REMICADE®
POWDER FOR INJECTION

infliximab

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

REMICADE 100 mg POWDER FOR INJECTION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of the REMICADE product contains infliximab 100 mg.

Infliximab is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by recombinant DNA technology. After reconstitution each mL contains 10 mg of infliximab.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Powder for injection

REMICADE Powder for Injection is to be reconstituted with 10 mL sterile Water for Injections and further diluted in 0.9% sodium chloride solution for infusion.

REMICADE is supplied as a white lyophilised powder in individually-boxed single-use glass vials with rubber stoppers and aluminium crimps protected by plastic caps.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

REMICADE is indicated for:

➢ Rheumatoid arthritis

REMICADE is a “Disease-Controlling Anti-Rheumatic Therapy” (DCART) indicated for:

- the reduction of signs and symptoms
- prevention of structural joint damage (erosions and joint space narrowing)
- improvement in physical function

in patients with active disease.

REMICADE should be given in combination with methotrexate.

➢ Ankylosing spondylitis

REMICADE is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

➢ Psoriatic arthritis

REMICADE is indicated for:

- the reduction of signs and symptoms of arthritis
- improvement in physical function
- reduction in psoriasis as measured by PASI (an index which combines symptom evaluation and body surface area)
- prevention of worsening of disability
- inhibition of the progression of structural damage of active arthritis, as measured by x-ray

in patients with active and progressive psoriatic arthritis.

REMICADE should be administered

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

➢ Crohn's disease

Adults (≥18 years)

REMICADE is indicated for:

- Treatment of moderate to severe Crohn's disease for the reduction of signs and symptoms, induction and maintenance of clinical remission, induction of mucosal healing, and improvement in quality of life in adult patients who have an inadequate response to conventional therapies. REMICADE enables patients to reduce or eliminate corticosteroid use
- Treatment of draining enterocutaneous fistulae in adult patients with fistulising Crohn's disease.

Children and adolescents (6 to 17 years)

REMICADE is indicated for treatment of moderate to severe, active Crohn's disease in children, aged 6 to 17 years, who have not responded to a full and adequate course of conventional therapy, or who are intolerant to or have medical contraindications to such therapy. Efficacy and safety beyond 54 weeks are unknown.

➢ Psoriasis

REMICADE is indicated for reducing signs and symptoms of psoriasis and improving quality of life in patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate.

➢ Ulcerative colitis in adults and in children and adolescents (6 to 17 years)

REMICADE is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.

Paediatric indications

Safety and efficacy of REMICADE in paediatric patients with juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, plaque psoriasis, and in children < 6 years old with Crohn's disease have not been established.

4.2 Dose and method of administration

REMICADE is administered by intravenous infusion.

At the discretion of the treating physician, treatment with REMICADE may be delayed if the patient has a planned surgical procedure (see risk of post-procedural complication in **section 4.8**), considering the long half-life of infliximab.

REMICADE is for intravenous infusion in adults (≥18 years) across all approved indications. REMICADE is approved for intravenous infusion in children and adolescents (6 to 17 years) for the indication of Crohn's disease and ulcerative colitis.

REMICADE treatment is to be administered under the supervision of specialised physicians experienced in the diagnosis and treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis, or inflammatory bowel diseases.

For adult and paediatric patients, administer the infusion solution over a period of not less than 2 hours.

In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of REMICADE (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. Shortened infusions at doses of > 6mg/kg have not been studied.

All patients administered REMICADE are to be observed for at least 1 hour post infusion for side effects. Medications, an artificial airway and other appropriate materials must be available for the treatment of these effects (see **section 4.4**).

Rheumatoid arthritis

Patients not previously treated with REMICADE: Initially 3 mg/kg intravenous infusion is to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8weeks thereafter. To optimise clinical response, consideration may be given to either incrementally adjusting the dose up to 10 mg/kg or administering the 3 mg/kg dose as often as every 4 weeks.

Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. If a patient has an inadequate response or loses response after this period, the dose may be adjusted as described above. If adequate response is achieved, patients should be continued on the selected dose or dose frequency.

Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment or after dose adjustment.

In carefully selected patients with rheumatoid arthritis who have tolerated 3 initial 2-hour infusions of REMICADE, consideration may be given to administering subsequent infusions over a period of not less than 1 hour.

REMICADE should be given in combination with methotrexate.

Ankylosing spondylitis

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

Psoriatic arthritis

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Efficacy has been demonstrated alone or in combination with methotrexate.

Moderate to severe Crohn's disease in adults and children 6 to 17 years old

For optimal long-term symptom control, 5 mg/kg given as a single intravenous infusion as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. For patients who have an incomplete response during maintenance treatment, consideration may be given to adjusting the dose up to 10 mg/kg.

Alternatively, an initial 5 mg/kg intravenous infusion administered may be followed by repeat infusions of 5 mg/kg when signs and symptoms of the disease recur; however, there is limited data on dosing intervals beyond 16 weeks.

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

Available data do not support further infliximab treatment in paediatric patients not responding within 10 weeks of the initial infusion.

Fistulising Crohn's disease

For the treatment of draining fistula(e) in Crohn's disease, infuse 5 mg/kg intravenously, followed with additional 5 mg/kg doses administered at 2 and 6 weeks after the first infusion. If a patient does not respond after these 3 doses, no additional treatment with infliximab should be given.

Psoriasis

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

Ulcerative colitis in adults and children and adolescents (6 to 17 years)

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion dose at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. In some patients, consideration may be given to adjusting the dose up to 10 mg/kg to sustain clinical response and remission.

Available data do not support further infliximab treatment in children and adolescent patients (6-17 years) not responding within 8 weeks of the initial infusion.

Readministration for Crohn's disease and rheumatoid arthritis

If signs and symptoms of disease recur, REMICADE can be readministered within 16 weeks following the last infusion. Readministration of a liquid formulation of infliximab, which is no longer in use, with a drug-free interval of 2 to 4 years following a previous infusion has been associated with a delayed hypersensitivity reaction in 10 patients with Crohn's disease (see

sections 4.4; **4.8**). After a drug free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following readministration is not known. Therefore, after a drug free interval of 16 weeks, readministration cannot be recommended.

Readministration for ulcerative colitis

Data supporting readministration, other than every 8 weeks, are not available at this time (see **sections 4.4**; **4.8**).

Readministration for ankylosing spondylitis

Data supporting readministration, other than every 6 - 8 weeks, are not available at this time (see **sections 4.4**; **4.8**).

Readministration for psoriatic arthritis

Data supporting readministration, other than every 8 weeks, are not available at this time (see **sections 4.4**; **4.8**).

Readministration for psoriasis

Experience from intermittent treatment with REMICADE in psoriasis after a period of no treatment suggests reduced efficacy and a higher incidence of infusion reactions when compared to the approved dosing guidance (see **sections 4.4**; **4.8**).

Traceability

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

4.3 Contraindications

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

REMICADE 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 REMICADE and anakinra (an interleukin-1 receptor antagonist) is contraindicated.

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

4.4 Special warnings and precautions

Infusion reactions and hypersensitivity reactions

Infliximab has been associated with acute infusion effects and a delayed hypersensitivity reaction. These differ in their time of onset. Hypersensitivity reactions, which include urticaria, dyspnoea, and/or bronchospasm, laryngeal oedema, pharyngeal oedema, and hypotension, have occurred during or within 2 hours of REMICADE infusion. Therefore, all patients receiving REMICADE should be observed for at least one hour post infusion for side effects.

To minimise the incidence of hypersensitivity reactions, including infusion reactions and serum sickness-like reactions, REMICADE should be administered as regular maintenance therapy after an induction regimen at weeks 0, 2, 6 (see **section 4.2**).

Acute infusion reactions may develop immediately or within a few hours of infusion and are most likely to occur during the first and second infusion. If acute infusion reactions occur, the

infusion must be interrupted immediately. Some of these effects have been described as anaphylaxis. Emergency equipment and medication for the treatment of these effects (e.g., paracetamol, antihistamines, corticosteroids and/or adrenaline) must be available for immediate use. Patients may be pretreated with antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects. The infusion rate may be slowed in order to decrease infusion reactions especially if infusion reactions have occurred previously.

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

A delayed hypersensitivity reaction has been observed in a significant number of patients (25% in one clinical trial) with Crohn's disease who were retreated with infliximab following a 2 to 4 year period without infliximab treatment. A delayed hypersensitivity reaction may be seen 3 to 12 days following the reinfusion. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash within 12 days following retreatment. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. These effects have sometimes been described as serum-sickness-like reactions. Advise patients to seek immediate medical advice if they experience any delayed adverse event (see **section 4.8** - **Delayed hypersensitivity**). If patients are retreated after a prolonged period, they should be closely monitored for signs and symptoms of delayed hypersensitivity.

Infusion reactions following re-administration of REMICADE

In a psoriasis clinical trial, a 3-dose re-induction of REMICADE after a period of no treatment resulted in a higher incidence of serious infusion reactions during the re-induction regimen (see **section 4.8**) than had been observed in rheumatoid arthritis, psoriasis, and Crohn's disease trials in which a period of no drug treatment was followed by regular maintenance therapy without re-induction. In the case where REMICADE maintenance therapy for psoriasis is interrupted, REMICADE should be reinitiated as a single dose followed by maintenance therapy. In general, the benefit-risk of re-administration of REMICADE after a period of no-treatment, especially as a re-induction regimen given at weeks 0, 2, and 6, should be carefully considered.

Infections

Bacterial (including sepsis and pneumonia), mycobacterial [including tuberculosis (frequently disseminated or extrapulmonary at clinical presentation)], invasive fungal, viral, and other opportunistic infections have been observed in patients receiving REMICADE. Some of these infections have been fatal.

Tumour necrosis factor alpha (TNFα) mediates inflammation and modulates cellular immune response. 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.

In clinical studies in rheumatoid arthritis, starting REMICADE therapy with doses higher than 3 mg/kg has been associated with an increased risk of infection compared to the risk of infection associated with the starting dose of 3 mg/kg. This increase in the risk of infection was not evident in patients receiving the starting regimen of 3 mg/kg at weeks 0, 2 and 6 and subsequently receiving higher or more frequent doses. However, caution should be exercised

when continuing a rheumatoid arthritis patient on doses above 3 mg/kg or administering infliximab more frequently than every 8 weeks.

REMICADE should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of REMICADE therapy in patients with a chronic infection or a history of recurrent infection. Patients should be advised of and avoid exposure to potential risk factors for infections as appropriate.

Opportunistic infections including tuberculosis, viral infections, invasive fungal infections, and other infections such as sepsis and pneumonia have been reported in patients treated with infliximab (see **section 4.8**).

Patients must be evaluated for the risk of tuberculosis (including close contact with a person with active tuberculosis) and tested for latent tuberculosis, prior to initiation of REMICADE. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray, should be performed in all patients (local recommendations may apply). Prescribers are reminded of the risk of false negative tuberculin skin test results especially in patients who are severely ill or immunocompromised. Patients who have clinically manifested infections and/or abscesses should be treated for these conditions prior to treatment with REMICADE.

If active tuberculosis is diagnosed, REMICADE therapy must not be initiated (see **section 4.3**). If treatment of latent tuberculosis is initiated, it must be initiated prior to treatment with REMICADE, in accordance with local recommendations. Use of anti-tuberculosis therapy should also be considered before the initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients must be monitored closely for infections, including miliary tuberculosis, while on and after treatment with REMICADE.

Use of anti-tuberculosis therapy should be considered before the initiation of REMICADE in patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis. The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

Cases of active tuberculosis have occurred in patients treated with REMICADE during and after treatment for latent tuberculosis. Patients receiving REMICADE should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative 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 REMICADE treatment.

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 REMICADE treatment should be carefully considered before initiation or continuation of REMICADE therapy.

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

There is limited safety experience of surgical procedures in REMICADE treated patients. A patient who requires surgery while on REMICADE should be closely monitored for infections, and appropriate actions should be taken.

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

Suppression of TNFα may also mask symptoms of infection such as fever. Treatment with REMICADE must be discontinued if a patient develops a serious infection or sepsis. As the elimination of REMICADE may take up to six months, close monitoring of the patients throughout this period is important.

Hepatobiliary events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the postmarketing experience of REMICADE. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between REMICADE and these events has not been established. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥ 5 times the upper limit of normal develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken.

As also observed with the use of other immunosuppressive drugs, reactivation of hepatitis B virus (HBV) has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive). Patients should be tested for Hepatitis B Virus (HBV) infection before initiating treatment with immunosuppressants, including REMICADE. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for evidence of prior HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, REMICADE should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Haematological reactions

There have been reports of pancytopaenia, leukopaenia, neutropaenia, and thrombocytopaenia in patients receiving TNF-blockers, including REMICADE. Caution should be exercised in patients treated with REMICADE who have a current or past history of significant cytopaenias. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant haematologic abnormalities.

Malignancies and lymphoproliferative disorders

Lymphoma: In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During clinical trials of REMICADE in subjects with rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, psoriasis and ulcerative colitis, the incidence of lymphoma in REMICADE-treated subjects was higher than expected in the general population, but the occurrence of lymphoma was rare. Furthermore, there is an increased risk background lymphoma risk even in the absence of TNF blocking therapy in rheumatoid arthritis and Crohn's disease patients with longstanding, highly active

inflammatory disease and/or active chronic exposure to immunosuppressant therapies, which complicates the risk estimation.

Non-lymphoma malignancy: In the controlled portions of some clinical trials of the TNF-blocking agents, more cases of non-lymphoma malignancy have been observed among patients receiving a TNF-blocker compared with control patients. In an exploratory clinical trial evaluating the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking.

Skin cancers: Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including REMICADE (see **section 4.8**). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

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

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

With the current knowledge, a possible 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.

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

Hepatosplenic T-cell lymphomas: Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blocking agents including REMICADE. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker. The vast majority of REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males.

It is uncertain whether the occurrence of the HSTCL is related to REMICADE or REMICADE in combination with these other immunosuppressants. When treating patients with inflammatory bowel disease, particularly in adolescents and young adults, consideration of whether to use REMICADE alone or in combination with other immunosuppressants should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with REMICADE monotherapy from the clinical trial data.

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

Colon Carcinoma/Dysplasia: 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. With current data it is not known if REMICADE treatment influences the risk for developing dysplasia or colon cancer (see **section 4.8**).

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

Auto-immune processes

Treatment with REMICADE may result in the formation of autoantibodies and in the development of a lupus-like syndrome.

The relative deficiency of TNFα caused by anti-TNF therapy may result in the initiation of an autoimmune process in a subgroup of genetically susceptible patients. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE and is positive for antibodies against double-stranded DNA, treatment should be discontinued (see **section 4.8**).

Neurological events

Infliximab and other agents that inhibit TNF alpha have been associated in cases with seizure, and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders including multiple sclerosis, and optic neuritis and peripheral demyelinating disorders, including Guillain-Barre syndrome (see **section 4.8**). Prescribers should exercise caution in considering the use of REMICADE in patients with these neurological disorders and should consider discontinuation of REMICADE if these disorders develop.

Concurrent administration of TNF-alpha inhibitor and anakinra

Concurrent administration of etanercept (another agent that inhibits TNFα) and anakinra (a recombinant, non-glycosylated form of the human interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, an increased risk of neutropaenia and no additional benefit compared to these medicinal products alone. The safety and efficacy of anakinra used in combination with infliximab has not been established. Therefore, combination of infliximab and anakinra is contraindicated.

Concurrent administration of TNF-alpha inhibitor and abatacept

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

Concurrent administration with other biological therapeutics

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

Switching between biological therapeutics

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

Vaccinations

It is recommended that all patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating REMICADE 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 REMICADE is not recommended.

Fatal outcome due to disseminated Bacille Calmette-Guérin (BCG) infection has been reported in an infant who received BCG vaccine after in utero exposure to infliximab. A twelve month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab, unless infliximab exposure was limited to the first trimester or if infant infliximab serum levels are undetectable. Administration of a live vaccine prior to 12 months of age might be considered if the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infants (see **section 4.6**).

Infant exposure via breastmilk

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see **section 4.6**).

Therapeutic infectious agents

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

Non-live vaccines

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

Special populations

Use in patients with congestive heart failure

REMICADE is contraindicated in patients with moderate or severe heart failure (NYHA class III/IV) (see **sections 4.3**).

REMICADE should be used with extreme caution in patients with mild heart failure (NYHA class I/II) and after consideration of other treatment options for their indicated conditions; the dose of REMICADE should not exceed 5 mg/kg. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE must not be continued if new or worsening symptoms of heart failure appear(see section 4.3 and 4.8).

Use in elderly

No major differences were observed in the pharmacokinetics of REMICADE in elderly (65-80 years) rheumatoid arthritis patients. The incidence of serious infections in REMICADE-treated patients 65 years and older was greater than in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general, therefore, caution should be used in treating the elderly. The pharmacokinetics of REMICADE

in elderly Crohn's disease patients has not been studied. Studies have not been performed in patients with liver or renal disease.

Use in children

Treatment with REMICADE has not been studied in paediatric patients ≤17 years with ankylosing spondylitis, psoriatic arthritis, or plaque psoriasis. REMICADE has not been studied in paediatric patients with juvenile rheumatoid arthritis (JRA) under the age of 4 years (see **section 4.8**). Treatment with REMICADE has not been studied in paediatric patients with ulcerative colitis or Crohn's patients under the age of 6 years. Until safety and efficacy data in the above mentioned groups of paediatric patents are available, such treatment is to be avoided. It should be noted that all paediatric patients in the Phase 3 trial in Crohn's disease (REACH) were required to be on a stable dose of either 6-mercaptopurine (6-MP), azathioprine (AZA) or methotrexate (MTX).

4.5 Interactions with other medicines and other forms of interactions

While specific studies on drug interactions with REMICADE have not been conducted, the majority of patients in clinical trials received concomitant medications normally used in Crohn's disease. These medications included antibiotics (including antiviral agents), corticosteroids, 6-mercaptopurine/ azathioprine and aminosalicylates. No adverse interactions were reported.

The formation of antibodies to infliximab has been shown to be reduced when REMICADE is administered concomitantly with methotrexate, azathioprine or 6-mercaptopurine but not with corticosteroids (see **section 4.8** - **Immunogenicity**). No other information is available regarding possible effects of other immunosuppressive drugs or their effects on the pharmacokinetics of infliximab.

Because corticosteroids alter electrolyte balance and fluid retention, the volume of distribution of infliximab was greater in patients taking corticosteroids. However no significant clinical sequelae were apparent.

Concurrent Use of REMICADE with other biological therapeutics

The combination of REMICADE with other biological therapeutics used to treat the same conditions as REMICADE, including anakinra and abatacept, is not recommended (see **section 4.4**).

Live vaccines / therapeutic infectious agents

It is recommended that live vaccines not be given concurrently with REMICADE. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab for 12 months following birth, unless infliximab exposure was limited to the first trimester or if infant infliximab serum levels are undetectable. Administration of a live vaccine prior to 12 months of age might be considered if the benefit of the vaccination clearly outweighs the theoretical risk of administration of live vaccines to the infant (see **section 4.4**).

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (see **section 4.6**).

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

4.6 Fertility, pregnancy and lactation

Effects on fertility

The effect of infliximab on fertility has not been investigated. No impairment of fertility was observed in a fertility and general reproduction study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα.

Use in pregnancy

(Category C)

Available observational studies in pregnant women exposed to REMICADE showed no increased risk of major malformations among live births as compared to those exposed to non-biologics. However, findings on other birth outcomes were not consistent across the studies. In one study conducted in a North American IBD pregnancy registry, REMICADE exposure was not associated with increased rates of miscarriage/still birth, low birth weight, small for gestational age, or infant infection in the first year of life as compared to exposure to non-biologics [Maternal exposure to REMICADE, Maternal exposure to Non-biologics: 294, 515]. In another study in Northern Europe among IBD and non-IBD patients, exposure to REMICADE in combination with immunosuppressants (mainly systematic corticosteroids and azathioprine), but not REMICADE as monotherapy, was associated with increased rates of preterm births, small for gestational age, low birth weight, and infant hospitalisation for infection compared with non-biologic systematic treatment [Live births with maternal exposure to REMICADE, Live births with maternal exposure to Non-biologics: 270, 6460]. Both studies have potential for confounding (e.g. the concomitant use of other medications or treatments was not controlled and disease severity was not assessed).

It is not known whether REMICADE can affect reproductive potential.

Since infliximab does not cross-react with TNFα in species other than human and chimpanzees, animal reproduction studies have not been conducted. In a development toxicity study conducted in mice using an analogous monoclonal antibody that selectively inhibits the functional activity of mouse TNFα, no evidence of maternal toxicity, embryotoxicity or teratogenicity was observed. However, since it takes 6 months to assure that REMICADE is not present in the blood system, it is recommended that 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.

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to twelve months following birth. The clinical significance of low serum levels of infliximab on the immune status in infants is unknown.

After *in utero* exposure to infliximab, infants may be at increased risk of infection, including disseminated infection that can become fatal (see **section 4.4 - Live Vaccines/Therapeutic Infectious Agents**).

Breast-feeding

REMICADE has been detected at low levels in human milk and in infant serum via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Limited data from published literature reported that infants exposed to infliximab through breast milk had no increase in rates of infections and developed normally.

The consideration of REMICADE use during breast-feeding should take into account the importance of REMICADE to the mother and health benefits of breast-feeding for the infant.

4.7 Effects on the ability to drive and use machines

REMICADE is unlikely to produce an effect on the ability to drive or operate machinery; however, patients who are fatigued should be cautioned to avoid driving or operating machinery.

4.8 Undesirable effects

In clinical trials with REMICADE, adverse drug reactions (ADRs) reasonably attributable to treatment were observed in 36% of placebo-treated patients and 57% of REMICADE-treated patients. Reasonably-related ADRs are listed in **Table 1** by system organ class and frequency (common >1/100 to <1/10; uncommon >1/1000 to <1/100; rare >1/10,000, <1/1000). Frequency is based on the excess incidence of the ADR compared with placebo in pooled data from clinical trials involving 227 patients receiving placebo and 1421 patients receiving REMICADE (Crohn's disease and rheumatoid arthritis). Most ADRs were mild to moderate in severity. Infusion-related reactions were the most common ADRs reported. The most common causes for the discontinuation of treatment were the infusion-related reactions: dyspnoea, flushing, rash, urticaria and headache.

Table 1: Undesirable Effects in Clinical Trials

Resistance mechanism disorders	
Common:	Viral infection (e.g. influenza, herpes infections), fever
Uncommon:	Abscess, cellulitis, moniliasis, sepsis, impaired healing, bacterial infection, fungal infection, tuberculosis
Rare	Granulomatous lesion
Neoplasms benign, malignant and unspecified	
Rare:	Lymphoma
Immune disorders	
Common:	Serum-sickness-like reactions
Uncommon:	Autoantibodies, lupus-like syndrome, complement factor abnormality
Rare:	Sarcoid-like reaction
Blood disorders	
Uncommon:	Anaemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropenia, thrombocytopenia
Psychiatric disorders	
Uncommon:	Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence, insomnia
Central and peripheral nervous system disorders	
Common:	Headache, vertigo/dizziness
Uncommon:	Exacerbation of demyelinating disease suggestive of multiple sclerosis
Rare:	Meningitis
Vision and hearing disorders	
Uncommon:	Conjunctivitis, endophthalmitis, keratoconjunctivitis
Cardiovascular disorders	
Common:	Flushing
Uncommon:	Ecchymosis/haematoma, hypertension, hypotension, syncope, petechia, thrombophlebitis, bradycardia, palpitation, vasospasm, cyanosis, peripheral ischaemia, arrhythmia, worsening heart failure*
Rare:	Circulatory failure, tachycardia
Respiratory system disorders	
Common:	Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, sinusitis
Uncommon:	Epistaxis, bronchospasm, pleurisy, respiratory tract allergic reaction, pulmonary oedema
Rare:	Pleural effusion

Gastrointestinal system disorders	
Common:	Nausea, diarrhoea, abdominal pain, dyspepsia
Uncommon:	Constipation, gastro-oesophageal reflux, cheilitis, diverticulitis, intestinal obstruction
Rare:	Intestinal perforation, intestinal stenosis, gastrointestinal haemorrhage
Liver and biliary system disorders	
Common:	Abnormal hepatic function
Uncommon:	Cholecystitis
Rare:	Hepatitis
Skin and appendages disorders	
Common:	Rash, pruritus, urticaria, increased sweating, dry skin
Uncommon:	Fungal dermatitis/onychomycosis, eczema/seborrhoea, hordeolum, bullous eruption, furunculosis, periorbital oedema, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/colouring, alopecia
Musculoskeletal system disorders	
Uncommon:	Myalgia, arthralgia, back pain
Urinary system disorders	
Uncommon:	Urinary tract infection, pyelonephritis
Reproductive disorders	
Uncommon:	Vaginitis
Body as a whole general disorders	
Common:	Fatigue, chest pain, infusion-related reactions
Uncommon:	Oedema, hot flushes, infusion syndrome, pain, chills/rigors, anaphylactic reactions
Administration/application site disorders	
Uncommon:	Injection site reactions
Investigations	
Uncommon	Weight increased**

*reported in early phase studies evaluating REMICADE® in patients with congestive heart failure

** At month 12 of the controlled period for adult clinical trials across all indications, the median weight increase was 3.50 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects. The median weight increase for inflammatory bowel disease indications was 4.14 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects, and the median weight increase for rheumatology indications was 3.40 kg for infliximab-treated subjects vs. 3.00 kg for placebo-treated subjects.

Vomiting and elevated hepatic transaminases were also reported.

Infusion-related reactions

An infusion-related reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. In phase 3 clinical studies, 18% of infliximab-treated patients compared with 5% of placebo-treated patients experienced an infusion-related reaction. Among all REMICADE infusions approximately 3% of infusions were accompanied by non-specific symptoms such as fever or chills, <1% were accompanied by pruritus or urticaria, 1% were accompanied by cardiopulmonary reactions (primary chest pain, hypotension, hypertension or dyspnoea) and 0.1% were accompanied by combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Discontinuation of treatment was required in 1.9% of patients; and all patients recovered with or without medical therapy. Infusion-related effects in patients were more likely to occur during the first (8%) infusion and less likely to occur on subsequent infusions (second, 7%; third, 6%; and fourth, 4%; etc).

Patients who became positive for antibodies to infliximab were more likely (approximately 2-3 fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion-related reactions.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), 66% of the patients (686 out of 1040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1040) received at least one shortened infusion of 60 minutes or less. Of the

infliximab-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15% of the patients and serious infusion reactions occurred in 0.4% of the patients.

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

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

Infusion reactions following re-administration of REMICADE

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

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

Delayed hypersensitivity

In a clinical trial of 41 patients retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients, the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial REMICADE therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilised formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to the different formulations administered to these patients in this study. Patients signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year. In the 3 psoriasis studies, 1% (15/1373) of patients experienced symptoms of arthralgia, serum sickness, myalgia, fever and rash. When these occurred, they were often early in the treatment course following REMICADE infusions. REMICADE treatment was discontinued and/or other treatment instituted in most cases with improvement or resolution of signs and symptoms.

Infections

In clinical trials, 35% of REMICADE-treated patients experienced infections compared with 22% of placebo-treated patients. Serious infections, such as pneumonia, were reported in 5% of both REMICADE-treated patients and placebo-treated patients.

Immunogenicity

Patients who developed antibodies to infliximab were more likely to develop infusion-related reactions. In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in approximately 24% of patients with any immunosuppressant therapy, and in approximately 37% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, approximately 8% of patients developed antibodies to infliximab. Of Crohn's disease patients who received maintenance treatment, approximately 6-13% developed antibodies to infliximab. The antibody incidence was 2-3 fold higher for patients treated episodically. Due to methodological shortcomings, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titers of antibodies to infliximab had evidence of reduced efficacy. 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 at baseline and in 26% of patients not receiving methotrexate at baseline. In the Phase III psoriasis study, 1% (4/366) of patients experienced symptoms of arthralgia, myalgia, fever and rash early in the treatment course following infliximab infusions.

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.

From August 1998 to August 2005, 1909 cases of suspected malignancies have been reported from post-marketing, clinical trials and registries (321 in Crohn's disease patients, 1302 in rheumatoid arthritis patients and 286 in patients with other or unknown indications). Among those there were 347 lymphoma cases. During this period, the estimated exposure is 1,909,941 patient years since first exposure (see **section 4.4 - Malignancies and lymphoproliferative disorders**).

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 REMICADE 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**).

During postmarketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in patients treated with REMICADE 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 – Malignancies and lymphoproliferative disorders**).

Heart failure

In a phase II study aimed at evaluating REMICADE in moderate to severe congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure was seen in patients treated with REMICADE, especially those treated with the higher dose of 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Antinuclear antibodies (ANA)/double-stranded DNA (dsDNA) antibodies

In clinical studies, approximately 52% of (1261) infliximab-treated patients who were ANA negative at baseline developed a positive ANA during the trial (compared with approximately 19% of 129 placebo-treated patients). Anti-dsDNA antibodies developed in approximately 17% of patients treated with REMICADE (compared with 0% of 162 placebo-treated patients. At the last evaluation, 150 of these 261 infliximab-treated patients (57%) remained anti-dsDNA positive. Clinical signs consistent with a lupus-like syndrome remain uncommon.

Hepatobiliary events

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

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE 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 REMICADE than in controls, both when REMICADE 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 REMICADE, or modification of concomitant medications.

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%

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

[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.

Paediatric patients

Paediatric Crohn's disease

In general, the adverse events in paediatric patients who received infliximab were similar in frequency and type to those seen in adult Crohn's disease patients. Differences from adults and other special considerations are discussed in the following paragraphs.

The following adverse events were reported more commonly in 103 paediatric Crohn's disease patients randomised at week 10 administered 5 mg/kg infliximab through 54 weeks (out of a total of 112 patients who entered the REACH trial, see also **Clinical Efficacy** section) than in adult Crohn's disease patients receiving a similar treatment regimen (ACCENT 1 trial, see also **Clinical Efficacy** section): anaemia (10.7%), blood in stool (9.7%), leukopaenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropaenia (6.8%), bone fracture (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%).

Infusion-related reactions:

Overall, in REACH, 17.5% of randomised patients experienced 1 or more infusion reactions, with 17.0% and 18.0% of patients in the q8 week and q12 week maintenance treatment groups, respectively. There were no serious infusion reactions, and 2 subjects in REACH had non-serious anaphylactic reactions.

Immunogenicity:

Antibodies to infliximab developed in 3 (2.9%) paediatric patients.

Infections:

Infections were reported in 56.3% of randomised paediatric subjects treated with infliximab (REACH trial), and in 50.4% of subjects in adult's Crohn's (ACCENT 1 trial). In the REACH trial, infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported in 3 patients, 2 in the q8 week and 1 in the q12 week maintenance treatment groups. Herpes zoster was reported in 2 patients in the q8 week maintenance treatment group.

During post-marketing experience, a rare type of hepatosplenic T-cell lymphoma has been reported in patients with Crohn's disease or ulcerative colitis treated with REMICADE, the majority of whom were adolescent or young adult males (see **section 4.4 – Malignancies and lymphoproliferative disorders**).

Paediatric ulcerative colitis (children and adolescents (6-17 years)

Overall proportions of patients with adverse events and serious adverse events were generally consistent in the paediatric ulcerative colitis and adult ulcerative colitis (ACT 1 and ACT 2) studies. In the paediatric ulcerative colitis study (C0168T72), the most common adverse event was worsening of ulcerative colitis, the incidence of which was higher in patients on the every 12 week vs. the every 8 week dosing regimen. In ACT 1 and ACT 2 studies, the most common adverse event was headache. The most common serious adverse event across these three studies was worsening of ulcerative colitis.

Infections

Infections were reported in 31 (51.7%) of 60 treated patients in C0168T72 and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in C0168T72 was similar to that in the paediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). Unlike REACH, in which infections were reported more frequently for patients who received every 8 week as opposed to every 12 week infusions; in C0168T72, the overall incidence of infections was similar in the every 8 week (13/22 [59.1%]) and every 12 week (14/23 [60.9%] maintenance treatment groups. In C0168T72, serious infections were reported for 3 of 22 (13.6%) patients in the every 8 week and 3 of 23 (13.0%) patients in the every 12 week maintenance treatment group. Upper respiratory tract infection (7/60 [11.7%]) and pharyngitis (5/60 [8.3%]) were the most frequently reported respiratory infections among all treated patients. The infections occurring in more than one patient in a treatment group that required antimicrobial treatment were pharyngitis (4/60 [6.7%]), urinary tract infection (4/60 [6.7%]), and bronchitis (2/60 [3.3%]).

Infusion-related reactions

Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the every 8 week and 3 of 23 (13.0%) in the every 12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

Immunogenicity

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

Paediatric study subgroups

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

Juvenile rheumatoid arthritis

The safety and efficacy of REMICADE were assessed in a multicentre, randomised, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension for a maximum of 44 weeks. A total of 120 patients with active JRA despite treatment with methotrexate (MTX) between the ages of 4 and 17 years received 3 mg/kg REMICADE or placebo intravenously at weeks 0, 2, and 6. Subjects randomised to placebo crossed over to receive 6 mg/kg REMICADE at weeks 14, 16 and 20, and the every 8 weeks through week 44. Subjects randomised to 3 mg/kg REMICADE continued to receive the same dose of REMICADE at weeks 14, 20 and then every 8 weeks through week 44.

Infusion reactions

Infusion reactions occurred in 35.0% of patients with JRA receiving 3 mg/kg REMICADE compared with 17.5% of patients receiving 6 mg/kg. In the 3 mg/kg REMICADE group, 4 out of 60 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 out of 57 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received infliximab by rapid infusion (duration time less than 2 hours).

Immunogenicity

Antibodies to infliximab developed in 37.7% of patients with JRA receiving 3 mg/kg of REMICADE compared with 12.2% of patients receiving 6 mg/kg. The antibody titres were notably higher for the 3 mg/kg compared to the 6 mg/kg group.

Infections

Infections occurred in 68.3% (41/60) children with JRA receiving infliximab 3 mg/kg in combination with methotrexate (MTX) over 52 weeks, 64.9% (37/57) children with JRA receiving infliximab 6 mg/kg in combination with methotrexate (MTX) over 38 weeks and 46.7% (28/60) children with JRA receiving placebo in combination with methotrexate (MTX) over 14 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

Post-marketing reports:

In postmarketing spontaneous reporting, infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location (see **section 4.4**), protozoal infections, and other opportunistic infections, such as atypical mycobacteria, pneumocystis carinii pneumonia (PCP), histoplasmosis, coccidioidomycosis, cryptococcosis, aspergillosis, listeriosis and oesophageal candidiasis and salmonellosis have been reported rarely (<1/1000) or very rarely (<1/10,000). Vaccine breakthrough infection (after *in utero* exposure to infliximab, including bovine tuberculosis (disseminated BCG infection)) has also been reported (see **section 4.4**).

In addition, central nervous system demyelinating disorders (such as multiple sclerosis and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), neuropathies, numbness, tingling, seizure, transverse myelitis, orbital apex syndrome, pancytopenia, haemolytic anaemia, idiopathic thrombocytopaenic purpura, thrombotic thrombocytic purpura, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme*,* linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions, agranulocytosis (including infants exposed *in utero* to infliximab), hepatocellular damage, hepatitis B reactivation, jaundice, autoimmune hepatitis, liver failure, pancreatitis, anaphylactic shock, systemic and cutaneous vasculitis, psoriasis, including new onset and pustular (primarily palmar/plantar), pericardial effusion, hepatosplenic T-cell lymphoma (primarily in adolescents and young adults with Crohn's disease and ulcerative colitis), paediatric malignancy, leukaemia, melanoma and Merkel cell carcinoma have been reported rarely (<1/1000) or very rarely (<1/10,000). Basal cell carcinoma, squamous cell carcinoma,cervical cancer, post-procedural complication (including infectious and non-infectious complications), and paradoxical drug-induced immune disorders (e.g., new onset psoriasis) have also been reported.

Cases of transient visual loss and myocardial ischemia/myocardial infarction occurring during or within 2 hours of REMICADE infusion have also been reported. Cerebrovascular accidents, myocardial ischemia/infarction (some fatal), and arrhythmia occurring within 24 hours of initiation of infusion have also been reported.

In addition, interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis) has been observed, which in some cases may be rapidly aggressive.

Spontaneous serious adverse events in the postmarking experience with REMICADE in the paediatric population have included malignancies, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive autoantibodies.

Hemophagocytic lymphohistiocytosis (HLH) has been very rarely reported in patients treated with REMICADE.

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://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Single doses up to 20 mg/kg have been administered to patients without direct toxic effects. In case of overdosage, it is recommended that patients be monitored for any symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately.

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

Pharmacotherapeutic group: tumour necrosis factor alpha (TNFα) inhibitors, ATC code: L04AB02

Mechanism of actions

Infliximab is a chimeric human-murine monoclonal antibody that binds to human tumour necrosis factor alpha (TNFα). TNFα is a pro-inflammatory and immunoregulatory cytokine that, when overexpressed, mediates chronic inflammation in diseases such as Crohn's disease and rheumatoid arthritis. Cellular responses to TNFα include:

- up-regulation of other pro-inflammatory cytokines such as interleukin (IL) 1 and IL-12
- up-regulation of chemokines such as IL-8
- priming and activation of neutrophils
- up-regulation of adhesion molecules and tissue factor by endothelial cells
- induction of proliferation and increased synthesis of IL-6 and metalloproteinases by fibroblasts.

Infliximab is a chimeric IgG1 monoclonal antibody composed of human constant and murine variable regions, having an approximate molecular weight of 149,100 daltons. Infliximab is produced by recombinant cell line cultured by continuous perfusion and it is purified by a series of steps that includes measures to inactivate and remove viruses.

Infliximab neutralises the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralise TNFβ (lymphotoxin α), a related cytokine that utilises the same receptors as TNFα.

Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity and induction of acute phase and other liver proteins. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* by complement or effector cells. Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilising human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells.

Pharmacodynamic effects

Elevated concentrations of TNFα have been found in the sera and stools of adult Crohn's disease patients and in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. Increased concentrations of TNFα have also been found in joint fluid/tissue and in psoriatic skin lesions in patients with psoriatic arthritis. In patients with Crohn's disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine; it also reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon γ. In patients with rheumatoid arthritis, treatment with REMICADE 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 treatment with REMICADE, all patients exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to their baseline values. In patients with rheumatoid arthritis, peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalization of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, treatment with REMICADE resulted in a reduction in the number of t-cells and blood vessels in the synovium and psoriatic skin as well as a reduction of macrophages in the synovium.

Clinical efficacy

Rheumatoid arthritis

The safety and efficacy of REMICADE 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 REMICADE 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 REMICADE treated groups had a significant reduction in signs and symptoms compared with methotrexate alone (Table 1). 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 REMICADE groups was observed ($p<0.05$). Higher degrees of clinical response (ACR50 and ACR70) were observed in all REMICADE groups at 30, 54 and 102 weeks compared to control.

Prevention of structural joint damage (erosions and joint space narrowing) was observed in all REMICADE 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 REMICADE 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 REMICADE treatment groups compared to control (**Table 3**) 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)	3 mg/kg q 8 wks (n = 86)	3 mg/kg q 4 wks (n = 86)	10 mg/kg q 8 wks (n = 87)	10 mg/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 der 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 REMICADE 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 escalation (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.

Ankylosing spondylitis

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

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 5** below:

Table 5: Effects on ACR, PASI and Physical Function in IMPACT and IMPACT 2

	IMPACT				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/A[a]**	**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%)

		IMPACT				IMPACT 2		
		Placebo (Week 16)	**Infliximab (Week 16)**	**Infliximab (Week 50)**	**Infliximab (Week 98)**	**Placebo (Week 24)**	**Infliximab (Week 24)**	**Infliximab (Week 54)**
PASI response*	75	0 (0%)	15 (68%)	13 (59%)	16 (64%)	1 (1%)	50 (60%)	31 (51%)
PASI response*	90	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 $\geq$2.5 at baseline for IMPACT, and patients with $\geq$3% BSA psoriasis skin involvement at baseline in IMPACT 2

[e] HAQ=Health Assessment Questionnaire

* p$\leq$0.01for infliximab vs. placebo at week 16 in IMPACT; P<0.001 for infliximab vs. placebo at week 24 for IMPACT 2

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54 respectively. 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 6: Summary of change from baseline in total modified van der Heijde modified Sharp score at weeks 24 and 54 (IMPACT 2)

	Placebo / infliximab 5 mg/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)

The safety and efficacy of single and multiple doses of REMICADE 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 REMICADE-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 REMICADE-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 REMICADE-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 REMICADE 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 REMICADE 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 REMICADE-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 REMICADE-treated group was 2 weeks. The median duration of response was 12 weeks. Additionally, closure of all fistulae was achieved in 55% of REMICADE-treated patients compared with 13% of placebo-treated patients (p=0.001).

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

The safety and efficacy of single and multiple doses of REMICADE 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).

Psoriasis

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 5 mg/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 7**.

Table 7: 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 8**.

Table 8: 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

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 7.

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 9**).

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 9**).

Table 9: Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30. Combined data from ACT 1 & 2

		Infliximab		
	Placebo	**5 mg/kg**	**10 mg/kg**	**Combined**
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 remission (in remission 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 ≤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 10**).

Table 10: Incidence of colectomy through 54 weeks after 1st infusion of infliximab

	Placebo	Infliximab 5 mg/kg	Infliximab 10 mg/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 ulcerative colitis (6 through 17 Years)

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.

5.2 Pharmacokinetic properties

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

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in paediatric (aged 6 to 17 years old) and adult patients with Crohn's disease or ulcerative colitis following the administration of 5 mg/kg infliximab.

At single doses of 3, 5, and 10 mg/kg, the median C_{max} values were 77, 118 and 277 μg/mL, respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after a single infusion. Following the 3-dose regimen a slight accumulation of infliximab was observed in the serum after the second dose and no further clinically relevant accumulation thereafter. The proportion of patients who had undetectable infliximab concentrations at 8 weeks, after a maintenance infusion, was approximately 20%.

5.3 Preclinical safety data

Carcinogenicity, mutagenicity and impairment of fertility

Longterm studies in animals have not been performed to evaluate the carcinogenic potential. No genotoxic effects of infliximab were observed in assays for chromosomal damage (an assay performed using human lymphocytes and the *in vivo* micronucleus test) or gene mutations (Salmonella-*Escherichia coli* (Ames) assay).

The effect of infliximab on fertility has not been investigated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium phosphate monobasic monohydrate

Sodium phosphate dibasic dihydrate

Sucrose

Polysorbate 80.

6.2 Incompatibilities

No physical biochemical compatibility studies have been conducted to evaluate the coadministration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.

6.3 Shelf-life

36 months when stored at 2°C to 8°C (Refrigerate). Do not use beyond expiration date.

REMICADE may be stored at temperatures up to a maximum of 30 °C for a single period of up to 12 months; but not exceeding the original expiration date. The new expiration date should be written on the carton. Upon removal from refrigerated storage, REMICADE cannot be returned to refrigerated storage.

Shelf-life after reconstitution

REMICADE infusion solution diluted in 0.9% sodium chloride is biochemically stable for 24 hours when stored between 2°C and 30°C. However, since no preservative is present, it is recommended that the infusion begin within 3 hours after preparation and the solution not be stored for reuse. To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage is necessary hold at 2°C to 8°C for no more than 24 hours. This product is for single use only and any unused portion of the solution should be discarded.

6.4 Special precautions for storage

REMICADE vials should be stored at 2°C to 8°C.

A single period of 12 months when stored at temperatures up to a maximum of 30°C; but not exceeding the original expiration date. Upon removal from refrigerated storage, REMICADE cannot be returned to refrigerated storage.

6.5 Nature and contents of container

Type 1 glass vial with rubber stopper and aluminium crimp protected by a plastic cap, containing 100 mg of infliximab.

REMICADE (infliximab 100 mg) is supplied as 1 vial per pack.

6.6 Special precautions for disposal and other handling

Instructions for use/handling

1. Calculate the required dose and the number of REMICADE vials. Each REMICADE vial contains 100 mg infliximab. Calculate the total volume of reconstituted REMICADE solution required.
2. Under aseptic conditions, reconstitute each REMICADE vial with 10 mL of preservative-free sterile Water for Injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. Upon reconstitution, each mL of reconstituted solution contains 10 mg of infliximab. Remove flip-top from the vial and wipe the top with a 70% alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of sterile Water for Injection to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilised powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE THE VIAL. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colourless to light yellow and opalescent. The solution may develop a few fine particles, as infliximab is a protein. Do not use if opaque particles, discolouration, or other foreign particles are present. After reconstitution, the vials should be used immediately.

3. Further dilute the REMICADE dose to a final volume of 250 mL with 0.9% sodium chloride solution for infusion, in either a 250 mL glass infusion bottle or infusion bag. Do not dilute the reconstituted REMICADE solution with any other diluent. Withdraw and discard a volume of 0.9% sodium chloride solution for infusion equal to the volume of the reconstituted REMICADE dose; then, slowly add the REMICADE to the bottle or bag of infusion solution. Gently mix. For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL, 1000 mL) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/mL.
4. Administer the infusion solution over a period of not less than the infusion time recommended for the specific indication. Use only an infusion set with an in-line, sterile, nonpyrogenic, low protein-binding filter (pore size 1.2 μm or less).
5. Visually inspect parenteral medicinal products for particulate matter or discolouration prior to administration. Do not use if visibly opaque particles, discolouration or foreign particulates are observed.
6. Discard any unused portion of solution.

7. MEDICINES SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

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NEW ZEALAND

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9. DATE OF FIRST APPROVAL

16 November 2000

10. DATE OF REVISION OF THE TEXT

06 Sep 2024

Summary table of changes

Section changes	Summary of new information
4.2	Addition of precautionary statement to delay treatment in case of planned surgical procedure
4.6	Additional information added relating to women of childbearing potential and contraception use
4.8	Addition of post procedural complication and paradoxical drug-induced immune disorders