NAME OF THE MEDICINAL PRODUCT
REMICADE® (infliximab)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial of REMICADE® contains 100 mg of infliximab, a chimeric IgG1 monoclonal antibody manufactured from a recombinant cell line cultured by continuous perfusion. Upon reconstitution each mL contains 10 mg of infliximab.
For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Powder for concentrate for solution for infusion.

CLINICAL PARTICULARS
Therapeutic Indications
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 despite treatment with MTX, and patients with active disease not previously treated with methotrexate.
Ankylosing spondylitis
REMICADE® is indicated for:
- reduction of signs and symptoms
- 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)

in patients with active psoriatic arthritis.
Psoriasis
REMICADE® is indicated for:
- the reduction of signs and symptoms of psoriasis
- improvement in quality of life

in the treatment of adult patients with severe plaque psoriasis who are candidates for systemic therapy, and for patients with moderate psoriasis for whom phototherapy is inadequate or inappropriate.
Adult and Pediatric Crohn's disease
REMICADE® is indicated for:
- reduction of signs and symptoms
- induction and maintenance of clinical remission
- induction of mucosal healing in adults
- improvement in quality of life

in patients with severe Crohn's disease who have an inadequate response to conventional therapies. REMICADE® therapy enables patients to reduce or eliminate corticosteroid use.

Fistulizing Crohn's disease

REMICADE® is indicated for:

- reduction in the number of draining enterocutaneous and rectovaginal fistulae and maintenance of fistula closure
- reduction of signs and symptoms
- improvement in quality of life

in patients with fistulizing Crohn's disease.

Ulcerative colitis

REMICADE® is indicated for:

- reducing signs and symptoms
- inducing and maintaining clinical remission
- inducing mucosal healing
- improving quality of life
- reducing or discontinuing administration of corticosteroids
- reducing ulcerative colitis-related hospitalizations

in patients with active ulcerative colitis who have had an inadequate response to conventional therapy.

Posology and Method of Administration

REMICADE® is for intravenous use.

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

The recommended infusion time is 2 hours. 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. The infusion rate may be slowed in order to decrease the risk of infusion related reactions especially if infusion related reactions have occurred previously (see *Special Warnings and Special Precautions for Use*).

Rheumatoid arthritis: Initially 3 mg/kg intravenous infusion over a 2-hour period is to be followed with additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. After 22 weeks of therapy, the dose may be increased up to 10 mg/kg if necessary. REMICADE® should be given in combination with methotrexate.

For patients with rheumatoid arthritis, the recommended infusion duration is over a period of not less than 2 hours in patients not previously treated with REMICADE®. 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. Shortened infusions at doses >6 mg/kg have not been studied.

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

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

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

Severe Crohn's disease in adults: For optimal long-term symptom control, 5 mg/kg given as a single intravenous infusion over a 2-hour period 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 over a 2-hour period 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.
Pediatric Crohn's disease: 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. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg.
Pediatric Crohn's disease patients who have had their dose adjusted to greater than 5 mg/kg every 8 weeks, may be at greater risk for adverse reactions. Continued therapy with the adjusted dose should be carefully considered in patients who show no evidence of additional therapeutic benefit after dose adjustment.
Fistulizing Crohn's disease in adults: 5 mg/kg intravenously over a 2-hour period and followed with additional 5 mg/kg doses administered at 2 and 6 weeks after the first infusion for treatment of fistula(s) in Crohn's disease. If a patient does not respond after these 3 doses, no additional treatment with infliximab should be given.
The strategies for continued treatment are:

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

In Crohn's disease, experience with readministration if signs and symptoms of disease recur is limited and comparative data on the benefit / risk of the alternative strategies for continued treatment are lacking.
Ulcerative colitis: 5 mg/kg given as an intravenous infusion over a 2-hour period 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.
Readministration for Crohn's disease and rheumatoid arthritis: If the signs and symptoms of disease recur, REMICADE® can be readministered within 16 weeks following the last infusion. Readministration of an alternate formulation of infliximab 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 *Special Warnings and Special Precautions for Use and Undesirable Effects*). 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 can not be recommended.
Readministration for ulcerative colitis: Data supporting readministration, other than every 8 weeks, are not available at this time (see *Special Warnings and Special Precautions for Use and Undesirable Effects*).
Readministration for ankylosing spondylitis: Data supporting readministration, other than every 6-8 weeks, are not available at this time (see *Special Warnings and Special Precautions for Use and Undesirable Effects*).
Readministration for psoriatic arthritis: Data supporting readministration, other than every 8 weeks, are not available at this time (see *Special Warnings and Special Precautions for Use and Undesirable Effects*).

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 *Special Warnings and Special Precautions for Use and Undesirable Effects*).

Contraindications

REMICADE® should not be given to patients with known sensitivity to any component of the product or to murine proteins.

REMICADE® is contraindicated in patients with severe infections, such as tuberculosis, sepsis, abscesses and opportunistic infections.

REMICADE® is contraindicated in patients with moderate or severe heart failure (NYHA class III/IV) (see *Special Warnings and Special Precautions for Use and Undesirable Effects*).

Special Warnings and Special Precautions for Use

Infections

Tumor 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 defense against infection is compromised in some patients treated with infliximab.

Caution should be exercised when considering the use of REMICADE® in patients with chronic infection or a history of recurrent infections. Patients should be advised of and avoid exposure to potential risk factors for infection 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 *Undesirable Effects*). Some of these infections have been fatal.

Patients must be evaluated for the risk of tuberculosis, including 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 must be treated for these conditions prior to treatment with REMICADE®.

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

For patients who have resided in or traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks

of REMICADE® treatment should be carefully considered before initiation or continuation of REMICADE® therapy.
In at risk 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.
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, a close monitoring of the patients throughout this period is important.
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 *Contraindications*).
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.
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.

Congestive Heart Failure

REMICADE® should only be used with extreme caution in patients with mild heart failure (NYHA class I/II) (see *Contraindications and Undesirable Effects*) 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 *Contraindications and Undesirable Effects*).

Infusion-related Reactions/Hypersensitivity Reactions

REMICADE® has been associated with acute infusion effects and a delayed hypersensitivity reaction. These differ in their time of onset. Therefore, all patients receiving REMICADE® should be observed for at least one hour post infusion for side effects.
To minimize 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 *Posology and Method of Administration*).
Acute infusion reactions may develop immediately or within a few hours of infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Some of these effects have been described as anaphylaxis. Medications (e.g., antihistamines, corticosteroids, adrenaline and/or paracetamol), an artificial airway and other appropriate materials for the treatment of these effects must be available for immediate use. Patients may be pretreated with e.g., antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

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 potentially are at greater risk of developing these antibodies. These antibodies can not 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 REMICADE® following a 2 to 4 year period without REMICADE® treatment. 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 edema, 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 *Undesirable Effects-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 induction of REMICADE® after a period of no treatment resulted in a higher incidence of serious infusion reactions during the re-induction regimen (see *Undesirable effects*) 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.

Autoimmune Processes

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 *Undesirable Effects*).

Neurological Events

REMICADE® and other agents that inhibit TNFα have been associated in rare cases with seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMICADE® in patients with these neurologic disorders and should consider discontinuation of REMICADE® if these disorders develop.

Hepatobiliary Events

Very rare 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, use of TNF blockers, including REMICADE®, has been associated with reactivation of hepatitis B virus in patients 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. Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of, during treatment with, and for several months following discontinuation of REMICADE®.

Malignancies

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 patients with rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, the incidence of lymphoma in REMICADE®-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

Pediatric Malignancy

Postmarketing 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 Lymphoma

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF blockers including REMICADE®. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All REMICADE® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority were reported in adolescent or young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to REMICADE®. Cases of hepatosplenic T-cell lymphoma have also occurred in Crohn's disease and ulcerative colitis patients receiving azathioprine or 6-mercaptopurine who were not treated with REMICADE®. Before initiating or continuing REMICADE® therapy in a

patient who has chronic inflammatory bowel disease and who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, carefully assess the need for continuing the immunosuppressant therapy in light of the potential risks of concomitant treatment. The causal relationship of hepatosplenic T-cell lymphoma to REMICADE® therapy remains unclear.

Leukemia

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

Non-lymphoma Malignancy

In the controlled portions of 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. The rate of non-lymphoma malignancies among REMICADE®-treated patients was similar to that expected in the general population, whereas the rate among control patients was lower than expected.

In an exploratory clinical trial evaluating the use of 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 *Undesirable Effects*). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

The potential role of TNF-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop a malignancy.

Concurrent Administration of TNF-alpha Inhibitor and Anakinra

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

Concurrent Administration of REMICADE® with 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 REMICADE® 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.

Hematologic Reactions

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia 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 cytopenias.

Vaccinations

No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently. 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 titers to a polyvalent pneumococcal vaccine, indicating that REMICADE® did not interfere with T-cell independent humoral immune responses. It is recommended that pediatric patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating REMICADE® therapy.

Pediatric Use

REMICADE® is indicated for reducing signs and symptoms and for inducing and maintaining clinical remission in pediatric patients who have severely active Crohn's disease. It should be noted that all pediatric patients in the Phase 3 trial (REACH) were required to be on a stable dose of either 6-MP, AZA, or MTX (see *Special Warnings and Special Precautions for Use: Vaccinations and Undesirable Effects*: *Adverse Reactions in Pediatric Crohn's disease*).

REMICADE® has not been studied in children with Crohn's disease < 6 years of age.

Safety and effectiveness of REMICADE® in pediatric patients with Juvenile Rheumatoid Arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and ulcerative colitis have not been established.

The pharmacokinetics of REMICADE® has been evaluated in pediatric patients with Crohn's disease (see *Pharmacokinetics*).

Geriatric Use

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.

Interactions with Other Medicinal Products and Other Forms of Interaction

Specific drug interaction studies have not been conducted with REMICADE®.

In rheumatoid arthritis and Crohn's disease patients, the formation of antibodies to infliximab has been shown to be reduced when REMICADE® is administered concomitantly with methotrexate and other immunomodulators. No other information is available regarding possible effects of other immunosuppressive drugs or their effects on the pharmacokinetics of infliximab.

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 *Special Warnings and Special Precautions for Use*).

Pregnancy and Lactation

Because the REMICADE® product does not cross-react with TNFα in lower species, animal reproduction studies have not been conducted. It is not known whether REMICADE® can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. REMICADE® should be given to a pregnant woman only if clearly needed. In a developmental toxicity study conducted in mice using an analogous 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 adequate contraceptive measures should be taken for at least 6 months after the last REMICADE® treatment.

Like other IgG antibodies, REMICADE® crosses the placenta and has been detected up to 6 months in the serum of infants born to patients treated with REMICADE® during pregnancy. Consequently, these infants may be at increased risk of infection, and caution is advised in the administration of live vaccines in these infants (see *Special Warnings and Special Precautions for Use*).

It is not known whether REMICADE® is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from REMICADE®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Effects on 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.

Undesirable Effects

Safety data from clinical trials are available from 5561 REMICADE®-treated patients including 1304 with rheumatoid arthritis, 117 with juvenile rheumatoid arthritis, 1566 with Crohn's disease (1427 adults and 139 children), 347 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis, 544 with ulcerative colitis (484 adults and 60 children) and 17 with other conditions. Infusion-related reactions (e.g., dyspnea, flushing, headache and rash) were among the most common causes for discontinuation, except in ulcerative colitis, pediatric Crohn's disease and psoriatic arthritis.

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in clinical trials, occurring in 25.3% of infliximab-treated patients compared with 16.5% of control patients. The most serious ADRs associated with the use of TNF blockers that have been reported for REMICADE® include HBV reactivation, CHF, serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, intestinal or perianal abscess (in Crohn's disease), and serious infusion reactions (see *Special Warnings and Special Precautions for Use*).

Table 1 lists ADRs based on experience from clinical studies as well as adverse reactions, some with fatal outcome, reported from post-marketing experience. Because postmarketing events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE® exposure.

Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10);

uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Undesirable effects in clinical studies and from post-marketing experience

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

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

Uncommon:	Bullous eruption, onychomycosis, seborrhoea, rosacea, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, furunculosis.
Musculoskeletal and connective tissue disorders	
Common:	Arthralgia, myalgia, back pain.
Renal and urinary disorders	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
Reproductive system and breast disorders	
Uncommon:	Vaginitis.
General disorders and administration site conditions	
Very common:	Infusion-related reaction, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, oedema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
Investigations	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal.

Infusion-related Reactions

An infusion-related reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In Phase 3 clinical studies, 18% of REMICADE®-treated patients compared with 5% of placebo-treated patients experienced an infusion-related reaction during infusion or within 1 hour post infusion. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Approximately 3% of patients discontinued treatment due to infusion reactions and all patients recovered with or without medical therapy.

In a clinical study of patients with rheumatoid arthritis (ASPIRE), sixty-six percent of the patients (686 out of 1040) received at least one shortened infusion of 90 minutes or less and 44% of the patients (454 out of 1040) received at least one shortened infusion of 60 minutes or less. Of the REMICADE®-treated patients who received at least one shortened infusion, infusion-related reactions occurred in 15% (74/494) of patients and serious infusion reactions occurred in 0.4% (2/494) of patients. Shortened infusions at doses > 6 mg/kg have not been studied (see *Clinical Efficacy-Rheumatoid Arthritis*).

Post-marketing surveillance has noted reports of anaphylactic-like reactions including laryngeal edema, pharyngeal edema, and severe bronchospasm. Rare cases of seizure have been associated with REMICADE® administration. Exceedingly rare cases of transient visual loss and myocardial ischemia/infarction occurring during or within 2 hours of REMICADE® 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 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, dyspnea, urticaria, facial edema, and hypotension. In all cases, REMICADE® treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Hypersensitivity/Reactions Following Re-administration

In a clinical trial of 41 patients retreated with REMICADE® following a 2 to 4 year period without REMICADE® 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 edema, 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. 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 Phase III psoriasis study, 1% of patients experienced symptoms of arthralgia, myalgia, fever, and rash early in the treatment course following infliximab infusions.

Immunogenicity

Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of 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 14% of patients with any immunosuppressant therapy, and in approximately 24% 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 a Phase III psoriasis study, in which patients were treated with infliximab induction followed by every 8-week maintenance infusions without concomitant immunosuppressive therapy, antibodies were detected in approximately 28% of patients.

Infections

In clinical studies, 36% of REMICADE®-treated patients were treated for infections compared with 28% of placebo-treated patients. No increased risk of serious infections was observed with REMICADE® compared with placebo in Crohn's disease studies and the Phase III study of psoriatic arthritis. In RA trials, the incidence of serious infections, including pneumonia, was higher in REMICADE® plus MTX-treated patients compared with methotrexate alone, especially at doses of 6 mg/kg or greater. In the psoriasis studies, 1.5% of patients (average of 41.9 weeks of follow-up) receiving REMICADE® and 0.6% of patients (average of 18.1 weeks of follow-up) receiving placebo developed serious infections.

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

Hepatobiliary Events

In post-marketing surveillance, very rare cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving REMICADE® (see *Special Warnings and Special Precautions for Use*).

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 1). 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 (see Table 2). 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

					Proportion of patients with increased ALT					
	Number of Patients[1]		Median Follow-up (wks)[2]		>1 to <3 x ULN		≥3 x ULN		≥5 x ULN	
	placebo	REMICADE®	placebo	REMICADE®	placebo	REMICADE®	placebo	REMICADE®	placebo	REMICADE®
Rheumatoid arthritis[3]	375	1087	58.1	58.3	24.0%	34.4%	3.2%	3.9%	0.8%	0.9%
Crohn's disease[4]	173	703	54.1	54.1	34.1%	38.8%	3.5%	5.1%	0.0%	1.7%
Pediatric Crohn's disease	n/a	139	n/a	53.0	n/a	18.2%	n/a	4.4%	n/a	1.5%
Ulcerative colitis	242	482	30.1	30.8	12.4%	17.4%	1.2%	2.5%	0.4%	0.6%
Ankylosing spondylitis	76	275	24.1	101.9	14.5%	51.1%	0.0%	9.5%	0.0%	3.6%
Psoriatic	98		18.1	39.1	16.3%	49.5%	0.0%	6.8%	0.0%	2.1%

arthritis		191								
Plaque Psoriasis	281	1175	16.1	50.1	23.8%	49.4%	0.4%	7.7%	0.0%	3.4%

[1] Number of patients evaluated for ALT.
[2] Median follow-up is based on patients treated.
[3] Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
[4] Placebo patients in 2 of the 3 Phase III trials in Crohn's disease, ACCENT I and ACCENT II, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis.

Malignancies and Lymphoproliferative Disorders

During clinical trials of REMICADE®, new or recurrent malignancies have been reported in REMICADE®-treated patients. The incidence of lymphoma in REMICADE®-treated patients was higher than expected in the general population. The observed incidences of non-lymphoma malignancies were similar to what would be expected in the general population whereas the rate among control patients was lower than expected. In an exploratory clinical trial involving patients with moderate to severe COPD who were either current smokers or ex-smokers, more malignancies were reported in REMICADE®-treated patients compared with control patients (see *Special Warnings and Special Precautions for Use – Malignancies*). The potential role of TNF-blocking therapy in the development of malignancies is not known.

Antinuclear Antibodies (ANA)/Anti-double-stranded DNA (dsDNA) Antibodies

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

Clinical signs consistent with a lupus-like syndrome remain uncommon.

Congestive 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 rare 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.

Adverse Reactions in JRA

The safety and efficacy of REMICADE® were assessed in a multicenter, randomized, 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 MTX between the ages of 4 and 17 years received 3 mg/kg REMICADE® or placebo intravenously at weeks 0, 2, 6. Subjects randomized to placebo crossed over to receive 6 mg/kg REMICADE® at weeks 14, 16, and 20, and then every 8 weeks through week 44. Subjects randomized 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 titers 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 MTX over 52 weeks, 64.9% (37/57) children with JRA receiving infliximab 6 mg/kg in combination with MTX over 38 weeks and 46.7% (28/60) children with JRA receiving placebo in combination with 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.

Adverse Reactions in Pediatric Crohn's Disease

In general, the adverse events in pediatric patients who received REMICADE® 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 randomized pediatric Crohn's disease patients administered 5 mg/kg REMICADE® through 54 weeks than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anemia (10.7%), blood in stool (9.7%), leukopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bone fracture (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%).

Infections were reported in 56.3% of randomized subjects in REACH, and in 50.3% of subjects receiving 5 mg/kg REMICADE® in ACCENT 1. Within REACH, 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.

Overall, in REACH, 17.5% of randomized 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.

Antibodies to REMICADE® developed in 3 (2.9%) pediatric patients.

Post-marketing Experience:

The most common serious adverse events reported in the postmarketing experience in children were infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions and hypersensitivity reactions. Spontaneous serious adverse events in the postmarking experience with REMICADE® in the pediatric population have included

malignancies, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive autoantibodies.
Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients with Crohn's disease and ulcerative colitis treated with REMICADE®, the majority of whom were adolescent or young adult males (see *Special Warnings and Special Precautions for Use-Malignancies, Lymphoma).*

Overdose

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumor necrosis factor alpha (TNFα), but not to lymphotoxin α (TNFβ). Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα and when administered after disease onset allows eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity.
Histologic evaluation of colonic biopsies, obtained before and 4 weeks after administration of the REMICADE® product, revealed a substantial reduction of detectable TNFα. REMICADE® treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker C-reactive protein (CRP). Total peripheral white blood cell counts were minimally affected in REMICADE®-treated patients, although changes in lymphocytes, monocytes and neutrophils reflected shifts toward normal ranges. Peripheral blood mononuclear cells (PBMC) from REMICADE®-treated patients showed undiminished proliferative responsiveness to stimuli compared to untreated patients, and no substantial changes in cytokine production by stimulated PBMC were observed following treatment with REMICADE®. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that REMICADE® treatment caused a reduction in the number of cells capable of expressing TNFα and interferonγ. Additional histologic studies provided evidence that treatment with REMICADE® reduces the infiltration of inflammatory cells into affected areas of the intestine and the presence of inflammation markers at these sites.
Elevated concentrations of TNFα have been found 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 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 REMICADE® treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and CRP compared to baseline. 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.

Clinical efficacy

Rheumatoid arthritis

The safety and efficacy of the REMICADE® product were assessed in two multicenter, randomized, 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, 3 mg/kg or 10 mg/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/wk) for 6 months prior to enrollment 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 3). This response was seen as early as 2 weeks, and was maintained through 102 weeks of treatment ($p < 0.001$). Improvement in the number of swollen and tender joints, patient's assessment of pain, patient's and evaluator's global assessment of disease, morning stiffness, fatigue and CRP in all 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 ACR20, Structural Joint Damage and Physical Function

		Infliximab[a]				
	Placebo[a]	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	All Infliximab
	(n = 88)	(n = 86)	(n = 86)	(n = 87)	(n = 81)	(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 naive 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 (optimized to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter.

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 ($p \leq 0.001$). There was no worsening in the SF-36 mental component summary score.

Ankylosing spondylitis

The pivotal trial was a double-blind, placebo-controlled, multicenter study evaluating infliximab in 70 patients with severe active ankylosing spondylitis. During the 3 month double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6 (35 patients in each group). Starting at week 12, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 6 weeks up to week 54. The results of this study were similar to those seen in 8 additional investigator initiated studies of 169 patients with active ankylosing spondylitis.

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), with 57% of infliximab treated patients achieving at least 50% reduction from baseline in BASDAI score, compared to 9% of placebo patients ($p < 0.01$). Improvement was observed as early as week 2, and was maintained through week 54.

Physical function was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) and the SF-36 compared to placebo patients. Patients treated with infliximab showed significantly greater improvement at week 12 in BASFI and the physical component summary score of the SF-36. These improvements were maintained through week 54.

Psoriatic arthritis: Efficacy and safety were studied in a double-blind, placebo-controlled, multicenter study evaluating infliximab in 104 patients with active polyarticular psoriatic arthritis. 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.

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 65% of infliximab-treated patients achieving ACR 20 at week 16, compared with 10% of placebo-treated patients ($p < 0.01$). The response was similar regardless of concomitant use of methotrexate. Improvement (ACR 20 and 50) was observed as early as week 2 and was maintained through week 50 (ACR20, 50, and 70). By week 16, the infliximab-treatment group had a mean DAS28 (Disease Activity Score) of 3.0 (a DAS28 of < 3.2 is considered to be indicative of low disease activity), while no change was observed in the placebo-treatment group ($p < 0.01$). At the end of week 50, both cohorts of subjects had similar DAS28 scores indicating that the infliximab-treated subjects maintained the DAS28 score over time, while the placebo-treated subjects had a reduction in DAS28 only after crossover to infliximab treatment. The total DAS28 responders was 88.5% in the infliximab group at week 16 compared with 25% in the placebo group ($p < 0.01$). Psoriatic Arthritis Response Criteria (PsARC) showed rapid improvement. By week 2, 56% of subjects in the infliximab group showed improvement versus 17% of subjects in the placebo group ($p < 0.01$). Week 16 results showed a 75% response in infliximab-treated subjects compared with 21% in placebo subjects ($p < 0.01$). Decreases in parameters of peripheral activity characteristic of psoriatic arthritis (such as number of swollen joints, number of painful/tender joints, dactylitis, and presence of enthesopathy) were seen in the infliximab-treated patients. In a subset of patients with baseline PASI (Psoriasis Area and Severity Index) ≥ 2.5, marked improvement in PASI was achieved at week 16, with 68% (15/22) of infliximab-treated patients achieving at least 75% improvement from baseline vs. 0% (0/16) of placebo-treated patients; improvement was sustained through week 50. Infliximab-treated

patients demonstrated improvement in physical function as assessed by HAQ (mean change from baseline to week 16 of 0.6 vs. 0 for placebo-treated patients). Improvement was sustained through week 50.

Psoriasis: The efficacy of infliximab was assessed in two multicenter, 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 percentage 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.

The proportion of patients with ≥ 75% improvement in PASI from baseline (PASI 75) at week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p < 0.001$ for each infliximab versus placebo comparison). At week 10, a significantly greater proportion of infliximab-treated patients (3 mg/kg: 45.5%; 5 mg/kg: 57.6%) achieved a marked response (≥ 90% improvement in PASI from baseline) compared to the placebo-treated patients (2.0%). In the 3 mg/kg group, 60.6% of patients maintained response through week 14 and 75.3% of patients in the 5 mg/kg group maintained response through week 18. By week 26, twenty weeks after the last induction dose, 30% of patients in the 5mg/kg group and 13.8% of patients in the 3mg/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 4.

Table 4 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 5.

Table 5 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			

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg	p-value
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.

Crohn's disease in adult patients

The safety and efficacy of single and multiple doses of REMICADE® were assessed in two randomized double-blinded, placebo-controlled studies in patients with moderate to severe, active Crohn's disease (Crohn's Disease Activity Index (CDAI) $\geq 220 \leq 400$), 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 analyzed separately from those not in response.

At week 2, 58% (335/573) of patients were in clinical response (decrease in CDAI $\geq$ 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 with 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 vs. 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 randomized, double-blinded, placebo-controlled study in 94 patients with fistulizing Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty-one of these patients were treated with 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 ($p = 0.001$).
The safety and efficacy of repeated infusions with infliximab in patients with fistulising Crohn’s disease were studied in a 1-year trial. A total of 306 patients received 3 doses of infliximab 5 mg/kg at weeks 0, 2 and 6. Among the randomized patients at baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, and 9% had rectovaginal fistulae. The median CDAI score was 180. 195 patients responding to the 3 doses (for definition of response see description of primary endpoint for the trial above) were randomised at week 14 to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46. At week 14, 65% (177/273) of randomized patients were in fistula response. Patients randomized to infliximab maintenance had a significantly longer time to loss of fistula response compared to the placebo maintenance group ($p < 0.001$). Median time to loss of response was > 40 weeks in the infliximab group compared with 14 weeks in the placebo group. At week 54, 38% (33/87) of REMICADE®-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients ($p = 0.02$). The

infliximab group showed greater improvement in CDAI score from baseline compared with placebo (p = 0.04). Patients who achieved a fistula response and subsequently lost response were eligible to receive REMICADE® maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg REMICADE®, and 57% (12/21) of REMICADE® maintenance patients responded to 10 mg/kg. Compared to placebo maintenance, patients on REMICADE® maintenance had a trend toward fewer hospitalizations.

Active Crohn's disease in pediatric patients

The safety and efficacy of single and multiple doses of REMICADE® were assessed in a randomized, single-dose, multicenter Phase II study in 21 pediatric patients with active Crohn's disease and in a randomized, multiple dose, open-label, multicenter Phase III study in 112 pediatric Crohn's disease patients (the REACH trial).

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 fistulizing disease had their fistulas closed for at least 1 evaluation visit (8 weeks).

In a 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 randomized 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 change 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 ($p < 0.001$).

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

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 6).

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 6).

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

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

Table 6 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

	Placebo	Infliximab		
		5 mg/kg	10 mg/kg	Combined
Subjects randomized	244	242	242	484
Percentage of subjects in clinical response and in sustained clinical response				
Clinical response at Week 8[a]	33.2%	66.9%	65.3%	66.1%
Clinical response at Week 30[a]	27.9%	49.6%	55.4%	52.5%
Sustained response (clinical response at both Week 8 and Week 30)[a]	19.3%	45.0%	49.6%	47.3%
Percentage of subjects in clinical remission, 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%
Randomized 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				

Pharmacokinetic Properties

Single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of REMICADE® 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 to 4.1 liters) was not dependent on the administered dose and indicated that REMICADE® is predominantly distributed within the vascular compartment. No time-dependency of the pharmacokinetics was observed. The elimination pathways for REMICADE® have not been characterized. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight or hepatic or renal function. No notable differences in single dose pharmacokinetic parameters were observed between pediatric and adult Crohn's disease patients.

At single doses of 3, 5, and 10 mg/kg, the median pharmacokinetic values for C_{max} were 77, 118 and 277 micrograms/ml, respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after 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. In most fistulising Crohn's disease patients, infliximab was detected in serum for 12 weeks (range 4 – 28 weeks) after administration of the regimen.

Preclinical Safety Data

Infliximab does not cross react with TNFα from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In reproductive toxicity studies conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of impairment of reproductive function, maternal toxicity, embryotoxicity or teratogenicity. It is not known whether REMICADE® can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Tumorigenicity studies in mice deficient in TNFα demonstrated no increase in tumors when challenged with known tumor indicators and/or promoters.

PHARMACEUTICAL PARTICULARS

List of Excipients

Sucrose, polysorbate 80, monobasic sodium phosphate [or monobasic sodium phosphate, monohydrate], dibasic sodium phosphate [or dibasic sodium phosphate, dihydrate].

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. (CCDS - specific drug interaction studies have not been conducted)

Shelf Life

Observe expiry date on the outer pack.

This product contains no preservative. It is recommended that the administration of the solution for infusion is to be started within 3 hours of reconstitution and dilution.

Special Precautions for Storage

Store at 2°C to 8°C. Do not use beyond expiration date.

Keep out of reach of children.

Nature and Contents of Container

REMICADE® (infliximab 100 mg) lyophilized powder is supplied in single-use vials.

Instructions for Use and 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. Reconstitute each REMICADE® vial with 10 ml of 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 center of the rubber stopper and direct the stream of water for injections to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colorless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted REMICADE® solution dose to 250 ml with 0.9% w/v sodium chloride solution for infusion. This can be accomplished by withdrawing a volume of the 0.9% w/v sodium chloride solution for infusion equal to the volume of reconstituted REMICADE® from the 0.9% w/v sodium chloride solution for

infusion 250-ml glass bottle or bag. Slowly add the total volume of reconstituted REMICADE® solution to the 250-ml infusion bottle or bag. Gently mix.

4. Administer the infusion solution over a period of not less than 2 hours (at not more than 2 ml/min). Use an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometer or less). Since no preservative is present, it is recommended that the administration of the solution for infusion be started as soon as possible and within 3 hours of reconstitution and dilution. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE® with other agents. Do not infuse REMICADE® concomitantly in the same intravenous line with other agents.
5. Visually inspect parenteral medicinal products for particulate matter or discoloration prior to administration. Do not use if visibly opaque particles, discoloration or foreign particulates are observed.
6. Discard any unused portion of the solution.

MANUFACTURED BY

See outer carton.

DATE OF REVISION OF THE TEXT

September 2012[1]

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[1] Aligned with CCDS dated August 2012