NEW ZEALAND DATA SHEET

1. PRODUCT NAME

REMSIMA® SC 120 mg solution for injection in pre-filled syringe
REMSIMA® SC 120 mg solution for injection in pre-filled pen

REMSIMA® SC is a biosimilar medicinal product.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REMSIMA® SC 120 mg solution for injection in pre-filled syringe
Each 1 mL single dose pre-filled syringe contains 120 mg of infliximab*.

REMSIMA® SC 120 mg solution for injection in pre-filled syringe with automatic needle guard
Each 1 mL single dose pre-filled pen contains 120 mg of infliximab*.

REMSIMA® SC 120 mg solution for injection in pre-filled pen
Each 1 mL single dose pre-filled pen contains 120 mg of infliximab*.

Excipient(s) with known effect
Sorbitol 45 mg per 1 mL

* Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology.

For the full list of excipients, see section 6.1. List of excipients.

REMSIMA® SC is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding interchangeability with other products. Additional information is available on the following website (http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp). Data comparing REMSIMA® to REMICADE can be found in section 5.1, Further Information of this datasheet.

3. PHARMACEUTICAL FORM

REMSIMA® SC 120 mg pre-filled syringe/pen – Solution for Injection
Clear to opalescent, colourless to pale brown solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Remsima SC 120mg solution for injection is indicated for

Rheumatoid arthritis in adults

Remsima® SC, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult 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 section 5.1).

Crohn's disease

Remsima® SC is indicated for:

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

Ulcerative colitis

Remsima® SC is indicated for treatment of moderately to severely active ulcerative colitis in adult 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.

Ankylosing spondylitis

Remsima® SC is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy.

Psoriatic arthritis

Remsima® SC is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate.
Remsima SC should be administered

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1).

Psoriasis

Remsima® SC is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen ultra-violet A (PUVA) (see section 5.1).

4.2 Dose and method of administration

Remsima SC 120mg solution for injection

REMSIMA® SC treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which REMSIMA SC is indicated. Patients treated with REMSIMA® SC should be given the package leaflet and the patient reminder card. Instruction for use is provided in the package leaflet.

For subsequent injections and after proper training in subcutaneous injection technique, patients may self-inject with REMSIMA® SC if their physician determines that it is appropriate and with medical follow-up as necessary. Suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions (see section 4.4).

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

It is important to check the product labels to ensure that the correct formulation (intravenous or subcutaneous) is being administered to the patient, as prescribed. REMSIMA® SC subcutaneous formulation is not intended for intravenous administration and should be administered via a subcutaneous injection only.

Dose

Adults (≥18 years)

Rheumatoid arthritis
Treatment with REMSIMA® SC administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 3 mg/kg given 2 weeks apart. The recommended dose for REMSIMA® SC subcutaneous formulation is 120 mg once every 2 weeks.

REMSIMA® SC 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 the first 12 weeks of treatment (see section 5.1).

Moderately to severely active Crohn's disease
Treatment with REMSIMA® SC administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for REMSIMA® SC subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after 2 doses of intravenous infusions, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

In responding patients, the recommended maintenance dose for REMSIMA SC subcutaneous formulation is 120 mg once every 2 weeks starting from 4 weeks after the last intravenous infusion.

Although comparative data are lacking, limited data in patients who initially responded to intravenous infusion of infliximab 5 mg/kg or subcutaneous injection of infliximab 120 mg but who lost response indicate that some patients may regain response with dose escalation, and increasing dose to 240 mg can be considered (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

Fistulising, active Crohn's disease
REMSIMA SC 120 mg given as a subcutaneous injection 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. If a patient does not respond after 6 doses (i.e. 2 intravenous infusions and 4 subcutaneous injections), no additional treatment with infliximab should be given.

In responding patients, the recommended maintenance dose for REMSIMA® SC subcutaneous formulation is 120 mg once every 2 weeks after the 6 doses.

Although comparative data are lacking, limited data in patients who initially responded to intravenous infusion of infliximab 5 mg/kg or subcutaneous injection of infliximab 120 mg but who lost response indicate that some patients may regain response with dose escalation, and increasing dose to 240 mg can be considered (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment.

In Crohn's disease, experience with re-administration if signs and symptoms of disease recur is limited and comparative data on the benefit/risk of the alternative strategies for continued treatment are lacking.

Ulcerative colitis
Treatment with REMSIMA® SC administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for REMSIMA® SC subcutaneous formulation is 120 mg once every 2 weeks.

Although comparative data are lacking, limited data in patients who initially responded to intravenous infusion of infliximab 5 mg/kg or subcutaneous injection of infliximab 120 mg but who lost response indicate that some patients may regain response with dose escalation, and increasing dose to 240 mg can be considered (see section 5.1).

Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. 2 intravenous infusions and 4 subcutaneous injections (see section 5.1). Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Ankylosing spondylitis
Treatment with REMSIMA® SC administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. If a patient does not respond by 6 weeks (i.e. after 2 intravenous infusions), no additional treatment with infliximab should be given.

Psoriatic arthritis
Treatment with REMSIMA® SC administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart.

Psoriasis
Treatment with REMSIMA® SC administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. If a patient shows no response after 14 weeks (i.e. 2 intravenous infusions and 5 subcutaneous injections), no additional treatment with infliximab should be given.

Re-administration for Crohn's disease and rheumatoid arthritis
From experience with intravenous infliximab, if the signs and symptoms of disease recur, infliximab can be re-administered within 16 weeks following the last administration. In clinical studies with intravenous infliximab, delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year (see sections 4.4 and 4.8). The safety and efficacy of re-administration after an infliximab-free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

Re-administration for ulcerative colitis
From experience with intravenous infliximab, the safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

Re-administration for ankylosing spondylitis
From experience with intravenous infliximab, the safety and efficacy of re-administration, other than every 6 to 8 weeks, has not been established (see sections 4.4 and 4.8).

Re-administration for psoriatic arthritis
From experience with intravenous infliximab, the safety and efficacy of re-administration, other than every 8 weeks, has not been established (see sections 4.4 and 4.8).

Re-administration for psoriasis
Limited experience from re-treatment with one single intravenous 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 section 5.1).

Limited experience from re-treatment of intravenous infliximab following disease flare by a re-induction regimen suggests a higher incidence of infusion reactions, including serious ones, when compared to 8-weekly maintenance treatment of intravenous infliximab (see section 4.8).

Re-administration across indications
In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen of intravenous infliximab is not recommended (see section 4.8). In this situation, infliximab should be re-initiated as a single dose of REMSIMA® SC subcutaneous formulation followed by the maintenance dose recommendations described above.

Switching to and from REMSIMA® SC subcutaneous formulation across indications
When switching from the maintenance therapy of infliximab intravenous formulation to the subcutaneous formulation of REMSIMA®, the subcutaneous formulation may be administered 8 weeks after the last administration of the intravenous infusions of infliximab.

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of REMSIMA® SC.

Information regarding switching patients from the subcutaneous formulation to the intravenous formulation of REMSIMA® is not available.

Missed dose
If patients miss an injection of REMSIMA® SC subcutaneous formulation, they should be instructed to take the missed dose immediately in case this happens within 7 days from the missed dose, and then remain on their original bi-weekly dosing schedule. If the dose is delayed by 8 days or more, the patients should be instructed to skip the missed dose, wait until their next scheduled dose, and then remain on their original bi-weekly dosing schedule.

Special populations

Elderly

Specific studies of infliximab in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies with infliximab intravenous formulations and the same is expected for subcutaneous formulation. No dose adjustment is required (see section 5.2). For more information about the safety of infliximab in elderly patients, see sections 4.4 and 4.8.

Renal and/or hepatic impairment

Infliximab has not been studied in these patient populations. No dose recommendations can be made (see section 5.2).

Paediatric population

The safety and efficacy of REMSIMA® SC subcutaneous therapy in children aged below 18 years of age have not yet been established. No data are available. Therefore, subcutaneous use of REMSIMA® SC is recommended for use only in adults.

Method of administration

REMSIMA® SC 120 mg solution for injection in pre-filled syringe or in pre-filled pen are administered by subcutaneous injection only. Full instructions for use are provided in the package leaflet.

For the two initial intravenous infusions, 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 section 4.4). The physician should ensure appropriate follow-up of patients for any systemic injection reaction and localised injection site reaction after the initial subcutaneous injection is administered.

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

Traceability

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

4.3 Contraindications

Infliximabis contraindicated in patients with severe infections, such as tuberculosis, sepsis, clinically manifested infections and/or abscesses and opportunistic infections.

Infliximab should not be given to patients with a history of hypersensitivity to infliximab (see section 4.8) to other murine proteins or to any excipient of the product.

Concurrent administration of Infliximab and anakinra (an interleukin-1 receptor antagonist) is contraindicated.

Infliximab is contraindicated in patients with moderate or severe heart failure (NYHA class III/IV) (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Infusion reactions and hypersensitivity reactions

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Systemic injection reaction/ localised injection site reaction/ hypersensitivity

Infliximab has been associated with systemic injection reactions, anaphylactic shock and delayed hypersensitivity reactions (see section 4.8).

Acute reactions including anaphylactic reactions may develop during (within seconds) or within a few hours following administration of infliximab. If acute reactions occur, medical treatment should be sought immediately. For this reason, the initial intravenous administrations should take place where emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway is immediately available. Patients may be pre-treated with e.g., an antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

Localised injection site reactions predominantly of mild to moderate in nature included the following reactions limited to injection site: erythema, pain, pruritus, swelling, induration, bruising, haematoma, oedema, coldness, paraesthesia, haemorrhage, irritation, rash, ulcer, urticaria, application site vesicles and scab were reported to be associated with infliximab subcutaneous treatment. Most of these reactions may occur immediately or within 24 hours after subcutaneous injection. Most of these reactions resolved spontaneously without any treatment.

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions when administered by intravenous infusion. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed with intravenously administered infliximab. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and in the case of intravenously administered infliximab, 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 infliximab must not be administered (see section 4.8).

In clinical studies, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing infliximab free interval. Patients should be advised to seek immediate medical advice if they experience any delayed adverse reaction (see section 4.8). If patients are re-treated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections

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

Caution should be exercised when considering the use of infliximab in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. 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 mask symptoms of infection such as fever. Early recognition of atypical clinical presentations of serious infections and of typical clinical presentation of rare and unusual infections is critical in order to minimise delays in diagnosis and treatment.

Patients taking TNF-blockers are more susceptible to serious infections.

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients treated with infliximab. Some of these infections have been fatal; 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 infliximab, should be monitored closely and undergo a complete diagnostic evaluation. Administration of infliximab should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled.

Tuberculosis

There have been reports of active tuberculosis in patients receiving infliximab. It should be noted that in the majority of

these reports tuberculosis was extrapulmonary, presenting as either local or disseminated disease.

Before starting treatment with infliximab, 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, (e.g. tuberculin skin test, chest X-ray, and/or Interferon Gamma Release Assay), should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient reminder card. 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, infliximab therapy must not be initiated (see section 4.3).

If latent tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of infliximab therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with antituberculosis therapy before the initiation of infliximab, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, antituberculosis therapy should be considered before the initiation of infliximab.

Use of anti-tuberculosis therapy should also be considered before the initiation of infliximab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Some cases of active tuberculosis have been reported in patients treated with infliximab during and after treatment for latent tuberculosis.

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 infliximab treatment.

Invasive fungal infections

In patients treated with infliximab, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if they develop a serious systemic 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 localised 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.

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

Fistulising Crohn's disease
Patients with fistulising Crohn's disease with acute suppurative fistulas must not initiate infliximab therapy until a source for possible infection, specifically abscess, has been excluded (see section 4.3).

Hepatitis B (HBV) 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 should be tested for HBV infection before initiating treatment with infliximab. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Carriers of HBV who require treatment with infliximab 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 antiviral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, infliximab should be stopped and effective antiviral therapy with appropriate supportive treatment should be initiated.

Hepatobiliary events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of infliximab. Isolated cases of liver failure resulting in liver transplantation or death have occurred. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥5 times the upper limit of normal develop(s), infliximab should be discontinued, and a thorough investigation of the abnormality should be undertaken.

Concurrent administration of TNF-alpha inhibitor and anakinra

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

Concurrent administration of TNF-alpha inhibitor and abatacept

In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of infliximab 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

Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse reactions, including infection.

Vaccinations

It is recommended that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remsima SC therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6).

In a subset of 90 adult patients with rheumatoid arthritis from the ASPIRE study a similar proportion of patients in each treatment group (methotrexate plus: placebo [n = 17], 3 mg/kg [n = 27] or 6 mg/kg infliximab [n = 46]) mounted an effective two-fold increase in titers to a polyvalent pneumococcal vaccine, indicating that infliximab did not interfere with T-cell independent humoral immune responses. However, studies from the published literature in various indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) suggest that non-live vaccinations received during treatment with anti-TNF therapies, including infliximab may elicit a lower immune response than in patients not receiving anti-TNF therapy.

Live vaccines/therapeutic infectious agents

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

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. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab (see section 4.6).

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 infliximab and is positive for antibodies against double-stranded DNA, further treatment with infliximab must not be given (see section 4.8).

Neurological events

Use of TNF-blocking agents, including infliximab, has been associated with cases of 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 Guillain-Barré syndrome. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop.

Malignancies and lymphoproliferative disorders

In the controlled portions of clinical studies of TNF-blocking agents, more cases of malignancies including lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical studies of infliximab across all approved indications the incidence of lymphoma in infliximab-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. In the post-marketing setting, cases of leukaemia have been reported in patients treated with a TNF-antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.

In an exploratory clinical study evaluating the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Caution should be exercised in considering treatment of patients with increased risk for 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 section 4.8). Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

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

Although subcutaneous administration is not indicated for children under age of 18 years, it should be noted that malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) 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 AZA or 6-MP 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. The potential risk with the combination of AZA or 6-MP and infliximab should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with infliximab cannot be excluded (see section 4.8).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including infliximab (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin 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. Periodic screening should continue in women treated with infliximab, including those over 60 years of age.

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 therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that infliximab treatment influences the risk for developing dysplasia or colon cancer.

Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with infliximab is not established, the risk and benefits of continued therapy to the individual patients should be carefully considered by the clinician.

Heart failure

Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and infliximab must not be continued in patients who develop new or worsening symptoms of heart failure (see sections 4.3 and 4.8).

Haematologic reactions

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of infliximab therapy should be considered in patients with confirmed significant haematologic abnormalities.

Others

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

Failure to respond to treatment for Crohn’s disease may indicate the presence of a fixed fibrotic stricture that may require surgical treatment. There is no evidence to suggest that infliximab worsens or causes fibrotic strictures.

Special populations

Elderly

The incidence of serious infections in infliximab-treated patients 65 years and older was greater than in those under 65 years of age. Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly (see section 4.8).

Sorbitol content

Remsima SC contains 45 mg sorbitol per 1 mL (in each 120 mg dose).

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

In rheumatoid arthritis, psoriatic 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 infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended (see section 4.4).

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 at least 6 months following birth (see section 4.4).

It is recommended that therapeutic infectious agents not be given concurrently with infliximab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should consider the use 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 section 5.3).

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 6 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 at least 6 months after birth (see sections 4.4 and 4.5). Cases of agranulocytosis have also been reported (see section 4.8).

Breast-feeding

It is unknown whether infliximab is excreted in human milk or absorbed systemically after ingestion. Because human immunoglobulins are excreted in milk, women must not breast-feed for at least 6 months after infliximab treatment..

Fertility
There are insufficient preclinical data to draw conclusions on the effects of infliximab on fertility and general reproductive function (see section 5.3).

4.7 Effects on ability to drive and use machinery

REMSIMA® SC may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of infliximab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials with infliximab, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for infliximab include HBV reactivation, CHF

(congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease) and serious infusion reactions (see section 4.4).

The safety profile of Remsima® SC subcutaneous formulation from active rheumatoid arthritis (evaluated in 168 and 175 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively), active Crohn's disease (evaluated in 59 and 38 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) and active ulcerative colitis patients (evaluated in 38 and 40 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) was overall similar to the safety profile of the intravenous formulation.

Tabulated list of adverse reactions

Table 1 lists ADRS based on experience from clinical studies as well as adverse reactions, some with fatal outcome, reported from post-marketing experience. Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥ 1/10); (common >1/100 to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10,000, <1/1000)); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effect are presenting in order of decreasing seriousness.

Table 1

Adverse reactions in clinical studies and from post-marketing experience of intravenous infliximab

Infections and infestations	
Very common:	Viral infection (e.g. influenza, herpes virus infection).
Common:	Bacterial infections (e.g. sepsis, cellulitis, abscess).
Uncommon:	Tuberculosis, fungal infections (e.g. candidiasis, onychomycosis).
Rare:	Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation.
Not known:	Vaccine breakthrough infection (after *in utero* exposure to infliximab)*.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare:	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer.
Not known:	Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease and ulcerative colitis), Merkel cell carcinoma.
Blood and lymphatic system disorders	
Common:	Neutropenia, leukopenia, anaemia, lymphadenopathy.
Uncommon:	Thrombocytopenia, lymphopenia, lymphocytosis.
Rare:	Agranulocytosis (including infants exposed *in utero* to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, haemolytic anaemia, idiopathic thrombocytopenic purpura.
Immune system disorders	
Common:	Allergic respiratory symptom.
Uncommon:	Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction.
Rare	Anaphylactic shock, vasculitis, sarcoid-like reaction
Psychiatric disorders	
Common:	Depression, insomnia.
Uncommon:	Amnesia, agitation, confusion, somnolence, nervousness.
Rare:	Apathy.

Nervous system disorders	
Very common:	Headache.
Common:	Vertigo, dizziness, hypoaesthesia, paraesthesia.
Uncommon:	Seizure, neuropathy.
Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
Not known:	Cerebrovascular accidents in close temporal association with infusion.
Eye disorders	
Common	Conjunctivitis
Uncommon	Keratitis, periorbital oedema, hordeolum
Rare	Endophthalmitis
Not known	Transient visual loss occurring during or within 2 hours of infusion
Cardiac disorders	
Common	Tachycardia, palpitation
Uncommon	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia
Rare	Cyanosis, pericardial effusion
Not known	Myocardial ischaemia/myocardial infarction
Vascular disorders	
Common	Hypotension, hypertension, ecchymosis, hot flush, flushing
Uncommon	Peripheral ischaemia, thrombophlebitis, haematoma
Rare	Circulatory failure, petechia, vasospasm
Respiratory, thoracic and mediastinal disorders	
Very common	Upper respiratory tract infection, sinusitis
Common	Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis
Uncommon	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion
Rare	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis)
Gastrointestinal disorders	
Very common:	Abdominal pain, nausea
Common:	Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation
Uncommon	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis
Hepatobiliary disorders	
Common:	Hepatic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.
Skin and subcutaneous tissue disorders	
Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.

Rare:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.
Not known:	Worsening of symptoms of dermatomyositis.
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia, myalgia, back pain.
Renal and urinary disorders	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
Reproductive system and breast disorders	
Uncommon:	Vaginitis.
General disorders and administration site conditions	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
Investigations	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal.

* including bovine tuberculosis (disseminated BCG infection), see section 4.4

Description of selected adverse drug reactions

Systemic injection reaction and localised injection site reaction in adult patients administered with Remsima® SC subcutaneous formulation

The safety profile of Remsima® SC subcutaneous formulation in combination with methotrexate was evaluated in a Phase I/III parallel group study in patients with active rheumatoid arthritis. The safety population consisted of 168 patients in the Remsima® SC subcutaneous group and 175 patients in the Remsima® intravenous group. For study details, see Section 5.1.

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

The incidence of localised injection site reactions (e.g. injection site erythema, pain, pruritus and swelling) was 17.6 per 100 patient-years in the Remsima® SC subcutaneous group (from Week 6) and 21.4 per 100 patient-years in those who switched to Remsima® SC subcutaneous administration (from Week 30). Most of these reactions were mild to moderate and resolved spontaneously without any treatment within a day.

In a Phase I study conducted in patients with active Crohn's disease and active ulcerative colitis, the safety population consisted of 97 patients in the Remsima® SC subcutaneous group (59 patients with active Crohn's disease and 38 patients with active ulcerative colitis) and 78 patients in the Remsima® intravenous group (38 patients with active Crohn's disease and 40 patients with active ulcerative colitis). For study details, see Section 5.1.

The incidence of systemic injection reactions (e.g. injection site erythema, pain, pruritis, bruising) was 23.9 per 100 patient-years in the Remsima® SC subcutaneous group (from week 6) and 8.4 per 100 patient-years in the Remsima® intravenous group who switched to Remsima® SC subcutaneous administration (from Week 30). All of these reactions were mild to moderate and mostly resolved spontaneously without any treatment within a few days.

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with infliximab intravenous administration (see section 4.4). Cases of

transient visual loss occurring during or within 2 hours of infliximab infusion have been reported. Events (some fatal) of myocardial ischaemia/infarction and arrhythmia have also been reported, some in close temporal association with infusion of infliximab; cerebrovascular accidents have also been reported in close temporal association with infusion of infliximab.

Delayed Hypersensitivity

In clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after infliximab-free intervals of less than 1 year. In the psoriasis studies with intravenous infliximab, delayed hypersensitivity reactions occurred early in the treatment course. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients experiencing pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache.

There are insufficient data on the incidence of delayed hypersensitivity reactions after infliximab-free intervals of more than 1 year but limited data from clinical studies suggest an increased risk for delay hypersensitivity with increasing infliximab-free interval (see section 4.4)

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

Immunogenicity

In rheumatoid arthritis patients, the incidence of anti-infliximab antibodies following the subcutaneous infliximab was demonstrated to be not higher than that of the intravenous infliximab and had no significant impact on efficacy (determined by disease activity score in 28 joints [DAS28] and American College of Rheumatology criteria 20 [ACR20]) and the safety profile.

In Crohn's disease and ulcerative colitis patients who received maintenance treatment of subcutaneous infliximab, the antibody incidence was not higher in patients who received subcutaneous infliximab in comparison to those who received intravenous infliximab and had no significant impact on efficacy (determined by clinical response and clinical remission according to CDAI score for Crohn’s disease patients or partial Mypo score for ulcerative colitis patients) and the safety profile.

In psoriatic arthritis patients who received 5 mg/kg with and without methotrexate, antibodies occurred overall in 15% of patients (antibodies occurred in 4% of patients receiving methotrexate and in 26% of patients not receiving methotrexate at baseline).

In psoriasis patients treated with intravenous infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab (see section 4.4: "Infusion reactions and hypersensitivity").

Infections

Tuberculosis, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections have been observed in patients receiving infliximab. Some of these infections have been fatal; the most frequently reported opportunistic infections with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis (see section 4.4).

In clinical studies 36% of infliximab-treated patients were treated for infections compared with 25% of placebo-treated patients.
In rheumatoid arthritis clinical studies, 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 section 4.4).

In post-marketing spontaneous reporting, infections are the most common serious adverse reaction. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been associated with infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extra-pulmonary location have been reported (see section 4.4).

Malignancies and lymphoproliferative disorders

In clinical studies with infliximab in which 5780 patients were treated, representing 5494 patient-years, 5 cases of lymphomas and 26 non-lymphoma malignancies were detected as compared with no lymphomas and 1 non- lymphoma malignancy in placebo-treated patients observed during 941 patient years.

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

Cases of malignancies, including lymphoma, have also been reported in the post-marketing setting (see section 4.4).

In an exploratory clinical trial involving patients with moderate to severe COPD who were either current smokers 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.

A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age (see section 4.4).

In addition, 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 or ulcerative colitis, and most of whom were adolescent or young adult males (see section 4.4).

Heart Failure

In a phase II study aimed at evaluating infliximab in 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 study 150 patients with NYHA Class II-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 wees, 9 of 101 patients treated with infliximab (2 at 5 mg/kg and 7 at 1 0mg/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.

Hepatobiliary Events

In post-marketing surveillance, very rare cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4). A causal relationship between infliximab and these events has not been established.

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 ULN have been observed (see Table 2). 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 therapy. In post-marketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving infliximab (see section 4.4).

Table 2: Proportion of patients with increased ALT activity in Clinical Trials

Indication	Number of patients evaluated for ALT		Median follow-up (wks)[3]		≥3 x ULN		≥5 x ULN	
	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]	173	703	54.1	54.1	3.5%	5.1%	0.0%	1.7%
Paediatric 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%
Paediatric 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 Phase III trials in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg
infliximab at study start and were on placebo in the maintenance phase. Patients who were randomised to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis.

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

Antinuclear Antibodies (ANA)/Double-stranded DNA (dsDNA) Antibodies

Approximately half of the infliximab-treated patients in clinical studies who were ANA negative at baseline developed a positive ANA during the study compared with approximately one fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of infliximab-treated patients compared with 0% of placebo-treated patients. At the last evaluation, 57% of infliximab-treated patients remained anti-dsDNA positive. Reports of lupus and lupus-like syndromes, however, remain uncommon (see section 4.4).

Other special populations

Elderly

In rheumatoid arthritis clinical studies, the incidence of serious infections was greater in infliximab plus methotrexate-treated patients 65 years and older (11.3%) than in those under 65 years of age (4.6%). In patients treated with methotrexate alone, the incidence of serious infections was 5.2% in patients 65 years and older compared to 2.7% in patients under 65 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Single doses up to 20 mg/kg have been administered without direct toxic effect and repeated doses of Remsima® SC subcutaneous formulation up to 240 mg have been administered without toxic effect. There is no specific treatment for Remsima® overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures

instituted as required.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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).

Pharmacodynamic effects

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 joint 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), and increased haemoglobin levels in rheumatoid arthritis patients with reduced haemoglobin levels, 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 normalisation 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 TNF_{α}. 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 TNF_{α} 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 markers at these sites. Endoscopic studies of intestinal mucosa have shown evidence of mucosal healing in infliximab-treated patients.

Clinical efficacy and safety

Adult Rheumatoid Arthritis

Intravenous formulation

The safety and efficacy of infliximab were assessed in two multicentre, randomised, double-blind pivotal trials: ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy) and ASPIRE (Active- controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti- inflammatory drugs was permitted.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology (ACR) criteria (ACR20 for ATTRACT, landmark ACR-N at week 54 for ASPIRE), the prevention of structural 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 the following 5 criteria: evaluator's global assessment, patient's global assessment, functional/disability measure, visual analogue pain scale and 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, through week 102, in physical function.

The ATTRACT trial evaluated responses at 30 weeks (reduction of signs and symptoms), 54 weeks (the prevention of structural damage) and 102 weeks (the improvement in physical function) 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, 3mg/kg or 10mg/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/week) for 6 months prior to enrolment and were to remain on stable doses throughout the study).

At week 30, a higher percentage of patients in all infliximab treated groups had a significant reduction in signs and symptoms compared with methotrexate alone (Table 3). This response was seen as early as 2 weeks, and was maintained through 102 weeks of treatment ($p<0.001$). Improvement in the number of swollen and tender joints, patient's assessment of pain, patient's and evaluator's global assessment of disease, morning stiffness, fatigue and CRP in all infliximab groups was observed ($p<0.05$). Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30, 54 and 102 weeks compared to control.

Prevention of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 3), and was seen as early as 30 weeks and maintained through 102 weeks ($p<0.001$). In the study population, 53% of all infliximab patients compared to 20% of control patients had no deterioration, defined as a ≤0 change from baseline in the total van der Heijde-modified Sharp score at week 54. Similar results were obtained for the individual component scores (erosion and joint space narrowing). Also, greater improvement in physical function (HAQ) through 102 weeks also observed in the infliximab treatment groups compared to control (Table3) and was observed as early as 54 weeks ($p<0.001$).

Table 3: Effects on ACR 20%, Structural Joint Damage and Physical Function

		Infliximab[a]				
	Placebo[a] (n=88)	3mg/kg q 8 wks (n=86)	3mg/kg q 4 wks (n=86)	10mg/kg q 8 wks (n=87)	10mg/kg q 4 wks (n=81)	All Infliximab (n=340)
ACR20 at week 30						
Patients evaluated	88	86	86	87	81	340
Pts with response (%)[b]	18 (20%)	43 (50%)	43 (50%)	45 (52%)	47 (58%)	178 (52%)
Total van de Heijde-modified Sharp scores, change from baseline to week 54[b]						
Patients evaluated	64	71	71	77	66	285
Mean ± SD	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	4.0	0.5	0.1	0.5	-0.5	0.0
Interquartile range	(0.5, 9.9)	(-1.5, 3.0)	(-2.5, 3.0)	(-1.5, 2.0)	(-3.0, 1.5)	(-1.8, 2.0)
Pts with no deterioration (%)[b]	13 (20%)	34 (48%)	35 (49%)	37 (48%)	44 (67%)	150 (53%)
HAQ change from baseline over time through week 102[b,c]						
Patients evaluated	88	86	85	87	81	339
Mean ± SD	0.3±0.4	0.4±0.3	0.5±0.4	0.5±0.5	0.4±0.4	0.5±0.4
Median	0.1	0.3	0.3	0.4	0.3	0.4
Interquartile range	(0.0, 0.4)	(0.1, 0.6)	(0.1, 0.7)	(0.2, 0.9)	(0.1, 0.5)	(0.1, 0.7)

[a] all patients (placebo and infliximab) received concomitant methotrexate and folate with some on corticosteroids and/or non-steroidal anti-inflammatory drugs

[b] $p<0.001$, for each infliximab treatment groups vs. control

[c] HAQ=Health Assessment Questionnaire disability index; greater values indicate less disability

The ASPIRE trial evaluated responses at 54 weeks in 1004 methotrexate naïve patients with early (≤3 years disease duration) active rheumatoid arthritis. Patients randomized had a median age of 51 years with a median disease duration

of 0.6 years, and median swollen and tender joint count of 19 and 31, respectively. All patients received methotrexate (optimised to 20 mg/wk by week 8) and either placebo, 3mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter.

In this trial, infusions were to be administered over 2 hours for the first 3 infusions. The duration of subsequent infusions could be shortened to not less than 40 minutes in patients who did not experience serious infusion reactions.

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 the infliximab + methotrexate groups, 15% of patients achieved a major clinical response vs. 8% in patients treated with methotrexate alone (p=0.003).

In ASPIRE, more than 90% of patients had at least two evaluable x-rays. Inhibition of progression of structural damage was observed at weeks 30 and 54 in the infliximab + methotrexate groups compared to methotrexate alone. Infliximab + methotrexate stopped the progression of joint disease in more patients compared to methotrexate alone, 97% vs. 86%, respectively. Infliximab + methotrexate maintained an erosion free state in a statistically significantly greater proportion of patients than methotrexate alone, 79% vs. 57%, respectively. Fewer patients in the infliximab + methotrexate groups (48%) developed erosions in uninvolved joints compared to methotrexate alone (59%).

Both infliximab treatment groups showed statistically significantly greater improvement in HAQ from baseline averaged over time through week 54 compared to methotrexate alone; 0.7 for infliximab + methotrexate vs. 0.6 for methotrexate alone (p<0.001). There was no worsening in the SF-36 mental component summary score.

Data to support infliximab dose adjustment in rheumatoid arthritis comes from both ATTRACT and ASPIRE, as well as from the START study. START was a randomised, multicentre, double-blind, 3-arm, parallel-group safety study. In one of the arms the secondary objective was to assess the safety and efficacy of dose escalation above 3 mg/kg of infliximab in 1.5 mg/kg increments to a maximum of 9 mg/kg, given every 8 weeks in subjects with an inadequate response to 3 mg/kg at week 22 and subsequent infusions. Results are shown in Table 4.

Table 4: Summary of responders by number of dose escalations (START)

	n	Responders n (%)
Patients in the study at Week 22	329	220 (66.9%)[a]
Patients who were dose escalated[b]	100	
Patients who received 1 dose escalations (final dose 4.5 mg/kg)	59	51 (86.4%)[c]
Patients who received 2 dose escalations (final dose 6.0 mg/kg)	21	17 (81.0%)[c]
Patients who received 3 dose escalations (final dose 7.5 mg/kg)	13	12 (92.3%)[c]
Patients who received 4 dose escalations (final dose 9.0 mg/kg)	7	0 (0.0%)[c]

[a]: responders are defined as subjects who achieved an ACR20 response at week 22

[b]: patients who met the criteria for dose escalation at week 22 or thereafter

[c]: responders are defined as subjects who achieved at least 20% improvement in the number of tender and swollen joints from baseline at 8 weeks after the last dose escalation

Rheumatoid arthritis associated anaemia

Evidence exists that TNFα plays a role in the inhibition of erythropoiesis in chronic inflammatory disease. In three clinical trials in patients with rheumatoid arthritis (ATTRACT, ASPIRE, START), 39.8% of patients with a baseline haemoglobin <12 g/dL had an increase in haemoglobin ≥1 g/dL at week 22 when receiving infliximab plus methotrexate, versus 19.3% in those receiving methotrexate alone (p<0.001). Additionally, 12.1% of patients treated with infliximab plus methotrexate had an increase ≥2 g/dL in haemoglobin vs. 4.5% of patients in the methotrexate arm alone (p<0.001). Significant results were also found for patients with baseline haemoglobin <10 g/dL.

Analyses of the data from ASPIRE showed that infliximab therapy improved rheumatoid arthritis associated anaemia

independent of its effect on ACR 20 response. Furthermore, it showed that among ACR20 responders, infliximab plus methotrexate improved anaemia significantly better than methotrexate alone. Improvement in haemoglobin significantly correlated with improvement in physical function and quality of life at week 22.

Subcutaneous formulation

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

In Part 2 of this study, among 357 patients who were enrolled to receive 2 doses of Remsima® 3 mg/kg intravenously at Weeks 0 and 2, 167 patients were randomised to receive REMSIMA® SC 120 mg subcutaneously at Week 6 and every 2 weeks up to Week 54, while 176 patients were randomised to receive Remsima® 3 mg/kg intravenously at Weeks 6, 14 and 22 and then switched to REMSIMA® SC 120 mg subcutaneous at Week 30 once-every 2 weeks up to Week 54. Methotrexate was given concomitantly.

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

The analysis of other efficacy endpoints showed that efficacy profile of Remsima® SC subcutaneous formulation compared to Remsima® SC intravenous formulation in RA patients was generally comparable in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to Week 54. The mean scores for DAS28 (CRP) and DAS28 (ESR) gradually decreased from baseline at each time point until Week 54 in each treatment arm (see Table 5 and Table 6, respectively).

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

	DAS28 (CRP)		**DAS28 (ESR)**	
Visit	**Remsima® IV 3 mg/kg[b] (N=174)**	**Remsima® SC 120 mg (N=165)**	**Remsima® IV 3 mg/kg[b] (N=174)**	**Remsima® SC 120 mg (N=165)**
Baseline	5.9 (0.8)	6.0 (0.8)	6.6 (0.8)	6.7 (0.8)
Week 6	4.1 (1.2)	4.0 (1.2)	4.8 (1.3)	4.6 (1.2)
Week 22	3.5 (1.2)[a]	3.3 (1.1)[a]	4.1 (1.3)	4.0 (1.1)
Week 54	2.9 (1.2)[b]	2.8 (1.1)	3.4 (1.3)[b]	3.4 (1.2)

a Two-sided 95% CI for difference in the mean change from baseline for DAS28 (CRP) at Week 22 was well above the pre-defined non-inferiority margin of -0.6
b Remsima® IV was switched to Remsima® SC at Week 30

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

	ACR20		**ACR50**		**ACR70**	
Visit	**Remsima® IV 3 mg/kg[a] (N=174)**	**Remsima® SC 120 mg (N=165)**	**Remsima® IV 3 mg/kg[a] (N=174)**	**Remsima® SC 120 mg (N=165)**	**Remsima® IV 3 mg/kg[a] (N=174)**	**Remsima® SC 120 mg (N=165)**
Week 6	103 (59.2%)	107 (64.8%)	45 (25.9%)	47 (28.5%)	18 (10.3%)	19 (11.5%)
Week 22	137 (78.7%)	139 (84.2%)	90 (51.7%)	85 (51.5%)	49 (28.2%)	46 (27.9%)
Week 54	125 (71.8%)[a]	132 (80.0%)	101 (58.0%)[a]	108 (65.5%)	68 (39.1%)[a]	77 (46.7%)

a Remsima® IV was switched to Remsima® SC at Week 30

Ankylosing Spondylitis

Intravenous formulation

Efficacy and safety of infliximab were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active ankylosing spondylitis (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score ≥4 and spinal pain ≥4 on a scale of 1-10). Improvement in signs and symptoms was measured using the ASAS 20 response criteria and/or the BASDAI 50. Improvement in physical function was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI). Improvement in range of axial motion was evaluated using both the Bath Ankylosing Spondylitis Metrology Index (BASMI) and/or clinical measurements of chest expansion. Health-related quality of life was assessed using the SF-36 (physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health).

In the first study (P01522), which had a 3-month double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2 and 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. After the first year of the study, 53 patients continued into an open-label extension to week 102.

At week 12, 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 to 9% of placebo patients ($p<0.01$). Improvement was observed as early as week 2, and was maintained through week 102.

Physical function, range of motion, and quality of life (SF-36) were improved similarly. The results of this study were similar to those seen in 8 additional investigator initiated studies of 169 patients with active ankylosing spondylitis.

In the second trial (ASSERT), 279 patients (78 patients in the placebo group and 201 in the infliximab group) were randomised to receive either placebo (Group 1) or 5 mg/kg infliximab (Group 2) at 0, 2 and 6 weeks and every 6 weeks thereafter through to week 96. At week 24, patients receiving placebo (Group 1) received 5 mg/kg infliximab every 6 weeks through to week 96. Starting with the week-36 infusion and continuing through the week-96 infusion, a patient in Group 2 who had a BASDAI ≥3 at 2 consecutive visits received a 7.5 mg/kg infliximab infusion and continued to receive 7.5 mg/kg infliximab infusions every 6 weeks thereafter through week 96.

At 24 weeks, the primary efficacy timepoint, improvement in signs and symptoms, as measured by the proportion of patients achieving an ASAS 20 response, was 61% in the infliximab-treated group vs. 19% in the placebo group ($p<0.001$). The improvement was observed as early as week 2. Significant improvement in signs and symptoms was also assessed by the BASDAI, with 51% of infliximab-treated subjects achieving at least 50% reduction from baseline in BASDAI score (mean baseline score was 6.5 in the infliximab group and 6.2 in the placebo group), compared with 10.7% of placebo patients ($p<0.001$). The median improvement from baseline in range of axial motion, as assessed by the BASMI was 1.0 for the infliximab-treated group vs. 0.0 for the placebo group ($p=0.019$). The median percent improvement from baseline in chest expansion was 17% for the infliximab-treated group and 0% for the placebo group ($p=0.037$). Physical function and quality of life as measured by the BASFI and the SF-36 were also improved significantly at week 24.

All improvements were maintained through week 102 and patients who crossed over to infliximab from placebo at week 24 showed improvement in all scores that were similar to the infliximab-treated group at week 102.

Psoriatic Arthritis

Intravenous formulation

Efficacy and safety were assessed in two multicentre, double-blind, placebo-controlled studies in patients with active psoriatic arthritis.

In the first study (IMPACT), efficacy and safety of infliximab were studies in 104 patients with active polyarticular psoriatic arthritis. In total, 74 subjects were on at least one concomitant DMARD, 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) with one or more of the following subtypes: arthritis involving DIP

joints, arthritis mutilans, asymmetric peripheral arthritis, polyarticular arthritis, and spondylitis with peripheral arthritis. Patients also had plaque psoriasis with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). Patients had previously been treated with NSAIDs (81.5%), DMARDs (79.5%) and corticosteroids (29.0%). 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, 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 are shown in Table 7 below:

Table 7: Effects on ACR, PASI and Physical Function in IMPACT and IMPACT 2

	IMPACT 1			IMPACT 2			
	Placebo (Week 16)	Infliximab (Week 16)	Infliximab (Week 50)	Infliximab (Week 98)	Placebo (Week 24)	Infliximab (Week 24)	Infliximab (Week 54)
Patients randomized	52	52	52	N/Aa	100	100	100
ACR response (% of patients)							
N	52	52	49	78	100	100	76
ACR20 response*	5 (10%)	34 (65%)	34 (69%)	48 (62%)	16 (16%)	54 (54%)	48 (63%)
ACR50 response*	0 (0%)	24 (46%)	26 (53%)	35 (45%)	4 (4%)	41(41%)	32 (42%)
ACR70 response*	0 (0%)	15 (29%)	19 (39%)	27 (35%)	2 (2%)	27 (27%)	20 (26%)
PASI response (% of patients)[b]							
N	16	22	22	25	87	83	61
PASI 50 response*	0 (0%)	22 (100%)	19 (86%)	19 (76%)	7 (8%)	62 (75%)	42 (69%)
PASI 75 response*	0 (0%)	15 (68%)	13 (59%)	16 (64%)	1 (1%)	50 (60%)	31 (51%)
PASI 90 response*	0 (0%)	8 (36%)	9 (41%)	12 (48%)	0 (0%)	32 (39%)	26 (43%)
HAQ (% improvement from baseline)[e]							
N	51	51	48	77	95	94	76
Mean (± SD)*	-2% (8)	50% (8)	43% (9)	38% (72)	-19% (103)	46% (42)	43% (96)

[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

[e] HAQ=Health Assessment Questionnaire

* p≤0.01for infliximab vs. placebo at week 16 in IMPACT; P<0.001 for infliximab vs. placebo at week 24 for IMPACT2

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54 respectively. The responses were similar regardless of concomitant use of methotrexate.

Treatment with infliximab also resulted in significant improvements in measures of disease activity, including swollen joints, tender joints, dactylitis, and enthesopathy as compared to placebo in both trials.

In the IMPACT and IMPACT 2 studies, 31% and 12% respectively of patients randomised to infliximab at baseline achieved a major clinical response (defined as achieving an ACR70 response at all visits for a continuous 24-week period) at week 98 and week 54 respectively. In contrast, 0% of patients in the placebo group in IMPACT (p<0.001) and 2% of patients in the placebo group in IMPACT 2 (p=0.006) achieved an ACR70 response at the last visit before receiving infliximab therapy.

Infliximab-treated patients demonstrated significant improvement in physical function and prevented worsening of disability 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.

Radiographic changes were assessed in both the IMPACT 2 and IMPACT studies. Radiographs of both the hands and feet were collected at baseline, weeks 24 and 54 in all patients in IMPACT 2, and at baseline, weeks 50 and 98 in subsets of patients in IMPACT. In IMPACT 2 infliximab treatment inhibited the progression of structural damage compared with placebo treatment at the Week 24 primary endpoint as measured by change from baseline in total modified vdH-S score. Differences between infliximab and placebo groups at week 24 were statistically significant for total modified vdH-S score, hands, feet, erosion and joint space narrowing (JSN) scores. Significantly more subjects in the placebo group had readily apparent radiographic progression at week 24 in total modified vdH-S, erosion, and JSN scores compared with the proportion of subjects in the infliximab group.

The maintenance of radiographic benefit was observed through 1 year. Supportive data from IMPACT demonstrated that the inhibition of progression of structural damage was sustained through 2 years.

The change from baseline at weeks 24 and 54 in the total modified vdH-S score in IMPACT 2 is presented in the table below:

Table 8: Summary of change from baseline in total modified van der Heijde modified Sharp score at weeks 24 and 54 (IMPACT 2)

	Placebo / infliximab 5mg/kg*	Infliximab 5 mg/kg
Subjects randomised	100	100
Change from baseline		
n	100	100
Week 24		
Mean ± SD	0.82 ± 2.62	-0.70 ± 2.53
p-value		< 0.001
Week 54		
Mean ± SD	0.53 ± 2.60	-0.94 ± 3.40
p-value		0.001

*placebo patients crossed over to infliximab at week 24

Crohn's Disease in adult patients (≥18 years)

Intravenous formulation

The safety and efficacy of single and multiple doses of infliximab were assessed in two randomised double- blinded, placebo-controlled studies in patients with moderate to severe, active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥220 ≤400) with 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.

In the single dose trial of 108 patients, 22/27 (81%) of infliximab-treated patients receiving a 5 mg/kg dose achieved a clinical response (decrease in CDAI by ≥70 points) 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.

In the multidose trial, 573 patients received 5 mg/kg at week 0 and were then randomised to one of three treatment groups; the placebo maintenance group received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at week 2 were randomised and analysed separately from those not in response.

At week 2, 58% (335/573) of patients were in clinical response (decrease in CDAI ≥25% and ≥70 points). A significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission at week 30, compared to patients in the placebo maintenance group. Patients in the infliximab maintenance groups had significantly longer time to loss of response than patients in the placebo maintenance group ($p<0.001$). Median time to loss of response was 46 weeks in the combined infliximab maintenance treatment group versus 19 weeks in the placebo maintenance group. Patients who achieved a response and subsequently lost response were eligible to receive infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomised. Eighty-

nine percent (50/56) of patients who lost clinical response on infliximab 5 mg/kg every eight week maintenance dosing, responded to a 10 mg/kg infliximab infusion.

Significant improvement in quality of life measures were seen in both the IBDQ (Inflammatory Bowel Disease Questionnaire) and SF-36 ($p<0.001$) scores in infliximab-treated patients at week 30.

For patients receiving corticosteroids at baseline, the proportion of these patients in clinical remission and not receiving corticosteroids at week 30 was 31% for the 5 mg/kg maintenance group and 37% for the 10 mg/kg maintenance group, compared with 11% of patients in the placebo maintenance group ($p=0.001$ for both the 5 mg/kg and 10 mg/kg maintenance groups). The median corticosteroid dose at baseline (20 mg/day) was reduced to 10 mg/day in the placebo maintenance group and 0 mg/day in the combined infliximab maintenance groups by week 30, indicating that at least 50% of the infliximab maintenance patients were able to discontinue steroid use.

At week 10 a significantly greater proportion of patients in the infliximab maintenance groups combined (31%) had healing of the mucosa compared to patients in the placebo group (0%, $p=0.010$). Results were similar at week 54.

The safety and efficacy were also assessed in a randomised, double-blinded, placebo-controlled study in 94 patients with fistulising 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 or surgery 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 the 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 ($p=0.001$).

Subcutaneous formulation

The efficacy of subcutaneous infliximab in active Crohn’s disease and active ulcerative colitis patients was assessed in an open-label, randomised, parallel-group, Phase I study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of PK of subcutaneous infliximab compared to intravenous infliximab treatment.

In Part 1 of this study, 45 patients with active Crohn’s disease were enrolled to receive 2 doses of Remsima® 5 mg/kg intravenously at Weeks 0 and 2 and subsequently 44 patients were randomised into four cohorts to receive Remsima® 5 mg/kg intravenously (n=13) at Week 6 and every 8 weeks up to Week 54, REMSIMA® SC 120 mg subcutaneously (n=11), Remsima® 180 mg subcutaneously (n=12) or Remsima® 240 mg subcutaneously (n=8) at Week 6 and every 2 weeks up to Week 54.

In Part 2 of this study, among 136 patients (57 patients with active Crohn’s disease and 79 patients with active ulcerative colitis) who were enrolled to receive 2 doses of Remsima® 5 mg/kg intravenously at Weeks 0 and 2, 66 patients (28 patients with active Crohn’s disease and 38 patients with active ulcerative colitis) were randomised to receive Remsima® 120/ 240 mg subcutaneously at Week 6 and every 2 weeks up to Week 54, while 65 patients (25 patients with active Crohn’s disease and 40 patients with active ulcerative colitis) were randomised to receive Remsim®a 5 mg/kg intravenously at Week 6, 14 and 22 and then switched to Remsima® SC 120/ 240 mg subcutaneous formulation at Week 30 once-every 2 weeks up to Week 54. The dosage of Remsima® SC 120/ 240 mg subcutaneous formulation was determined based on the patient’s body weight at Week 6 for those who received Remsima® subcutaneously and at Week 30 for those who switched to Remsima® SC subcutaneous formulation (Remsima® SC subcutaneous 120 mg for patients <80 kg; 240 mg for patients ≥80 kg).

The pooled data analysis of efficacy endpoints from Part 1 and Part 2 showed that the efficacy profile of Remsima® SC subcutaneous formulation compared to Remsima® intravenous formulation in active Crohn’s disease patients was generally comparable in terms of clinical response, defined as a decrease in CDAI by ≥70 points and ≥100 points from baseline and clinical remission, defined as an absolute CDAI score of <150 points (Table 9, Table 10).

Table 9
Proportion of Patients Achieving Clinical Response According to the CDAI-70 and CDAI-100 Criteria
Combined Data from Part 1 and 2

	CDAI-70			CDAI-100		
Visit	**Remsima® IV 5 mg/kg (N=37)**	**Remsima® SC 120 mg (N=31)**	**Remsima® SC 120/ 180/ 240 mg (N=46)**	**Remsima® IV 5 mg/kg (N=37)**	**Remsima® SC 120 mg (N=31)**	**Remsima® SC 120/ 180/ 240 mg (N=46)**
Week 6	28 (75.7%)	26 (83.9%)	42 (72.4%)	24 (64.9%)	20 (64.5%)	30 (51.7%)
Week 30	25 (67.6%)	24 (77.4%)	43 (74.4%)	23 (62.2%)	24 (77.4%)	43 (74.4%)

Note: A patient was defined as having a CDAI-70 response if there was a decrease in CDAI score of 70 points or more from the baseline value. A patient was defined as having a CDAI-100 response if there was a decrease in CDAI score of 100 points or more from the baseline value.

Table 10
Proportion of Patients Achieving Clinical Remission According to CDAI Score
Combined Data from Part 1 and 2

Visit	**Remsima® IV 5 mg/kg (N=37)**	**Remsima® SC 120 mg (N=31)**	**Remsima® SC 120/ 180/ 240 mg (N=46)**
Week 6	15 (40.5%)	18 (58.1%)	23 (39.7%)
Week 30	21 (56.8%)	23 (74.2%)	39 (67.2%)

Note: Clinical remission was defined as an absolute CDAI score of less than 150 points.

The analysis of efficacy endpoints showed that efficacy profile of Remsima® subcutaneous formulation compared to Remsima® intravenous formulation in active ulcerative colitis patients was generally comparable in terms of clinical response and clinical remission according to partial Mayo scores (Table 11, Table 12).

Table 11
Proportion of Patients Achieving Clinical Response According to Partial Mayo Score

Visit	**Remsima® IV 5 mg/kg (N=39)**	**Remsima® SC 120 mg (N=28)**	**Remsima® SC 120/ 240 mg (N=38)**
Week 6	31 (79.5%)	19 (67.9%)	28 (73.7%)
Week 30	29 (74.4%)	23 (82.1%)	33 (86.8%)

Note: A patient was defined as having a clinical response according to partial Mayo score if there was a decrease from baseline in partial Mayo score at least 2 points, with an accompanying decrease from baseline in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1.

Table 12
Proportion of Patients Achieving Clinical Remission According to Partial Mayo Score

Visit	**Remsima® IV 5 mg/kg (N=39)**	**Remsima® SC 120 mg (N=28)**	**Remsima® SC 120/ 240 mg (N=38)**
Week 6	12 (30.8%)	10 (35.7%)	14 (36.8%)
Week 30	21 (53.8%)	18 (64.3%)	26 (68.4%)

Note: Clinical remission according to partial Mayo score was defined as a partial Mayo of 1 point or lower.

The mucosal healing in active Crohn's disease and active ulcerative colitis patients for Remsima® SC subcutaneous formulation and Remsima® intravenous formulation was evaluated at Week 22 and the results are summarised in Table 13.

Table 13
Proportion of Patients Achieving Mucosal Healing in Crohn's Disease and Ulcerative Colitis

Visit	Remsima® IV 5 mg/kg (N=64)	Remsima® SC 120 mg (N=48)	Remsima® SC 120/ 240 mg (N=66)
Week 22	16/39 (41.0%)	19/40 (47.5%)	26/54 (48.1%)

Note: For patients with Crohn's disease, mucosal healing was defined as an absolute overall SES-CD of 2 points or less without inaccessible or missing. Percentages were calculated by using the number of patients who had Overall SES-CD at each visit and who had confirmed mucosal abnormalities regardless of exploration result or Overall SES-CD of 0 with inaccessible exploration result or with missing exploration result at baseline as the denominator. For patients with ulcerative colitis, mucosal healing was defined as absolute endoscopic subscore of 0 or 1 from Mayo scoring system. Percentages were calculated using the number of patients who had results at both baseline and each visit as the denominator.

Psoriasis

Intravenous formulation

The efficacy of infliximab was assessed in two multicentre, randomised, 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. Marked responders were identified as patients who achieved ≥90% improvement in PASI from baseline.

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 median baseline BSA was 27.0%, the median baseline PASI score was 18.9; 62.2% of patients had a baseline PGA score of "moderate" and 24.9% of patients had a baseline PGA score of "marked" or "severe." Prior therapy with PUVA, methotrexate, cyclosporin or acitretin had been received by 81.5% of the patients. The proportion of patients with ≥75% improvement in PASI from baseline (PASI 75) at week 10 was 79.8% in the combined infliximab group, 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 ($p<0.001$ for each infliximab versus placebo comparison). At week 10, a significantly greater proportion of infliximab-treated patients, both in the combined group (51.5%) and in the individual groups (3 mg/kg: 45.5%; 5 mg/kg: 57.6%), achieved a marked response (≥90% improvement in PASI from baseline) compared to the placebo-treated patients (2.0%). In the 3 mg/kg group, 60.6% of patients maintained response through week 14 and 75.3% of patients in the 5 mg/kg group maintained response through week 18. By week 26, twenty weeks after the last induction dose, 30% of patients in the 5mg/kg group and 13.8% of patients in the 3 mg/kg group were PASI 75 responders, suggesting the need for maintenance therapy.

Health related quality of life was assessed with the DLQI. The median baseline DLQI was 12. The median change from baseline in DLQI at week 10 was -8.0 and -10.0 for the infliximab 3 mg/kg and 5 mg/kg groups, respectively, compared with 0.0 in the placebo group ($p<0.001$ for all infliximab versus placebo comparisons), demonstrating a substantial improvement in quality of life for patients on infliximab therapy.

EXPRESS evaluated the efficacy of infliximab induction and maintenance therapy in 378 patients with plaque psoriasis who were candidates for phototherapy or systemic therapy. 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).

In EXPRESS, the median baseline BSA was 29%, the median baseline PASI score was 21.1 and the majority of patients (89.9%) had a PGA score of moderate, marked, or severe. Prior therapy with PUVA, methotrexate, cyclosporin, or acitretin had been received by 71.4% of patients. At week 10 PASI 75 response was achieved by 80.4% in the infliximab group vs. a placebo group rate of 2.6%, $p<0.001$). Median time to PASI 75 was between 2 and 6 weeks. Improvement in PASI was consistent across subgroups defined by baseline demographics, clinical disease characteristics and psoriasis medication history. Marked responses (PASI 90) at week 10 was achieved by 57.1% of the infliximab group compared to 1.3% in the placebo group ($p<0.001$). The response was maintained through the 24 week, the placebo-controlled period. PASI response rates through week 50 are presented in Table 14.

Table 14: Summary of PASI Response Through Week 50 by Visit, EXPRESS

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg	P-value
Week 2			
n	77	298	
≥ 90% improvement	0 (0.0%)	3 (1.0%)	
≥ 75% improvement	0 (0.0%)	16 (5.4%)	
≥ 50% improvement	3 (3.9%)	106 (35.6%)	
Week 6			
n	77	295	
≥ 90% improvement	1 (1.3%)	94 (31.9%)	
≥ 75% improvement	4 (5.2%)	184 (62.4%)	
≥ 50% improvement	6 (7.8%)	264 (89.5%)	
Week 10			
n	77	301	
≥ 90% improvement	1 (1.3%)	172 (57.1%)	<0.001
≥ 75% improvement	2 (2.6%)	242 (80.4%)	<0.001
≥ 50% improvement	6 (7.8%)	274 (91.0%)	
Week 24			
n	77	276	
≥ 90% improvement	1 (1.3%)	161 (58.3%)	<0.001
≥ 75% improvement	3 (3.9%)	227 (82.2%)	<0.001
≥ 50% improvement	5 (6.5%)	248 (89.9%)	
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%)	

At week 10, 82.9% of infliximab patients achieved a PGA score of minimal or cleared compared to 3.9% of placebo patients (p<0.001). PGA scores at weeks 6, 10, 24 and 50 are presented in Table 15.

Table 15: Summary of PGA Scores Through Week 50 by Visit, EXPRESS

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg	P-value
Week 2			
n	77	298	
PGA of cleared (0) or minimal (1)	3 (3.9%)	59 (19.8%)	
PGA of cleared (0), minimal (1), or mild (2)	9 (11.7%)	208 (69.8%)	
Week 6			
n	77	295	
PGA of cleared (0) or minimal (1)	2 (2.6%)	205 (69.5%)	
PGA of cleared (0), minimal (1), or mild (2)	16 (20.8%)	272 (92.2%)	
Week 10			
n	77	292	
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)	< 0.001
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)	< 0.001

Week 24			
n	77	276	
PGA of cleared (0) or minimal (1)	2 (2.6%)	203 (73.6%)	< 0.001
PGA of cleared (0), minimal (1), or mild (2)	15 (19.5%)	246 (89.1%)	< 0.001
Week 50			
n	68	281	
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%)	

The median baseline value for the DLQI was 12.5. The mean baseline values were 45.6 for the SF-36 physical component and 45.7 for the mental component. Quality of life improved significantly compared to placebo at weeks 10 and 24 when evaluated by both DLQI and SF-36.

The median baseline NAPSI score for nail psoriasis was 4 and the median number of nails involved with psoriasis was 10. Patients treated with infliximab showed a clear improvement in nail psoriasis from baseline compared to placebo treated patients, as measured by NAPSI score, and by the decrease in number of nails involved.

Ulcerative colitis

Intravenous formulation

The safety and efficacy of infliximab were assessed in two (ACT 1 and ACT 2) randomised, 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-mercaptopurine (6-MP), azathioprine (AZA)]. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. In both studies, patients were randomised to receive either placebo 5 mg/kg infliximab, or 10 mg/kg infliximab at weeks 0, 2, 6, 14 and 22. Corticosteroid taper was permitted after week 8.

In both studies, a significantly greater percentage of patients in the infliximab groups were in clinical response and clinical remission at week 8 when compared to placebo. Furthermore, in both ACT 1 and ACT 2, a significantly greater proportion of patients treated with 5 mg/kg or 10 mg/kg infliximab experienced clinical response and clinical remission at week 30 compared to placebo treatment. In addition, the proportion of patients in sustained response (i.e., were in clinical response at both week 8 and week 30) in the infliximab groups was at least twice as large as in the placebo group. Results from weeks 8 and 30 are shown in Table 9.

Of patients treated with corticosteroids at baseline, a significantly greater proportion of patients in the infliximab-treated groups were in clinical remission at week 30 and able to discontinue corticosteroids compared to the placebo-treated patients (22.3% versus 7.2%, respectively, see Table 16).

Additionally, at weeks 8 and 30, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg dose groups in ACT 1 and ACT 2 achieved mucosal healing compared to patients in the placebo group. The proportion of subjects with mucosal healing was similar between the 2 infliximab dose groups in the two studies (see Table 16).

Table 16: Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/kg	Combined
Subjects randomised	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, sustained remission, and in remission without Corticosteroids				
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 response (clinical response at both Week 8 and Week 30)[a]	5.3%	19.0%	24.4%	21.7%
Randomised subjects with corticosteroids at baseline	139	130	139	269
Subjects without corticosteroids and in clinical remission at Week 30[b]	7.2%	21.5%	23.0%	22.3%
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
[b]: $p \leq 0.001$, 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 a greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.6% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportions of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in the placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

A greater proportion of patients in the combined infliximab treatment group were able to discontinue corticosteroids while remaining in clinical remission compared to the placebo treatment group at both week 30 (22.3% vs. 7.2%, $p \leq 0.001$, see Table 9) and week 54 (21.0% vs. 8.9%, $p=0.022$).

The cumulative incidence of colectomy after the first infusion of infliximab through week 54 was collected and pooled from the ACT 1 and ACT 2 studies and their extensions, see Table 17).

Table 17: Incidence of colectomy through 54 weeks after 1st infusion of infliximab

		Infliximab		
	Placebo	5mg/kg	10mg/kg	Combined
Subjects randomized	244	242	242	484
Subjects with colectomy through 54 weeks	36 (16.5%)*	28a (12.2%)*	18b (7.9%)*	46c (10.1%)*

* : Percentages based on the Kaplan-Meier estimates

a : p=0.166 for infliximab treatment versus placebo

b : p=0.007 for infliximab treatment versus placebo

c : p=0.015 for the combined infliximab treatment group versus placebo

The pooled data analysis from the ACT 1 and ACT 2 studies and their extensions, analysed from baseline through week 54, demonstrated a statistically significant reduction of ulcerative colitis related hospitalizations (p= 0.003) and ulcerative colitis related surgical procedures (p= 0.026) in the combined infliximab treatment group compared to the placebo treatment group.

In ACT 1 and ACT 2, infliximab improved Quality of Life, as 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.

Paediatric population

Active Crohn's disease in paediatric patients (6 to17 years)

Intravenous formulation

The safety and efficacy of single and multiple doses of infliximab were assessed in a randomised, single-dose, multicentre Phase II study in 21 paediatric patients with active Crohn's disease and in a randomised, multiple dose, open-label, multicentre Phase III study in 112 paediatric Crohn's disease patients (the REACH trial). In REACH, all subjects were required to be on a stable dose of 6-mercaptopurine (6-MP), azathioprine (AZA) or methotrexate (MTX) (35% were also receiving corticosteroids at baseline).

In the Phase II single-dose trial of 21 patients (11 to 17 years old, median age 15.0 years), all patients achieved a clinical response (decrease in CDAI ≥70 points or decrease in PCDAI ≥10) at some point in the 20 weeks following the single dose of infliximab, and clinical remission (defined as a reduction in the modified CDAI score to below 150 points or a reduction in the PCDAI to below 10) was achieved by 10 (47.6%) patients. Of the 3 doses administered (1, 5, or 10 mg/kg), the 5 mg/kg and 10 mg/kg treatment groups had a larger proportion of patients achieving clinical remission (16.7% in the 1 mg/kg infliximab treatment group as compared with 57.1% and 62.5% in the 5 mg/kg and 10 mg/kg infliximab treatment groups, respectively). All 7 patients who had fistulising disease had their fistulas closed for at least 1 evaluation visit (8 weeks).

In the multiple dose Phase III trial (REACH), 112 patients (6 to 17 years, median age 13.0 years) received 5 mg/kg infliximab at weeks 0, 2, and 6. Patients assessed by the investigator to be in clinical response at week 10 were randomised and received either 5 mg/kg infliximab q8 weeks or q12 weeks as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose or shorter dosing interval was allowed.

In REACH, clinical response at Week 10 was 88.4% (99/112) as compared with 66.7% (128/192) in adults (ACCENT 1). Similarly, the proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112) as compared with 39.1% (75/192) in adults (ACCENT 1).

At week 30; the proportion of subjects in clinical response was significantly higher in the q8 week (73.1%, 38/52) than in the q12 week maintenance treatment group (47.1%, 24/51; p=0.007). At week 54, the proportion of subjects in clinical response was also significantly higher for subjects in the q8 week (63.5%, 33/52) than in the q12 week maintenance treatment group (33.3%, 17/51; p=0.002).

At week 30, the proportion of patients in clinical remission was significantly higher in the q8 week maintenance treatment group (59.6%, 31/52) than in the q12 week maintenance treatment group (35.3%, 18/51; p=0.013). At week 54, the proportion of patients in clinical remission was also significantly higher for patients in the q8 week (55.8%, 29/52) than in the q12 week (23.5%, 12/51; p<0.001) maintenance treatment groups.

In REACH, the change from baseline in average daily corticosteroid use was significant at weeks 10, 30, and 54 ($p<0.001$). For patients receiving corticosteroids at baseline in REACH, clinical remission achieved with no corticosteroids at week 30 was 45.8% for the q8 week and 33.3% for the q12 week maintenance treatment group. At week 54, 45.8% of patients in the q8 week and 16.7% of subjects in the q12 week maintenance treatment group were in clinical remission and not receiving corticosteroids.

Quality of life was assessed using the IMPACT III score (a QOL questionnaire specifically developed and validated for paediatric patients with inflammatory bowel disease). It was administered only to subjects in North America. The mean changes (negative change indicates improvement) from baseline of the IMPACT III score at Weeks 10, 30 and 54 (-22.9, -21.1, and -24.3, respectively) were all significant ($p<0.001$).

The height z-score is a measure of the deviation of the paediatric patient's height from the expected height for a population of the same age and gender. In the population studied, the median z-score at baseline was -1.6. The median changes from baseline in the z-scores were 0.3 and 0.4 for week 30 and week 54, respectively. The z scores were significantly improved from baseline at both week 30 ($p<0.001$) and week 54 ($p<0.001$).

Paediatric Ulcerative Colitis (6 through 17 Years)

Intravenous formulation

The efficacy and safety of induction and maintenance infliximab were assessed in a multicentre, randomised, open-label, parallel group clinical study (C0168T72) in 60 paediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severe active ulcerative colitis (Mayo score of 6 to 12; endoscopic subscore ≥2) with an inadequate response to conventional therapies. At baseline 53% of patients were receiving aminosalicylates, 53% were receiving immunomodulator therapy [6-mercaptopurine (6-MP), azathioprine (AZA) and /or methotrexate (MTX)] and 62% of patients were receiving corticosteroids. Discontinuation of immunomodulators and corticosteroid taper were permitted after week 0. 77% of patients had extensive disease as indicated by endoscopy.

All patients received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients who did not respond to infliximab at Week 8 (n=15) received no further drug and returned for safety follow-up. At week 8, 45 patients were randomised and received 5 mg/kg infliximab at either every 8 weeks or every 12 weeks as a maintenance treatment regimen.

The primary endpoint was clinical response at week 8, defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, including a decrease in the rectal bleeding subscore by ≥ 1 points or achievement of a rectal bleeding subscore of 0 or 1. The proportion of patients in clinical response at week 8 was 73.3% (44/60). Clinical response at week 8 was similar between those with or without concomitant immunomodulator use at baseline. Clinical remission at Week 8 was measured by the Mayo score, defined as a Mayo score of ≤ 2 points with no individual subscore > 1. Clinical remission was also assessed at Week 8 and Week 54 using the Paediatric Ulcerative Colitis Activity Index (PUCAI) score and was defined by a PUCAI score of < 10 points. Clinical remission at Week 8 was 40% (24/60) as measured by the Mayo score and 33.3% (17/51) as measured by the PUCAI score.

At week 54, the proportion of patients in clinical remission as measured by the PUCAI score was 38% (8/21) in the every 8 weeks maintenance group and 18% (4/22) in the every 12 weeks 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 every 8 weeks and 0% (0/13) for the every 12 weeks maintenance treatment group.

Mucosal healing was defined as an endoscopy subscore (from the Mayo score) of 0 or 1. The proportion of patients with mucosal healing at week 8 was 68.3% (41/60) of which 33% (20/60) of patients achieved complete mucosal healing defined as having an endoscopy subscore of 0.

Although endoscopy was optional at week 54, 9 patients who had mucosal healing at week 8 had endoscopies at week 54. 89% (8/9) of these patients were still in mucosal healing.

FURTHER INFORMATION

Intravenous formulation

As part of the pharmaceutical and nonclinical development programme of REMSIMA®, 33 *in vitro* tests in comparison to Remicade® have been conducted. These tests covered investigations of the binding affinity of REMSIMA® and Remicade for human TNFα, for soluble human TNFα in trimeric and monomeric forms, for tmTNFα-Jurkat cells, Fcγ receptors (FcγRI, FcγRIIa and FcγRIIIa), neonatal Fc receptor, and to C1q as well as tests on tissues cross reactivities. Overall, these tests found that REMSIMA® and Remicade are comparable. In addition, functional tests showed that

REMSIMA® and Remicade are comparable with regard to neutralising TNFα, complement-dependent cytotoxicity (CDC), apoptosis, antibody-dependent cell-mediated cytotoxicity (ADCC). Both products did not show any binding affinity for TNFß.

A randomised, double-blind, multicentre, single-dose intravenous (i.v.) infusion, parallel-group, prospective Phase 1 study (CT-P13 1.1) in patients with ankylosing spondylitis showed that the pharmacokinetic profile of REMSIMA® was comparable with the reference product. The ratio (90% CI) of geometric means (REMSIMA® to reference treatment) was 104.48 % (94.32% – 115.75%) for AUCt and 101.53% (94.67% – 108.89%) for Cmax,ss

Results from the pivotal Phase 3 study (CT-P13 3.1) conducted in patients with rheumatoid arthritis support the results of the PK equivalence study (CT-P13 1.1) with similar Cmin and Cmax values observed for REMSIMA® and the reference product throughout the dosing period.

Therapeutic equivalence of REMSIMA® and Remicade was demonstrated in a double-blind, randomised, multicentre, parallel-group, prospective Phase 3 study in adult patients with RA not receiving adequate response with methotrexate alone.

The primary efficacy endpoint was the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30.

In the all-randomized population, the proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 was similar in 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 equivalence between the treatment groups.

The efficacy results of REMSIMA® up to Week 54 were comparable to those of Remicade for all endpoints with the exception of time to onset of ACR20 response. The results from 2 statistical analyses indicated that patients in the REMSIMA® treatment group had a higher likelihood of achieving clinical response according to the ACR20 criteria than patients in the Remicade treatment group. There was evidence to suggest that the time to onset of clinical response was shorter for patients in the REMSIMA® treatment group than patients in the Remicade treatment group.

Comparative efficacy of REMSIMA® with Remicade throughout controlled 54 weeks was similar for ACR20, ACR50, ACR70, EULAR and DAS28 at all time-points.

The efficacy in terms of ACR20, ACR50, ACR70, EULAR and DAS28 following single way transition from Remicade to REMSIMA® was sustained throughout 54 week extension phase.

The efficacy of REMSIMA® was also demonstrated in a randomized, double-blind, multicenter, parallel-group, study designed to assess the pharmacokinetic (PK) equivalence, efficacy and safety of multiple doses of either REMSIMA® or Remicade reference product (5 mg/kg) administered by a 2-hour intravenous (IV) infusion per dose in patients with active ankylosing spondylitis (AS).

REMSIMA® and Remicade treatment groups showed comparable effect in terms of efficacy with regard to ASAS20 and ASAS40 responses at Weeks 14, 30 and 54.

Patients who received Remicade in the initial study underwent a single way transition to REMSIMA®.

The efficacy outcomes in both the initial and extension studies demonstrate that the effect of REMSIMA® and Remicade on ASAS20 and ASAS40 increased slightly between week 14 and was consistently maintained until the end of the extension study CT-P13 1.3

With overlapping 95% confidence intervals for ASAS20 and ASAS40 treatment difference estimates throughout the entire treatment period, there were no discernable differences between REMSIMA® and Remicade in the initial study and between REMSIMA® maintenance and switch treatment groups in extension studies, respectively.

There were no notable changes in pattern of ASAS20 and ASAS40 response following transition of Remicade treated patients to REMSIMA®.

5.2 Pharmacokinetic properties

Absorption and distribution

Single subcutaneous injections of 120, 180 and 240 mg of infliximab yielded approximately dose proportional increases in

the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC). The apparent volume of distribution during the terminal phase (mean of 7.3 to 8.8 litres) was not dependent on the administered dose.

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

The bioavailability of infliximab subcutaneous, estimated in a population PK model, is 58% (95% CI: 54% - 62%).

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

After administration of infliximab 120 mg subcutaneously every 2 weeks (from Week 6 after 2 doses of intravenous infliximab at Weeks 0 and 2) to patients with active Crohn's disease and active ulcerative colitis, the mean (CV%) C_{trough} level at Week 22 was 20.0 µg/mL (48.9%) at steady state.

Elimination

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.

In studies in healthy subjects, the mean (± SD) apparent clearance of REMSIMA® SC 120 mg administered subcutaneously was 19.3 ± 6.9 mL/hr.

In the RA patients, the mean (± SD) clearance of REMSIMA® SC 120 mg subcutaneous at Week 22 was 18.8 ± 8.3 mL/hr at steady state. In the active Crohn's disease and active ulcerative colitis patients, the mean (± SD) clearance of REMSIMA® SC 120 mg subcutaneous at Week 22 was 16.1 ± 6.9 mL/hr at steady state.

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

Special populations

Elderly

The pharmacokinetics of infliximab injected via subcutaneous route in elderly patients has not been studied.

Paediatric population

Subcutaneous administration of Remsima® is not recommended for paediatric use and no data are available on the use of Remsima® administered subcutaneously in the paediatric population.

Hepatic and renal impairment

Studies with infliximab have not been performed in patients with liver or renal disease.

5.3 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.

The subcutaneous administration of Remsima to New Zealand White rabbits was well tolerated at the actual concentration to be used in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid
Sodium acetate trihydrate
Sorbitol
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

30 months

6.4 Special precautions for storage

REMSIMA® SC pre-filled syringes should be stored at 2°C to 8°C.

Do not freeze. Keep the medicinal product in its outer carton in order to protect from light. The medicinal product may be stored at temperatures up to a maximum of 25ºC for a period of up to 14 days. The medicinal product must be discarded if not used within the 14-day period.

6.5 Nature and contents of container

REMSIMA® SC 120 mg solution for injection in pre-filled syringe
REMSIMA® SC 120 mg solution for injection in single-use pre-filled syringe (type I glass) with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:

- 1 prefilled syringe (1 mL sterile solution) with 2 alcohol pads.

REMSIMA® SC 120 mg solution for injection in pre-filled syringe with automatic needle guard
REMSIMA® SC 120 mg solution for injection in single-use pre-filled syringe with automatic needle guard. The syringe is made from type I glass with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:

- 1 prefilled syringe with automatic needle guard (1 mL sterile solution) with 2 alcohol pads.

REMSIMA® SC 120 mg solution for injection in pre-filled pen
REMSIMA® SC 120 mg solution for injection in single-use pre-filled pen. The syringe inside the pen is made from type 1 glass with a plunger stopper (flurotec-coated elastomer) and needle with a rigid needle shield.

Packs of:

- 1 prefilled pen (1 mL sterile solution) with 2 alcohol pads.

6.6 Special precautions for disposal and other handling

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

After use, place the pre-filled syringe/ pre-filled syringe with automatic needle guard/ pre-filled pen into a puncture resistant container and discard as required by local regulations. Do not recycle the injecting device. Always keep the medicinal product out of the sight and reach of children.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Celltrion Healthcare New Zealand Limited
Floor 1, 103 Carlton Gore Road
Newmarket, Auckland,
New Zealand

Phone: 0800 838 899

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 01 June 2023

10. DATE OF REVISION OF THE TEXT

N/A

Summary table of changes

Section changed	Summary of new information
N/A	New Subcutaneous Datasheet