A	6.7%	N/A	1.7%
Ankylosing spondylitis	76	275	24.1	101.9	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	0.0%	6.8%	0.0%	2.1%
Plaque psoriasis	281	1175	16.1	50.1	0.4%	7.7%	0.0%	3.4%

[1] Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.

[2] Placebo patients in the 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. Patient who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase IIIb trial in Crohn's disease, SONIC, placebo patients received AZA 2.5 mg/kg/day in addition to placebo infusions.

[3] Number of patients evaluated for ALT.

[4] Median follow-up is based on patients treated.

Special Populations

Pediatrics

Pediatric Crohn's Disease Patients

The following adverse events were reported more commonly in pediatric Crohn's disease patients in the REACH trial (see section 5.1) than in adult Crohn's disease patients; anemia (10.7%), blood in stool (9.7%), leukopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bone fracture (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8 %). Other special considerations are discussed below;

Infusion-Related Reactions

Overall, in REACH, 17.5% of randomised patients experienced 1 or more infusion reactions. There were no serious infusion reactions, and 2 subjects in REACH had non-serious anaphylactic reactions.

Immunogenicity

Antibodies to infliximab were detected in 3 (2.9%) pediatric patients.

Infections

In the REACH trial, infections were reported in 56.3% of randomised subjects treated with infliximab. Infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73.6% and 38.0%) respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Three cases of pneumonia (1 serious) and 2 cases of herpes zoster (both non-serious) were reported.

Pediatric Ulcerative Colitis Patients

Overall proportions of patients with adverse events and serious adverse events were generally consistent in the pediatric ulcerative colitis and adult ulcerative colitis (ACT 1 and ACT 2) studies. In the pediatric ulcerative colitis study (Study Peds UC), the most common adverse event was worsening of ulcerative colitis which was greater in patients on the q12 week vs. the q8 week dosing regimen. In the ACT1 and ACT 2 studies, the most common adverse event was headache. The most common serious adverse event across these three studies was worsening of the disease under study.

Infections were reported in 31 (51.7%) of 60 treated patients in Study Peds UC and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in Study Peds UC was similar to that in the pediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). Unlike REACH, in which infections were reported more frequently for patients who received q8 week as opposed to q12 week infusions; in Study Peds UC, the overall incidence of infections was similar in the q8 week (13/22 [59.1%]) and q12 week (14/23 [60.9%]) maintenance treatment groups. In Study Peds UC, serious infections were reported for 3 of 22 (13.6%) patients in the q8 week and 3 of 23 (13.0%) patients in the q12 week maintenance treatment group. Upper respiratory tract infection (7/60 [11.7%]) and pharyngitis (5/60 [8.3%]) were the most frequently reported respiratory system infections among all treated patients. The infections occurring in more than one patient in a treatment group that required antimicrobial treatment were pharyngitis (4/60 [6.7%]), urinary tract infection (4/60 [6.7%]), and bronchitis (2/60 [3.3%]).

Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the q8 week and 3 of 23 (13.0%) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

Antibodies to infliximab were detected in 4 (7.7%) patients through week 54.

In Study Peds UC, there were more patients in the 12 to 17 year age group than in the 6 to 11 year age group (45/60 [75.0%] vs.15/60 [25.0%]). While the numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on safety events, there were higher proportions of patients with serious adverse events and discontinuation due to adverse events in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group, for serious infections, the proportions were similar in the two age groups. Overall proportions of adverse events and infusion reactions were similar between the 6 to 11 and 12 to 17 year age groups.

Post-Marketing Experience

Post-marketing spontaneous serious adverse events with infliximab in the paediatric population have included malignancies including hepatosplenic T-cell lymphomas, transient hepatic enzyme abnormalities, lupus-like syndrome, and positive autoantibodies (see *Warnings and Precautions, and Adverse Reactions, Malignancies and Lymphoproliferative Disorders*).

Frequency unknown

Basal cell carcinoma, squamous cell carcinoma

Overdose

Single doses up to 20mg/kg have been administered without toxic effects. There is no clinical experience of overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic Group

Pharmacotherapeutic group: immunosuppressants, tumour necrosis factor alpha (TNF_{α}) inhibitors, ATC code: L04AB02.

Pharmacodynamic Properties

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNFα but not to lymphotoxin α (TNFβ). Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity.

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joints as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP) compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalization of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, short term treatment with infliximab reduced the number of T-cells and blood vessels in the synovium and psoriatic skin.

Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable TNFα. Infliximab treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, CRP. Total peripheral white blood cell counts were minimally affected in infliximab-treated patients, although changes in lymphocytes, monocytes and neutrophils reflected shifts towards normal ranges. Peripheral blood mononuclear cells (PBMC) from infliximab-treated patients showed undiminished proliferative responsiveness to stimuli compared with untreated patients, and no substantial changes in cytokine production by stimulated PBMC were observed following treatment with infliximab. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that infliximab treatment caused a reduction in the number of cells

capable of expressing TNFα and interferon γ. Additional histological studies provided evidence that treatment with infliximab reduces the infiltration of inflammatory cells into affected areas of the intestine and the presence of inflammation markets at these sites.

Clinical Trials

REMSIMA® is a biosimilar medicinal product.

The clinical development programme to show biosimilarity between REMSIMA® and the reference product is based on

- a pivotal Phase 3 equivalent efficacy and safety study (CT-P13 3.1) in 606 patients with rheumatoid arthritis (RA) of which 302 patients received REMSIMA®.
- a pivotal equivalent pharmacokinetics (PK) phase 1 study (CT-P13 1.1) in 250 patients with ankylosing spondylitis (AS) of which 125 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.

The post authorization clinical trial to show noninferiority of REMSIMA® compared to the reference product is based on

- a phase 3 study to demonstrate noninferiority in efficacy and to assess safety of REMSIMA® compared to REMICADE® (CT-P13 3.4) in 220 patients with active crohn's disease (CD) of which 166 patients received REMSIMA®

A summary of the design and subject demographics of the studies is presented in **Table 4**.

Table 4: Patient demographics and study design

STUDY	Design	Dosage, route of administration and duration	Number of patients	Mean age (range)	Gender and Race n (%)
CT-P13 1.1	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

CT-P13 3.1	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
CT-P13 3.4	Prospective Phase 3, randomized, double blind, multicenter, multiple-dose IV infusion, parallel-group study to demonstrate noninferiority in patients with	REMSIMA®,EU-approved REMICADE® or US-lisenced REMICADE® (5 mg/kg) administered as 2h IV infusion ; at Weeks 0, 2, 6, then every 8	220	35.7 (18 to 69)	123 (55.9%) male 97 (44.1%) female 165 (75.0%) White 54 (24.5%) Asian 1 (0.5%) Other

	active crohn's disease	weeks up to 54 weeks Patients with active CD were randomly assigned in a 1:1:1:1 ratio to one of four treatment groups; Total N= 220; - REMSIMA® followed by REMSIMA® at Week 30 - REMSIMA® followed by REMICADE® at Week 30 - REMICADE® followed by REMICADE® at Week 30 - REMICADE® followed REMSIMA® at Week 30			

Comparative Pharmacokinetic Studies

Pivotal Pharmacokinetic Study CT-P13 1.1

CT-P13 1.1 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 5**. 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 5: Serum Pharmacokinetic Parameters of the PK Population between Week 22 and 30 (Study CT-P13 1.1 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, $C_{max,ss}$, $C_{min,ss}$ and $T_{1/2}$ 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 6**.

Table 6: Mean (CV) Serum Pharmacokinetic Parameters of Infliximab for Injection: Pharmacokinetic Population (Study CT-P13 1.1 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)				
C_{max} *(µg/mL)*	n=113	158 (24.0)	n=110	154 (27.5)
C_{min} *(µg/mL)*	n=112	4.50 (83.6)	n=110	4.80 (75.2)
T_{max} *(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 CT-P13 3.1

CT-P13 3.1 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 7: Geometric mean (%CV) of Infliximab for Injection at Week 30 (PK population) – Study CT-P13 3.1 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; T_{MAX}=Time to reach C_{MAX};

*T_{max} was reported as median (minimum, maximum)

Table 8: Geometric mean (%CV) of Infliximab for Injection at Week 54 (PK population) – Study CT-P13 3.1 in Rheumatoid Arthritis

Parameter	REMSIMA ®	REMICADE®

	(3 mg/kg) (n=290)	(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 $C_{MAX;}$

*T_{max} was reported as median (minimum, maximum)

Study CT-P13 1.1 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, C_{max}, C_{min}, 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.

Supportive Pharmacokinetic Study CT-P13 3.4

CT-P13 3.4 is a Randomized, Double-Blind, Parallel-Group, Phase 3 Study to Demonstrate Noninferiority in Efficacy and to Assess Safety of CT-P13 Compared to REMICADE® in Patients with Active Crohn's Disease. Total 220 male or female patients with active CD were randomly assigned in a 1:1:1:1 ratio to one of four treatment groups in this study; Group 1: REMSIMA® followed by REMSIMA® from Week 30 (REMSIMA® – REMSIMA®), Group 2: REMSIMA® followed by REMICADE® from Week 30 (REMSIMA® – REMICADE®), Group 3: REMICADE® followed by REMICADE® from Week 30 (REMICADE® – REMICADE®), Group 4: REMICADE® followed by CT-P13 from Week 30 (REMICADE® –REMSIMA®). One of the tertiary objectives was to evaluate the pharmacokinetics of REMSIMA® in comparison with REMICADE® reference product up to Week 22.

The PK population consisted of all patients who receive at least 1 dose (full) of study drug and had at least 1 post-treatment PK concentration data value. Pharmacokinetic samples were collected on dosing days prior to the beginning of the study drug infusion and within 15 minutes after the end of the study drug infusion up to Dose 5. At Week 22, PK samples were collected on dosing day only prior to the beginning of the study drug infusion.

Table 9 : Mean (SD) Peak and Trough Descriptive Statistics of Serum Concentrations of Infliximab (PK population) - Study CT-P13 3.4 in crohn's disease.

Parameter	REMSIMA® (5 mg/kg) (N=111)	REMICADE® (5mg/kg) (N=109)

C_{max} (µg/mL)				
Week 0	n=111	105.6 (41.92)	n=109	94.05 (36.99)
Week 2	n=109	118.6 (37.68)	n=107	119.5 (40.64)
Week 6	n=106	118.1 (52.36)	n=106	121.3 (57.02)
Week 14	n=102	120.9 (55.02)	n=98	121.4 (68.32)
C_{trough} (µg/mL)				
Week 0	n=108	30.42 (45.36)	n=107	22.48 (9.02)
Week 2	n=106	17.18 (17.03)	n=107	16.56 (19.68)
Week 6	n=101	4.68 (3.72)	n=98	5.56 (8.62)
Week 14	n=96	5.46 (14.12)	n=92	3.07 (2.92)

REMSIMA®=REMSIMA®–REMSIMA® and REMSIMA®–REMICADE® treatment group

REMICADE®= REMICADE®–REMICADE® and REMICADE®–REMSIMA® treatment group

C_{max}=observed maximum serum concentration between the end of one infusion and the start of the next infusion

C_{trough}=Trough concentration immediately before the next infusion

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 7** and **Table 8**.

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 CT-P13 3.1 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 CT-P13 3.1 (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 CT-P13 3.1 (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 (REMSIMA® – REMICADE®) using the exact binomial test.

Safety (RA)

In Study CT-P13 3.1, 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 CT-P13 1.1 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)
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.

Safety (AS)

In CT-P13 1.1 (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.

Efficacy (CD)

The primary objective of CT-P13 3.4 was to demonstrate that REMSIMA® is noninferior to REMICADE® at Week 6, in terms of efficacy, as determined by the crohn's disease activity index (CDAI)-70 response rate.

The primary efficacy endpoint (the proportion of patients achieving clinical response according to the CDAI-70 criteria at Week 6) is summarized for the all-randomized population in **Table 14**.

Table 14 : Proportion of Patients Achieving CDAI–70 response at Week 6 – Study CT-P13 3.4 in active CD patients: All-Randomized Population

Treatment group	n/N (%)	Estimate of treatment difference	Lower bound of 95% CI of treatment difference
REMSIMA®	77/111 (69.4)	-4.9	-17.0
REMICADE®	81/109 (74.3)		

REMSIMA®=REMSIMA®–REMSIMA® and REMSIMA®–REMICADE® treatment group; REMICADE®= REMICADE®–REMICADE® and REMICADE®–REMSIMA® treatment group

CDAI=Crohn's disease activity index, CI=Confidence interval, n=the number of patients with a response; N=Number of all patients in each group

The proportion of patients achieving CDAI-70 response in the REMSIMA® treatment group was noninferior to that in the REMICADE® treatment group in the all randomized population (77 [69.4%] patients and 81 [74.3%] patients in the REMSIMA® and REMICADE® treatment groups, respectively). The treatment difference estimates using exact binomial method were -4.9% (lower bound of 95% CI, -17.0) in the all randomized population.

The proportion of patients achieving clinical remission, and CDAI-100 responses at weeks 6, 14, 30, and 54, as well as CDAI-70 response at Week 14, 30, and 54 are compared between REMSIMA® and the referenced product are summarized for the all-randomized population in **Table 15** and **Table 16**.

Table 15 : Proportion of Patients Achieving Clinical Response According to CDAI-100 at Weeks 6, 14, 30 and 54, as well as CDAI-70 at Weeks 14, 30 and 54 – Study CT-P13 3.4: All-Randomized Population

	n/N (%)			
	REMSIMA® – REMSIMA®	**REMSIMA® – REMICADE®**	**REMICADE® – REMICADE®**	**REMICADE® – REMSIMA®**
CDAI-70 at Week 14	96/111 (86.5)		96/109 (88.1)	
CDAI-70 at Week 30	85/111 (76.6)		82/109 (75.2)	
CDAI-70 at Week 54	44/56 (78.6)	39/55 (70.9)	38/54 (70.4)	42/55 (76.4)
CDAI-100 at Week 6	67/111 (60.4)		70/109 (64.2)	
CDAI-100 at Week 14	78/111 (70.3)		83/109 (76.1)	
CDAI-100 at Week 30	80/111 (72.1)		80/109 (73.4)	
CDAI-100 at Week 54	43/56 (76.8)	38/55 (69.1)	34/54 (63.0)	41/55 (74.5)

CDAI=Crohn's disease activity index, CI=Confidence interval, n=the number of patients with a response; N=Number of all patients in this group.

Table 16 : Proportion of Patients Achieving clinical remission at Weeks 6, 14, 30 and 54 – Study CT-P13 3.4: All-Randomized Population

	n/N (%)			
	REMSIMA® – REMSIMA®	**REMSIMA® – REMICADE®**	**REMICADE® – REMICADE®**	**REMICADE® – REMSIMA®**
Remission at Week 6	47/111 (42.3)		49/109 (45.0)	
Remission at Week 14	59/111 (53.2)		60/109 (55.0)	
Remission at Week 30	61/111 (55.0)		62/109 (56.9)	
Remission at Week 54	35/56 (62.5)	32/55 (58.2)	29/54 (53.7)	33/55 (60.0)

CDAI=Crohn's disease activity index, CI=Confidence interval, n=the number of patients with a response; N=Number of all patients in this group

Clinical Remission is defined as an absolute CDAI score of less than 150 points.

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 for Injection 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 for Injection 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 17** and **Table 18**. The number of patients with positive immunogenicity test results was examined in each treatment group at each time point in the two studies.

Table 17: Summary of Immunogenicity Testing: Safety Population - CT-P13 1.1 in Ankylosing Spondylitis

	REMSIMA® 5 mg/kg (N=128) n (%)	**REMICADE® 5 mg/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)

	REMSIMA® 5 mg/kg (N=128) n (%)	REMICADE® 5 mg/kg (N=122) n (%)	Total (N=250) n (%)
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 18: Summary of Immunogenicity Testing - Safety Population - CT-P13 3.1

	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 CT-P13 1.1) in **Table 19**. ADA titre data for rheumatoid arthritis (RA) patients receiving the 3 mg/kg dose of REMSIMA® or REMICADE® (Study CT-P13 3.1) are provided in **Table 20**.

Table 19: Descriptive Statistics of Anti-Drug Antibody (ADA) Titre in Study CT-P13 1.1 (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

Visit	Statistic	REMSIMA® 5 mg/kg (N=128)	REMICADE® 5 mg/kg (N=122)	Total (N=250)
	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 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.

Table 20: Descriptive Statistics of Anti-Drug Antibody (ADA) Titre in Study CT-P13 3.1 (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
	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 CT-P13 1.1 and Study CT-P13 3.1, 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 21** for Study CT-P13 1.1. For Study CT-P13 3.1, the data for ADA titre by category are provided in **Table 22**.

Table 21: Distribution of Patients per ADA Titre Category Administered either 5 mg/kg REMSIMA® or REMICADE® in Study CT-P13 1.1 (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%)
	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 22 : Distribution of Patients per Anti-Drug Antibody (ADA) Titre Category Administered either 3 mg/kg REMSIMA® or REMICADE® in Study CT-P13 3.1 (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 REMSIMA® 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.

Safety (CD)

In CT-P13 3.4 (Crohn's disease) study, the proportion of patients who experienced at least 1 TEAE was similar between the 4 treatment groups (36 [64.3%], 34[68.5%], 37[68.5%], and 40[72.7%] in the C-C, C-R, R-R, and R-C treatment groups respectively). The most frequently reported TEAEs were abdominal pain (5.4%, 16.4%, 9.3% and 7.3%), anemia (8.9%, 9.1%, 9.3% and 7.3%), infusion-related reaction (Before drug switching, 7.2% and 8.3% in CT-P13 and REMICADE® treatment groups. Over 1 year, 14.3%, 3.6%, 9.3% and 7.3% in C-C, C-R, R-R and R-C treatment groups respectively), and arthralgia (5.4%, 1.8%, 7.4% and 7.3%). The majority of TEAEs were considered by the investigator to be unrelated to the study drug. Treatment-emergent AEs considered by the investigator to be related to study drug were reported for 17 (30.4%), 12 (21.8%), 17 (31.5%), and 17 (30.9%) patients in the C-C, C-R, R-R, and R-C treatment groups, respectively. Treatment-emergent AEs leading to permanent discontinuation of study drug were reported for 3 (5.4%), 3 (5.5%), 3 (5.6%), and 3 (5.5%) patient in the C-C, C-R, R-R, and R-C treatment groups, respectively. No deaths or malignancy were reported during the study. Overall, REMSIMA® was well tolerated and the safety profile of REMSIMA® was similar to that of REMICADE®.

Psoriatic Arthritis, Plaque Psoriasis and Ulcerative Colitis

Randomized clinical trials have not been conducted to compare REMSIMA® and REMICADE® in psoriatic arthritis, plaque psoriasis, 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, and ulcerative colitis is based on the demonstrated comparability, in terms of product quality, non-clinical, human pharmacokinetic, and clinical characteristics.

Clinical Efficacy

Rheumatoid Arthritis

The efficacy of infliximab was assessed in two multicentre, randomised, double-blind, pivotal trials: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs were permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College Rheumatology criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of following 5 criteria: (1) evaluator's global assessment, (2) patient's global assessment, (3) functional/disability measure, (4) visual analogue pain scale and (5) erythrocyte sedimentation rate or C-reactive protein. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percent improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ, scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function.

The ATTRACT trial evaluated responses at 30, 54 and 102 weeks in a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate. Approximately 50% of patients were in functional Class III. Patients received placebo, 3 mg/kg or 10 mg/kg infliximab at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter. All patients were on stable methotrexate doses (median 15 mg/wk) for 6 months prior to enrolment and were to remain on stable doses throughout the study.

Results from week 54 (ACR20, HAQ and total van der Heijde-modified Sharp score) are shown in **Table 23**. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (**Table 23**).

The effects observed at 54 weeks were maintained through 102 weeks. Due to a number of treatment withdrawals, the magnitude of the effect difference between infliximab and the methotrexate alone group cannot be defined.

Table 23

Effects on ACR20, Structural Joint Damage and Physical Function at week 54

		infliximab[b]				
	Control[a]	**3 mg/kg q8wks**	**3 mg/kg q4wks**	**10 mg/kg q8wks**	**10 mg/kg q4wks**	**All infliximab[b]**
Patients with ACR20 response/ patients evaluated(%)[c]	15/88 (17%)	36/86 (42%)	41/86 (48%)	51/87 (59%)	48/81 (59%)	176/340 (52%)
Total score[d] (van der Heijde-modified Sharp score)						
Change from baseline (Mean± SD[C])	7.0±10.3	1.3±6.0	1.6±8.5	0.2±3.6	-0.7±3.8	0.6±5.9
Median[c] (interquartile range)	4.0 (0.5,9.7)	0.5 (-1.5,3.0)	0.1 (-2.5,3.0)	0.5 (-1.5,2.0)	-0.5 (-3.0,1.5)	0.0 (-1.8,2.0)
patients with no deterioration/ patients evaluated (%)[c]	13/64 (20%)	34/71 (48%)	35/71 (49%)	37/77 (48%)	44/66 (67%)	150/285 (53%)
HAQ change from base line over time[e] (patients evaluated)	87	86	85	87	81	339
Mean±SD[C]	0.2±0.3	0.4±0.3	0.5±0.4	0.5±0.5	0.4±0.4	0.4±0.4

a: control= All patients had active RA despite treatment with stable methotrexate doses for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs was permitted, and folate supplementation was given.

b: all infliximab doses given in combination with methotrexate and folate with some on corticosteroids and/or non-steroidal anti-inflammatory drugs

c: p< 0.001, for each infliximab treatment group vs. control

d: greater values indicate more joint damage

e: HAQ=Health Assessment Questionnaire; greater values indicate less disability.

The ASPIRE trial evaluated responses at 54 weeks in 1004 methotrexate naïve patients with early (≤ 3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (optimized to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8

weeks thereafter. Results from week 54 are shown in **Table 24**.

After 54 weeks of treatment, both doses of infliximab + methotrexate resulted in statistically significantly greater improvement in signs and symptoms compared to methotrexate alone as measured by the proportion of patients achieving ACR20, 50 and 70 responses.

In ASPIRE, more than 90% of patients had at least two evaluable X-rays. Reduction in the rate of progression of structure damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone.

Table 24

Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE

	Infliximab + MTX			
	Placebo + MTX	**3 mg/kg**	**6 mg/kg**	**Combined**
Subjects randomized	282	359	363	722
Percentage ACR improvement				
Mean ± SD[a]	24.8±59.7	37.3±52.8	42.0±47.3	39.6±50.1
Change from baseline in total van der Heijde modified Sharp score[b]				
Mean ± SD[a]	3.70±9.61	0.42±5.82	0.51±5.55	0.46±5.68
Median	0.43	0.00	0.00	0.00
Improvement from baseline in HAQ averaged over time from week 30 to week 54[c]				
Mean ± SD[d]	0.68±0.63	0.80±0.65	0.88±0.65	0.84±0.65

a: p< 0.001, for each infliximab treatment group vs. control

b: greater values indicate more joint damage.

c: HAQ= Health Assessment Questionnaire; greater values indicate less disability.

d: p= 0.030 and < 0.001 for the 3 mg/kg and 6 mg/kg treatment groups respectively vs. placebo + MTX

Adult Crohn's Disease

Induction Treatment in Moderately to Severely Active Crohn's Disease

The efficacy of a single does treatment with infliximab was assessed in 108 patients with active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥220≤400) in a randomized, double-blinded, placebo-controlled, close-response study. Of these 108 patients, 27 were treated with the recommended dosage of infliximab 5 mg/kg. All patients had experienced an inadequate response to prior conventional therapies. Concurrent use of stable doses of conventional therapies was permitted, and 92% of patients continued to receive these medications.

The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥ 70 points from baseline at the 4-week evaluation and without an

increase in Crohn's disease medications or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients in clinical remission at week 4 (CDAI <150) and clinical response over time.

At week 4, following a singles dose of study medication, 22/27 (81%) of infliximab-treated patients receiving a 5 mg/kg dose achieved a clinical response vs. 4/25 (16%) of the placebo-treated patients ($p < 0.001$). Also at week 4, 13/27 (48%) of infliximab-treated patients achieved a clinical remission (CDAI<150) vs. 1/25 (4%) of placebo-treated patients. A response was observed within 2 weeks, with a maximum response at 4 weeks. At the last observation at 12 weeks, 13/27 (48%) of infliximab-treated patients were still responding.

Maintenance treatment in Moderately to Severely active Crohn's disease
The efficacy of repeated infusions with infliximab was studied in a 1- year clinical study.

A total of 573 patients with active Crohn's disease (DCAI ≥220≤ 400) received a single infusion of 5 mg/kg at week0. Sixty-eight of these patients (12%) belonged to the population defined in the indication (see *Indications).* Three hundred and thirty-five patients (58%) responding to the 5 mg/kg infusion at week 2 were randomized to one of three treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group, receiving repeated infusions at week 2, 6, and every eight weeks.

At week 30, a significantly greater proportion of patients in the combined infliximab maintenance treatment group (42%) achieved clinical remission, compared with patients in the placebo maintenance group (21%). Median time to loss of response was 46 weeks in the combined infliximab maintenance treatment group vs. 19 weeks in the placebo maintenance group ($p<0.001$). Similar results were obtained in the subgroup analyses of the population defined in the indication (see *Indications*).

Improvements in quality of life measures were seen for both the IBDQ and SF-36 scores in the infliximab maintenance groups compared with the placebo maintenance group at week 30 ($p < 0.001$).

Infliximab with or without AZA was assessed in a randomized, double-blind, active comparator study (SONIC) of 508 adult patients with moderate to severe Crohn's disease (CDAI · 220 · 450) who were naive to biologics and immunosuppressants and had a median disease duration of 2.3 years. At baseline 27.4% of patients were receiving systemic corticosteroids, 14.2% of patients were receiving budesonide, and 54.3% of patients were receiving 5-ASA compounds. Patients were randomized to receive AZA monotherapy, infliximab monotherapy, or infliximab plus AZA combination therapy. Infliximab was administered at a dose of 5 mg/kg at weeks 0, 2, 6, and then

every 8 weeks. AZA was given at a dose of 2.5 mg/kg daily.

The primary endpoint of the study was corticosteroid-free clinical remission at Week 26, defined as patients in clinical remission (CDAI of <150) who, for at least 3 weeks, had not taken oral systemic corticosteroids (prednisone or equivalent) or budesonide at a dose > 6 mg/day. For results see **Table 25**. The proportions of patients with mucosal healing at Week 26 were significantly greater in the infliximab plus AZA combination (43.9%, p<0.001) and infliximab monotherapy groups (30.1%, p=0.023) compared to the AZA monotherapy group (16.5%).

Table 25

Percent of patients achieving corticosteroid-free clinical remission at Week 26, SONIC

	AZA Monotherapy	Infliximab Monotherapy	Infliximab + AZA Combination Therapy
Week 26			
All randomized patients	30.0% (51/170)	44.4% (75/169) (p=0.006)*	56.8% (96/169) (p<0.001)*

* P-values represent each infliximab treatment group vs. AZA monotherapy

Similar trends in the achievement of corticosteroid-free clinical remission were observed at Week 50. Furthermore, improved quality of life as measured by IBDQ was observed with infliximab.

Induction Treatment in Fistulizing Active Crohn's Disease

The efficacy was assessed in a randomized, double-blinded, placebo-controlled study in 94 patients with fistulizing Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty-one of these patients were treated with infliximab 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these medications. Patients received three doses of either placebo or infliximab at weeks 0, 2, and 6. Patients were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥ 50% reduction from baseline in the number of fistulae draining upon gentle compression on at least two consecutive visits (4 weeks apart), without an increase in medication for Crohn's disease.

Sixty-eight percent (21/31) of infliximab-treated patients receiving a 5 mg/kg dose regimen achieved a clinical response vs. 26% (8/31) placebo-treated patients (p=0.002). The median time to onset of response in infliximab-treated group was 2 weeks. The median duration of response was 12 weeks. Additionally, closure of all fistulae was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients (p=0.001).

Maintenance Treatment in Fistulizing Active Crohn's Disease

The efficacy of repeated infusion with infliximab in patients with fistulizing Crohn's disease was studied in a 1-year clinical study. A total of 306 patients received 3 doses of infliximab 5 mg/kg at week 0, 2, and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. At week 14, 282 patients were assessed for clinical response and randomised to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46.

Week-14 responders (195/282) were analyzed for the primary endpoint, which was time from randomisation to loss of response (see **Table 26**). Corticosteroid tapering was permitted after week 6.

Table 26

Effects on response rate, data from ACCENT II (Week-14 responders)

	ACCENT II (Week-14 responders)		
	Placebo Maintenance (n=99)	Infliximab Maintenance (5 mg/kg) (n=96)	p-value
Median time to loss of response through week 54	14 weeks	>40 weeks	< 0.001
Week 54			
Fistula Response (%) [a]	23.5	46.2	0.001
Complete fistula response (%) [b]	19.4	36.3	0.009

a: A ≥ 50% reduction from baseline in the number of draining fistulas over a period of ≥ 4 weeks

b: Absence of any draining fistulas

Beginning at week 22, patients who initially responded to treatment and subsequently lost their response were eligible to cross over to active re-treatment every 8 weeks at a dose of infliximab 5 mg/kg higher than the dose to which they were originally randomised. Among patients in the infliximab 5 mg/kg group who crossed over because of loss of fistula response after week 22, 57% (12/21) responded to re-treatment with infliximab 10 mg/kg every 8 weeks.

There was no significant difference between placebo and infliximab for the proportion of patients with sustained closure of all fistulas through week 54, for symptoms such as proctalgia, abscesses and urinary tract infection or for number of newly developed fistulas during treatment.

Maintenance therapy with infliximab every 8 weeks significantly reduced disease-related hospitalisations and surgeries compared with placebo. Furthermore, a reduction in corticosteroid use and improvements in quality of life were observed.

Paediatric Crohn's disease (6 to 17 years)

In the REACH trial, 112 patients (6 to 17 years, median age 13.0 years) with moderate to severe, active Crohn's disease (median PCDAI of 40) and an inadequate response to conventional therapies were to receive 5 mg/kg infliximab at weeks 0, 2, and 6. All patients were required to be on a stable dose of 6-MP, AZA or MTX (35% were also receiving corticosteroids at baseline). Patients assessed by the investigator to be in clinical response at week 10 were randomized and receive 5 mg/kg infliximab either q8 weeks or q12 weeks as maintenance treatment regimen. If response was lost during treatment, crossing over to a higher dose (10 mg/kg) and/or shorter dosing interval (q8 weeks) was allowed. Thirty-two (32) evaluable paediatric patients crossed over (9 subjects in the q8 weeks and 23 subjects in the q12 weeks maintenance groups). Twenty four of these patients (75.0%) regained clinical response after crossing over.

The proportion of subject in clinical response at week 10 was 88.4% (99/112). The proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112).

At week 30, the proportion of subjects in clinical remission was higher in the q8 week (59.6%, 31/52) than q12 week maintenance treatment group (35.3%, 18/51; p=0.013) at week 54, the figures were 55.8% (29/52) and 23.5% (12//51) in the q8 weeks and q12 weeks maintenance groups, respectively (p<0.001).

Data about fistulas were derived from PCDAI score. Of the 22 subjects that had fistulas at baseline, 63.6% (14/22), 59.1% (13/22) and 68.2% (15/22) were in complete fistulas response at week 10, 30 and 54, respectively, in the combined q8 weeks and q12 weeks maintenance groups.

In addition, statistically and clinically significant improvements in quality of life and height, as well as a significant reduction in corticosteroid use, were observed versus baseline.

Ulcerative Colitis

The safety and efficacy of infliximab were assessed in two (ACT 1 and ACT 2) randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12, Endoscopy subscore ≥2) with an inadequate response to conventional therapies [oral corticosteroids, aminosalicylates and/or immunomodulators (6-MP, AZA)]. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agent were permitted. In both studies, patients were randomized to receive either placebo, 5 mg/kg infliximab, or 10 mg/kg infliximab at weeks 0, 2, 6, 14 and 22, and in ACT 1 at weeks 30, 38 and 46. Corticosteroid taper was permitted after week 8.

Table 27

Effect on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
Subject randomized	244	242	242	484
Percentage of subjects in clinical response and in sustained clinical response				
Clinical response at Week 8[a]	33.2%	66.9%	65.3%	66.1%
Clinical response at Week 30[a]	27.9%	49.6%	55.4%	52.5%
Sustained response (clinical response at both Week 8 and Week 30)[a]	19.3%	45.0%	49.6%	47.3%
Percentage of subjects in clinical remission and sustained remission				
Clinical remission at Week 8[a]	10.2%	36.4%	29.8%	33.1%
Clinical remission at Week 30[a]	13.1%	29.8%	36.4%	33.1%
Sustained remission (in remission at both Week 8 and Week 30)[a]	5.3%	19.0%	24.4%	21.7%
Percentage of subjects with mucosal healing				
Mucosal healing at Week 8[a]	32.4%	61.2%	60.3%	60.7%
Mucosal healing at Week 30[a]	27.5%	48.3%	52.9%	50.6%

a: $p<0.001$, for each infliximab treatment group vs. placebo

The efficacy of infliximab through week 54 was assessed in the ACT 1 trial.

At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p<0.001$). Clinical remission and mucosal healing occurred in greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.5% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportion of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

Infliximab improved Quality of Life, confirmed by statistically and clinically significant improvement in both disease specific measure, IBDQ, and by improvement in the generic 36-item short form survey SF-36.

From baseline through week 30 in the pooled data from ACT 1 and ACT 2, the mean number of hospitalizations was 50% lower in the combined infliximab treatment group than in the placebo treatment group (9 versus 18 hospitalizations per 100 subjects, $p=0.005$). No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab treatment groups.

A greater proportion of patients in the combined infliximab treatment group were able to

discontinue corticosteroids in clinical remission compared to the placebo treatment group at both week 30 (22.3% versus 7.2%, p<0.001) and week 54 (21.0% vs. 8.9%, p=0.022).

Ulcerative Colitis in Pediatric Patients

The safety and efficacy of infliximab were assessed in a multi-center, randomized, open-label, parallel-group Phase 3 clinical study in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12; Endoscopic subscore ≥ 2) with an inadequate response to conventional therapies (Study Peds UC). At baseline 53% of patients were receiving immunomodulator therapy (6-mercaptopurine (6-MP)/ azathioprine (AZA)/ methotrexate (MTX)) and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

All patients received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients (15) who did not respond to infliximab at Week 8 received no further drug and returned for safety follow-up. At Week 8, 45 patients were randomized in a 1:1 ratio to one of two maintenance treatment regimens: 5 mg/kg infliximab every 8 weeks (q8 week) through Week 46 or every 12 weeks (q12 week) through Week 42.

The primary endpoint was clinical response at Week 8, defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

Major secondary endpoints included clinical remission measured by the Mayo score at Week 8, remission by the Pediatric Ulcerative Colitis Activity Index (PUCAI)31 score at Week 8 and Week 54, and mucosal healing at Week 8. For patients receiving corticosteroids at baseline, reduction in median corticosteroid use, and remission combined with elimination of corticosteroid use at Week 54 was evaluated.

Clinical Response, Clinical Remission and Mucosal Healing

Of the 60 patients treated, 44 (73.3%) were in clinical response at Week 8 (95% CI: 62.1%, 84.5%). The proportions of patients achieving clinical response at Week 8 were similar between those taking concomitant immunomodulators at baseline (72%) and those not taking concomitant immunomodulators at baseline (75%).

Clinical remission was defined by a Mayo score of ≤ 2 points, with no individual subscore > 1. Remission was also defined by a PUCAI score of <10 points. At Week 8, infliximab induced clinical remission in 40% (24/60) of patients as measured by the Mayo score and in 33.3% (17/51) of patients as measured by the PUCAI score.

The proportion of patients in remission at Week 54 as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance treatment group and 18% (4/22) in the q12 week maintenance treatment group.

Mucosal healing was defined as an endoscopy subscore (from the Mayo score) of 0 or 1. At Week 8, 68.3% (41/60) of patients were in mucosal healing with 33.3% (20/60) having an endoscopy subscore of 0 (indicating normal or inactive disease). Of the 9 patients who had an optional endoscopy at Week 54, 8 were in mucosal healing.

Overall, although some differences were noted between the age groups in the efficacy measures examined, efficacy was observed in both age groups and no consistent pattern indicating greater efficacy in one of the age groups was apparent. The differences between the 6 to 11 and the 12 to 17 year old age groups, however, are difficult to assess because of the small sample sizes, particularly in the 6 to 11 year old age group (15 patients).

Corticosteroid use and Remission

Median average daily corticosteroid (prednisone equivalent) dose (mg/kg/day) through Week 54 is presented in Figure 1 for all randomized patients taking corticosteroids at baseline (14 patients in each maintenance treatment group).

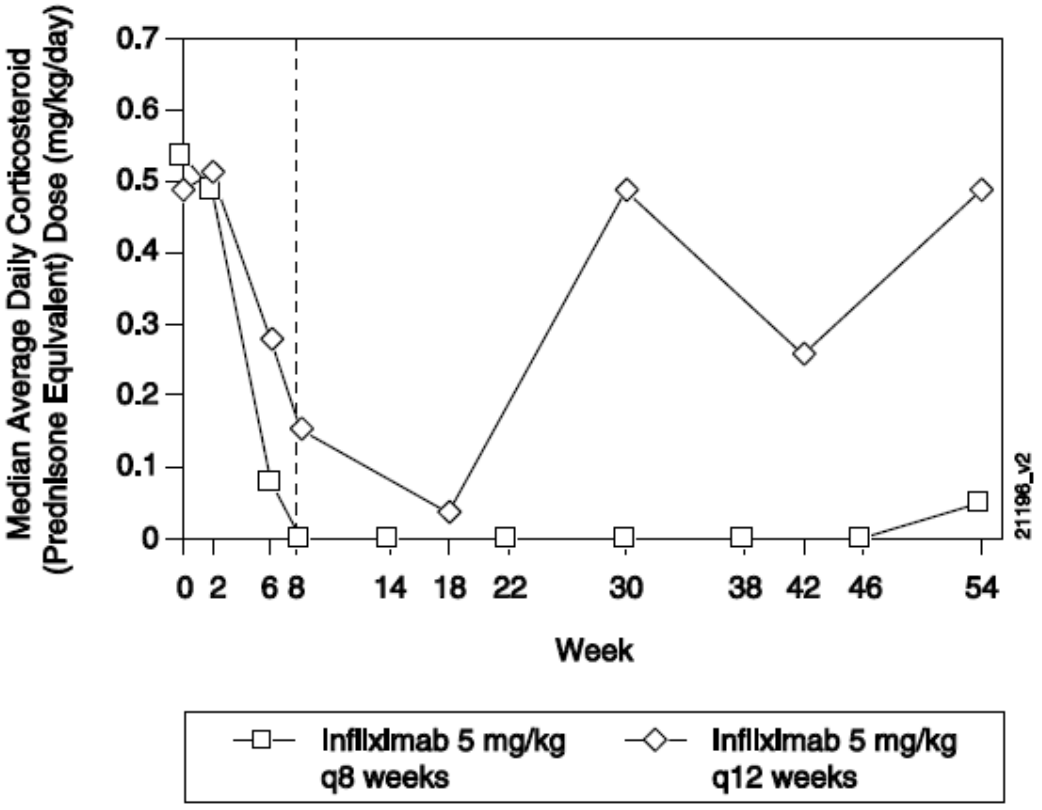


Figure 1: Line plot of median average daily corticosteroid (prednisone equivalent) dose (mg/kg/day) through Week 54; randomized patients taking corticosteroids at baseline

At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the q8 week maintenance group and 18% (4/22) in the q12 week maintenance treatment group. For patients receiving corticosteroids at baseline, the proportion of patients in remission and not receiving corticosteroids at week 54 was 38.5% (5/13) for the q8 week and 0% (0/13) for the q12 week maintenance treatment group.

For patients receiving corticosteroids at baseline in Study Peds UC, the proportion of these patients in remission and not receiving corticosteroids at Week 54 was 38.5% (5 of 13) for the q8 week and 0% (0 of 13) for the q12 week maintenance treatment group.

Ankylosing Spondylitis

Efficacy and safety were studied in a double-blind, placebo-controlled investigator initiated, multicenter study evaluating infliximab in 70 patients with active ankylosing spondylitis (disease activity [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score > 4] and pain [NRS score >4]). During the 3-month double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). Starting at week 12, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 6 weeks up to week 54.

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the BASDAI, with 57% of infliximab treated patients achieving at least 50% reduction from baseline in BASDAI score (mean baseline score was 6.5 in the infliximab group and 6.3 in the placebo group, compared with 9% of placebo patients ($p<0.01$). Improvement was observed at week 2 and was maintained through week 54. Physical function and quality of life (SF36) were improved similarly. In the trial, efficacy was not shown in HLA-B27 negative patients (n=7).

Psoriatic Arthritis

Efficacy and safety were studied in a double-blind, placebo-controlled, multicenter study evaluating infliximab in 104 patients with active polyarticular psoriatic arthritis. In total 74 subjects were on at least one concomitant DMRD, and among those 58 patients were treated with methotrexate. During the 16-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 and 14 (52 patients in each group). Starting at week 16, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 8 weeks up to week 46. After the first year of the study, 78 patients continued into an open-label extension to week 98.

In the second trial (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥5 swollen joints and ≥5 tender joints). Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14 and 22 (100 patients in

each group). At week 16, 47 placebo patients with < 10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At week 24, all placebo treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46.

Key efficacy results for IMPACT and IMPACT 2 and shown in **Table 28** below:

Table 28

Effects on ACR and PASI in IMPACT and IMPACT 2

	IMPACT			**IMPACT 2***		
	Placebo (Week 16)	**Infliximab (Week16)**	**Infliximab (Week 98)**	**Placebo (Week 24)**	**Infliximab (Week 24)**	**Infliximab (Week 54)**
Patients randomized	52	52	N/A[a]	100	100	100
ACR response (% of patients)						
N	52	52	78	100	100	100
ACR 20 response*	5(10%)	34(65%)	48(62%)	16(16%)	54(54%)	53(53%)
ACR 50 response*	0(0%)	24(46%)	35(45%)	4(4%)	41(41%)	33(33%)
ACR 70 response*	0(0%)	15(29%)	27(35%)	2(2%)	27(27%)	20(20%)
PASI response (% of patients)[b]						
N				87	83	82
PASI 75 response**				1(1%)	50(60%)	40(48.8%)

* ITT-analysis where subjects with missing data were included as non-responders

[a] Week 98 data for IMPACT includes combined placebo crossover and infliximab patients who entered the open-label extension

[b] Based on patients with PASI>2.5 at baseline for IMPACT, and patients with >3% BSA psoriasis skin involvement at baseline in IMPACT 2

** PASI 75 response for IMPACT not included due to low N; $p<0.001$ for infliximab vs. placebo at week 24 for IMPACT 2

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54 respectively. Efficacy has been demonstrated with or without concomitant use of methotrexate. Decreases in parameters of peripheral activity characteristic of psoriatic arthritis (such as number of swollen joints, number of painful/tender joints, dactylitis and presence of enthesopathy) were seen in the infliximab-treated patients.

Infliximab-treated patients demonstrated significant improvement in physical function as assessed by HAQ. Significant improvements in health-related quality of life were also demonstrated as measured by the physical and mental component summary scores of the SF-36 in IMPACT 2.

Psoriasis

The efficacy of infliximab was assessed in two multicenter, randomized, double blind studies: SPIRIT and EXPRESS. Patients in both studies had plaque psoriasis (Body Surface Area [BSA] ≥10% and Psoriasis Area and Severity Index [PASI] score ≥12). The primary endpoint in both studies was the percent of patients who achieved ≥75% improvement in PASI from baseline at week 10.

SPIRIT evaluated the efficacy of infliximab induction therapy in 249 patients with plaque psoriasis that had previously received PUVA or systemic therapy. Patients received either 3 or, 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6. Patients with a PGA score ≥3 were eligible to receive an additional infusion of the same treatment at week 26.

In SPIRIT, the proportion of patients achieving PASI 75 at week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p<0.001$).

By week 26, twenty weeks after the last induction dose, 30% of patients in the 5 mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of > 20 weeks. No rebound was observed.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis. Patients received 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6 followed by maintenance therapy every 8 weeks through week 22 in the placebo group and through week 46 in the infliximab group. At week 24, the placebo group crossed over to infliximab induction therapy (5 mg/kg) followed by infliximab maintenance therapy (5 mg/kg). Prior therapy with PUVA, methotrexate, cyclosporine, or acitretin had been received by 71.4% of patients, although they were not necessarily therapy resistant. Key results are presented in **Table 29**. In infliximab treated subjects, significant PASI 50 responses were apparent at the first visit (week 2) and PASI 75 responses by the second visit (week 6). Efficacy was similar in the subgroup of patients that were exposed to previous systemic therapies compared to the overall study population.

Table 29

Summary of PASI response, PGA response and percent of patients with all nails cleared at Week 10, 24 and 50. EXPRESS

	Placebo→Infliximab 5 mg/kg (at week 24)	**Infliximab 5 mg/kg**
Week 10		
n	77	301
≥90% improvement	1(1.3%)	172(57.1%)[a]

≥75% improvement	2(2.6%)	242(80.4%)[a]
≥50% improvement	6(7.8%)	274(91.0%)
PGA of cleared (0) or minimal (1)	3(3.9%)	242(82.9%)[ab]
PGA of cleared (0), minimal (1),or mild (2)	14(18.2%)	275(94.2%)[ab]
Week 24		
n	77	276
≥90% improvement	1(1.3%)	161(58.3%)[a]
≥75% improvement	3(3.9%)	227(82.2%)[a]
≥50% improvement	5(6.5%)	248(89.9%)
PGA of cleared (0) or minimal (1)	2(2.6%)	203(73.6%)[a]
PGA of cleared (0), minimal (1),or mild (2)	15(19.5%)	246(89.1%)[a]
Week 50		
n	68	281
≥90% improvement	34(50.0%)	127(45.2%)
≥75% improvement	52(76.5%)	170(60.5%)
≥50% improvement	61(89.7%)	193(68.7%)
PGA of cleared (0) or minimal (1)	46(67.6%)	149(53.0%)
PGA of cleared (0), minimal (1),or mild (2)	59(86.8%)	189(67.3%)
All nails cleared [c]		
Week 10	1/65(1.5%)	16/235 (6.8%)
Week 24	3/65 (4.6%)	58/223 (26,0%) [a]
Week 50	27/64 (42.2%)	92/226 (40.7%)

a: p<0.001, for each infliximab treatment group vs. control

b: n=292

c: Analaysis was based on subjects with nail psoriasis at baseline (81.8% of subjects). Mean baseline NAPSI scores were 4.6 and 4.3 in infliximab and placebo group.

Significant improvements from baseline were demonstrated in DLQI (p<0.001) and the physical and mental component scores of the SF 36 (p<0.001 for each component comparison).

Pharmacokinetic Properties

Adults

Single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median V_d of 3.0 to 4.1 litres) was not dependent on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. No time-dependency of the pharmacokinetics was observed. The elimination pathways for infliximab have not been characterised. Unchanged infliximab was not detected in urine. No major age- or weight-related differences in clearance or volume of distribution were

observed in rheumatoid arthritis patients. The pharmacokinetics of infliximab in elderly patients has not been studied. Studies have not been performed in patients with liver or renal disease.

At single doses of 3, 5, or 10 mg/kg, the median C_{max} values were 77, 118 and 277 micrograms/ml, respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after the recommended single dose of 5 mg/kg for Crohn's disease and the rheumatoid arthritis maintenance dose of 3 mg/kg every 8 weeks.

Repeated administration of infliximab (5 mg/kg at 0, 2 and 6 weeks in fistulizing Crohn's disease, 3 or 10 mg/kg every 4 or 8 weeks in rheumatoid arthritis) resulted in a slight accumulation of infliximab in serum after the second dose. No further clinically relevant accumulation was observed. In most fistulising Crohn's disease patients, infliximab was detected in serum for 12 weeks (range 4-28 weeks) after administration of the regimen.

Pediatrics

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were generally similar in pediatric (aged 6 to 17 years) and adult patients with Crohn's Disease or Ulcerative Colitis following the administration of 5 mg/kg infliximab.

Population pharmacokinetic analysis based on data obtained from patients with ulcerative colitis (N=60), Crohn's disease (N=112), juvenile rheumatoid arthritis (N=117) and Kawasaki disease (N=16) with an overall age range from 2 months to 17 years indicated that the total clearance of infliximab did not increase linearly with increasing body weight. As a result, following administration of 5 mg/kg infliximab every 8 weeks, the predicted median steady-state infliximab exposure (area under concentration-time curve at steady state, AUCss) in pediatric patients aged 6 to 17 years was approximately 20% lower than the median steady-state drug exposure in adults. The median AUCss in pediatric patients aged 2 to less than 6 years was predicted to be approximately 40% lower than that in adults, although the number of patients supporting this estimate is limited.

Preclinical Safety Data

Infliximab does not cross react with TNFα from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice,

using the same analogous antibody against mouse TNFα, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.
Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNFα demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

PHARMACEUTICAL PARTICULARS

List of Excipients

Sucrose, polysorbate 80, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate dihydrate.

Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf Life

48 months
Chemical and physical stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (25℃). From a microbiological point of view, the product should be used as soon as possible but within 3 hours of reconstitution and dilution. If not used immediately, in use storage times and conditions prior to use is the responsibility of the user and should not be longer than 24 hours at 2 to 8℃.

Special Precautions for Storage

Store at 2℃-8℃.
Keep out of the sight and reach of children.

Nature and Contents of Container

REMSIMA® is supplied as a lyophilised powder in single-use glass (Type 1) vials with rubber stoppers and aluminum crimps protected by plastic caps, sealed with a flip-off button. REMSIMA® is available in packs of 1, 2 or 3 vials. Not all pack sizes may be marketed.

Instructions for Use and Handling and Disposal

1. Calculate the dose and the number of REMSIMA® vials needed. Each REMSIMA® vial contains 100 mg infliximab. Calculate the total volume of reconstituted REMSIMA® solution required.
2. Under aseptic conditions, reconstitute each REMSIMA® vial with 10 ml of water for injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. Remove flip-top from the

vial and wipe the top with a 70% alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of water for injections to the glass wall of the vial. Gently swirls the solution by rotating the vial to dissolve the lyophilised 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. Check that the solution is colorless to light yellow and opalescent. The solution may develop a few fine 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 sodium chloride solution for infusion 9 mg/ml (0.9%). Do not dilute the reconstituted REMSIMA® solution with any other diluent. This can be accomplished by withdrawing a volume of the sodium chloride solution for infusion 9 mg/ml (0.9%) from the 250-ml glass bottle or infusion bag equal to the volume of reconstituted REMSIMA®. Slowly add the total volume of reconstituted REMSIMA® solution to the 250-ml infusion bottle or bag. Gently mix.
4. Administer the infusion solution over a period of not less than 2 hours (at not more than 2 ml/min). Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometer or less). Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of reconstitution and dilution. When reconstitution and dilution are performed under aseptic conditions, REMSIMA® infusion solution can be used within 24 hours if stored at 2℃ to 8℃. Do not store any unused portion of the infusion solution for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMSIMA® with other agents. Do not infuse REMSIMA® concomitantly in the same intravenous line with other agents.
6. Visually inspect parenteral medicinal products for particulate matter or discoloration prior to administration. Do not use if visibly opaque particles, discoloration or foreign particulates are observed.
7. Discard any unused portion of the solution.

PRODUCT LICENSE HOLDER

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18 August 2022