centocor Schering-Plough

Date: 7 June 2006

Cases of hepatosplenic T-cell lymphoma in adolescent and young adult patients with Crohn's disease treated with Remicade (infliximab)

Dear Healthcare Professional:

Following discussion at EU level and with the Irish Medicines Board (IMB), Centocor B.V. and Schering-Plough are writing to inform you of important safety information for REMICADE® (infliximab), a TNF-α blocking monoclonal antibody indicated for the treatment of adults with rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis.

- Since launch in 1998, six cases of hepatosplenic T-cell lymphoma have been reported in patients with Crohn's disease treated with REMICADE. Five of them were in the age range of 12 to 19 years. All patients were on concomitant treatment with azathioprine or 6-mercaptopurine.

- From September 1998 to February 2006, it is estimated that approximately 270,000 patients with Crohn's disease have been exposed to infliximab worldwide, of which approximately 10,000 patients with Crohn's disease below 18 years of age were in the United States.

- A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Remicade cannot be excluded. However, the benefit/risk remains positive for the approved indications in Crohn's disease in adults and other approved indications (see attached Summary of Product Characteristics [SPC]).

- The EU SPC and Package Leaflet (PL) have been reworded (see below).

- Health care professionals are encouraged to report any suspected cases to the company and/or the IMB in the usual way.

- Further assessment of this finding is currently ongoing.

Further details

The six patients were from the US, and five of them died as a result of their lymphoma. In those patients for whom the duration of REMICADE use was reported, exposure ranged from one or two infusions of REMICADE to approximately four years of maintenance therapy. There have been no other cases of hepatosplenic T-cell lymphoma reported to Centocor or Schering-Plough out of approximately 500,000 patients treated worldwide with REMICADE with other underlying inflammatory diseases such as rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and ulcerative colitis. This includes about 430,000 rheumatoid arthritis patients treated with REMICADE and concomitant methotrexate, a potent immunosuppressant.

Centocor estimates that approximately 10,000 paediatric Crohn's disease patients in the US have been treated with REMICADE between the product's launch in 1998 to December 2005 through off-label use of the product. During this same time period it is also estimated that about 27,000 US adult Crohn's disease patients between 18 and 30 years of age have received REMICADE out of a

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worldwide total of approximately 270,000 Crohn's disease patients. The use of infliximab in patients below the age of 18 years is not approved in the EU. The magnitude of off-label use in this patient group in the EU is unknown.

Hepatosplenic T-cell lymphoma is a very rare form of non-Hodgkin's lymphoma (NHL) reported to occur most commonly in adolescent and young adult males. The background incidence of hepatosplenic T-cell lymphoma is unknown, as only approximately 150 documented cases have been published in the medical literature since it was first recognized as a distinct lymphoma subtype in the early 1990s. This disease usually presents with marked hepatosplenomegaly with bone marrow involvement and cytopenia, most often thrombocytopenia. Patients may have symptoms characteristic of B-cell lymphomas with fever, weight loss and night sweats but without lymphadenopathy or significant peripheral blood lymphocytosis. The tumor expresses one of two T-cell receptor phenotypes ($\gamma\delta$ or $\alpha\beta$). The clinical course of the disease is extremely aggressive with a fatal outcome in most patients within 2 years of diagnosis. Cases described in the medical literature include 3 patients with Crohn's disease treated with azathioprine long-term.[1, 2, 3] Cases have also been described in chronically immunosuppressed solid organ allograft recipients, usually occurring several years after transplant, many of whom were reported to have received azathioprine in addition to other immunosuppressants.[4] Both azathioprine and 6-mercaptopurine are mutagenic and are known to cause chromosomal aberrations in animals and humans. Azathioprine is classified as a human carcinogen.[5]

Centocor and Schering-Plough are committed to ensuring that REMICADE is used safely and effectively and to providing you with the most current product information for REMICADE. Should you have any questions or require further information regarding the use of REMICADE, please contact the REMICADE Medical Information Centre at 0044 (0)1707 363636.

Sincerely,

Willem Jan Atsma, MD MSCE
Qualified Person for Pharmacovigilance
Centocor B.V.

James Parker, MB ChB FRCP FFPM
Medical Director
Schering-Plough UK and Ireland

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2.) Navarro JT, Ribera JM, Mate JL, et al. Hepatosplenic T-gammadelta lymphoma in a patient with Crohn's disease treated with azathioprine. *Leuk Lymphoma* 2003; 44 (3):531-533.

3.) Lemann M, Gerard de la Valussiere F, Bouhnik Y, et al. Intravenous cyclosporine for refractory attacks of Crohn's disease (CD): long-term follow-up of patients [abstract]. *Gastroenterology* 1998; 114, No. 4, Pt. 2, A1020.

4.) Rajakariar R, Bhattacharyya M, Norton A, et al. Post-transplant T-cell lymphoma: a case series of four patients from a single unit and review of the literature. *Am J Transplant* 2004; 4:1534-1538.

5.) World Health Organization International Agency for Research on Cancer (IARC), IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 1981; 26: 47. Available at: http://monographs.iarc.fr/ENG/Monographs/vol26/volume26.pdf. Accessed on 18 May 2006.

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Remicade Summary of Product Characteristics; updated sections

- **Section 4.4: Special Warnings and Special Precautions for use; Malignancies and lymphoproliferative disorders**

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with Remicade. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with Remicade have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with Remicade cannot be excluded (see sections 4.2 and 4.8).

- **Section 4.8: Undesirable Effects; Malignancies and lymphoproliferative disorders**

Six cases of a rare type of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with Remicade in the United States (see section 4.4). It is estimated that approximately 270,000 Crohn' disease patients have been exposed to infliximab, and in the United States, approximately 10,000 patients with Crohn's disease below 18 years of age.

Remicade Package Leaflet; updated section

- **Section: BEFORE YOU USE REMICADE, Take special care with Remicade**

On rare occasions, in young or adolescent patients with Crohn's disease treated with Remicade plus azathioprine or 6-MP, a specific and severe type of lymphoma has been reported.

This SPC was approved by the CHMP on 1 June 2006 and is pending formal endorsement by the European Commission.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Remicade 100 mg powder for concentrate for solution for infusion.

2. 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. After reconstitution each ml contains 10 mg of infliximab.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis:
Remicade, in combination with methotrexate, is indicated for:
the reduction of signs and symptoms as well as the improvement in physical function in:

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

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by x-ray, has been demonstrated (see section 5.1).

Crohn's disease:
Remicade is indicated for:

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

Ulcerative colitis:
Remicade is indicated for:
Treatment of moderately to severely active ulcerative colitis in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

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

Psoriatic arthritis:
Remicade, in combination with methotrexate, is indicated for:
Treatment of active and progressive psoriatic arthritis in patients who have responded inadequately to disease-modifying anti-rheumatic drugs.

Psoriasis:
Remicade is indicated for:
Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA (see section 5.1).

4.2 Posology and method of administration

Remicade is for intravenous use in adults and has not been studied in children (0-17 years).

Remicade treatment is to be administered under the supervision and monitoring of specialised physicians experienced in the diagnosis and treatment of rheumatoid arthritis, inflammatory bowel diseases, or ankylosing spondylitis. Patients treated with Remicade should be given the package leaflet and the special Alert card.
The recommended infusion time is 2 hours. All patients administered Remicade are to be observed for at least 1-2 hours post infusion for acute infusion-related reactions. Emergency equipment, such as adrenaline, antihistamines, corticosteroids and an artificial airway must be available. Patients may be pretreated with e.g., an antihistamine, hydrocortisone and/or paracetamol and infusion rate may be slowed in order to decrease the risk of infusion related reactions especially if infusion-related reactions have occurred previously (see section 4.4).
During Remicade treatment, other concomitant therapies, e.g., corticosteroids and immunosuppressants should be optimised.

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

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

Severe, active Crohn's disease
5 mg/kg given as an intravenous infusion over a 2-hour period. Available data do not support further infliximab treatment, in patients not responding within 2 weeks to the initial infusion. In responding patients, the alternative strategies for continued treatment are:

- Maintenance: Additional infusions of 5 mg/kg at 2 and 6 weeks after the initial dose, followed by infusions every 8 weeks or
- Readministration: Infusion of 5 mg/kg if signs and symptoms of the disease recur (see 'Readministration' below and section 4.4).

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

In responding patients, the strategies for continued treatment are:

- Additional infusions of 5 mg/kg every 8 weeks or
- Readministration if signs and symptoms of the disease recur followed by infusions of 5 mg/kg every 8 weeks (see 'Readministration' below and section 4.4).

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 doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

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

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

Psoriatic arthritis
5 mg/kg given as 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. Efficacy and safety have been demonstrated in combination with methotrexate.

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. If a patient shows no response after 14 weeks (i.e. after 4 doses), no additional treatment with infliximab should be given.

Readministration for Crohn's disease and rheumatoid arthritis
If the signs and symptoms of disease recur, Remicade can be readministered within 16 weeks following the last infusion. In clinical studies, delayed hypersensitivity reactions have been uncommon and have occurred after drug free intervals of less than 1 year (see section 4.4 and 4.8: delayed hypersensitivity). The safety and efficacy of readministration after a drug free interval of more than 16 weeks has not been established. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

Readministration for ulcerative colitis
The safety and efficacy of readministration, other than every 8 weeks, has not been established.

Readministration for ankylosing spondylitis
The safety and efficacy of readministration, other than every 6 to 8 weeks, has not been established.

Readministration for psoriatic arthritis
The safety and efficacy of readministration, other than every 8 weeks, has not been established.

Readministration for psoriasis
Limited experience from retreatment with one single infliximab dose in psoriasis after an interval of 20 weeks suggests reduced efficacy and a higher incidence of mild to moderate infusion reactions when compared to the initial induction regimen (see section 5.1).

For preparation and administration instructions, see section 6.6.

4.3 Contraindications

Patients with tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see section 4.4).

Patients with moderate or severe heart failure (NYHA class III/IV) (see sections 4.4 and 4.8).

Remicade must not be given to patients with a history of hypersensitivity to infliximab (see section 4.8), to other murine proteins, or to any of the excipients.

4.4 Special warnings and special precautions for use

Infusion reactions and hypersensitivity
Infliximab has been associated with acute infusion-related reactions, including, anaphylactic shock, and delayed hypersensitivity reactions (see section 4.8: "Undesirable effects").

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

Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. A low proportion of the infusion reactions was serious allergic reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed. Concomitant administration of immunomodulators has been associated with lower incidence of antibodies to infliximab and a reduction in the frequency of infusion reactions. The effect of concomitant immunomodulator therapy was more profound in episodically treated patients than in patients given maintenance therapy. Patients who discontinue immunosuppressants prior to or during Remicade treatment are at greater risk of developing these antibodies. Antibodies to infliximab 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 (see section 4.8: "Immunogenicity").

In clinical trials, delayed hypersensitivity reactions have been reported. Available data suggest an increased risk for delayed hypersensitivity with increasing drug free interval. Advise patients to seek immediate medical advice if they experience any delayed adverse event (see section 4.8: "Delayed hypersensitivity"). If patients are retreated after a prolonged period, they must be closely monitored for signs and symptoms of delayed hypersensitivity.

Infections
Patients must be monitored closely for infections including tuberculosis before, during and after treatment with Remicade. Because the elimination of infliximab may take up to six months, monitoring should be continued throughout this period. Further treatment with Remicade must not be given if a patient develops a serious infection or sepsis.
Tumour necrosis factor alpha (TNF_α) mediates inflammation and modulates cellular immune responses. Experimental data show that TNF_α is essential for the clearing of intracellular infections. Clinical experience shows that host defence against infection is compromised in some patients treated with infliximab. It should be noted that suppression of TNF_α may also mask symptoms of infection such as fever.

Opportunistic infections and other infections including sepsis and pneumonia have been observed in patients treated with infliximab; some of these infections have been fatal.

Cases of active tuberculosis including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported in patients treated with Remicade. Some of these cases had a fatal outcome.

Before starting treatment with Remicade, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient's alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Remicade therapy must not be initiated (see section 4.3).
If inactive ('latent') tuberculosis is diagnosed, prophylactic anti-tuberculosis therapy must be started before the initiation of Remicade, and in accordance with local recommendations. In this situation, the benefit/ risk balance of Remicade therapy should be very carefully considered.

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

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.

Reactivation of hepatitis B occurred in patients receiving Remicade who are chronic carriers of this virus (i.e. surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with Remicade.

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

Concurrent administration of TNF-alpha inhibitor and anakinra
Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF_{α}-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 TNF_{α}-blocking agents. Therefore, the combination of Remicade and anakinra is not recommended.

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.

Autoimmune processes
The relative deficiency of TNF_{α} caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Remicade and is positive for antibodies against double-stranded DNA, further treatment with Remicade must not be given (see section 4.8: "Anti-nuclear antibodies (ANA)/Double-stranded DNA (dsDNA) antibodies").

Neurological events
Infliximab and other agents that inhibit TNF_α have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disorders, including multiple sclerosis. In patients with pre-existing or recent onset of central nervous system demyelinating disorders, the benefits and risks of Remicade treatment should be carefully considered before initiation of Remicade therapy.

Malignancies and lymphoproliferative disorders
In the controlled portions of clinical trials of TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. However, the occurrence was rare, and the follow up period of placebo patients was shorter than for patients receiving TNF-blocking therapy. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with longstanding, highly active, inflammatory disease, which complicates the risk estimation. 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. No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving Remicade. Thus additional caution should be exercised in considering Remicade treatment of these patients as well as in patients with increased risk for malignancy due to heavy smoking. With the current knowledge, a risk for the development of lymphomas or other malignancies in patients treated with a TNF-blocking agent cannot be excluded (see Section 4.8).
Caution should also be exercised in patients with psoriasis and a medical history of extensive immunosuppressant therapy or prolonged PUVA treatment.

Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with Remicade. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All of these hepatosplenic T-cell lymphomas with Remicade have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with Remicade cannot be excluded (see sections 4.2 and 4.8).

All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. With current data it is not known if infliximab treatment influences the risk for developing dysplasia or colon cancer (see section 4.8).

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

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

Others
Treatment with Remicade has not been studied in children 0-17 years with rheumatoid arthritis or Crohn's disease. Until safety and efficacy data in children are available, such treatment is to be avoided.

The pharmacokinetics of infliximab in elderly patients has not been studied. Studies have not been performed in patients with liver or renal disease (see section 5.2).

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

In rheumatoid arthritis and Crohn's disease patients, there are indications that concomitant use of methotrexate and other immunomodulators reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. However, the results are uncertain due to limitations in the methods used for serum analyses of infliximab and antibodies against infliximab.
Corticosteroids do not appear to affect the pharmacokinetics of infliximab to a clinically relevant extent. The combination of Remicade and anakinra is not recommended (see section 4.4).
Nothing is known regarding possible interactions between infliximab and other active substances.

4.6 Pregnancy and lactation

Pregnancy
Post-marketing reports from approximately 300 pregnancies exposed to infliximab, do not indicate unexpected effects on pregnancy outcome. Due to its inhibition of TNFα, infliximab administered during pregnancy could affect normal immune responses in the newborn. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, there was no indication of maternal toxicity, embryotoxicity or teratogenicity (see section 5.3).
The available clinical experience is too limited to exclude a risk, and administration of infliximab is therefore not recommended during pregnancy.

Women of childbearing potential
Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last Remicade treatment.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Table 1
Undesirable Effects in Clinical Studies

Infections and infestations		
	Common:	Viral infection (e.g. influenza, herpes infections)
	Uncommon:	Abscess, cellulitis, moniliasis, sepsis, bacterial infection, tuberculosis, fungal infection, hordeolum
Blood and lymphatic disorders		
	Uncommon:	Anaemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropenia, thrombocytopenia
Immune system disorders		
	Common:	Serum sickness-like reactions
	Uncommon:	Lupus-like syndrome, respiratory tract allergic reactions, anaphylactic reactions
Psychiatric disorders		
	Uncommon:	Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence, insomnia
Nervous system disorders		
	Common:	Headache, vertigo/dizziness
	Uncommon:	Exacerbation of demyelinating disease suggestive of multiple sclerosis
	Rare:	Meningitis
Eye disorders		
	Uncommon:	Conjunctivitis, endophthalmitis, keratoconjunctivitis, periorbital oedema
Cardiac disorders		
	Uncommon:	Syncope, bradycardia, palpitation, cyanosis, arrythmia, worsening heart failure
	Rare:	Tachycardia
Vascular disorders		
	Common:	Flushing
	Uncommon:	Ecchymosis/haematoma, hot flushes, hypertension, hypotension, petechia, thrombophleblitis, vasospasm, peripheral ischaemia
	Rare:	Circulatory failure
Respiratory, thoracic and mediastinal disorders		
	Common:	Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, sinusitis
	Uncommon:	Epistaxis, bronchospasm, pleurisy, pulmonary oedema
	Rare:	Pleural effusion
Gastrointestinal disorders		
	Common:	Nausea, diarrhoea, abdominal pain, dyspepsia
	Uncommon:	Constipation, gastroesophageal reflux, cheilitis, diverticulitis
	Rare:	Intestinal perforation, intestinal stenosis, gastrointestinal haemorrhage
Hepatobiliary disorders		
	Uncommon:	Abnormal hepatic function, cholecystitis
	Rare:	Hepatitis
Skin and subcutaneous tissue disorders		
	Common:	Rash, pruritus, urticaria, increased sweating, dry skin
	Uncommon:	Fungal dermatitis/onychomycosis, eczema/seborrhoea, bullous eruption, furunculosis, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/ colouration, alopoecia

Musculoskeletal and connective tissue disorders	
Uncommon:	Myalgia, arthralgia, back pain
Renal and urinary disorders	
Uncommon:	Urinary tract infection, pyelonephritis
Reproductive system and breast disorders	
Uncommon:	Vaginitis
General disorders and administration site conditions	
Common:	Fatigue, chest pain, infusion-related reactions, fever
Uncommon:	Injections site reactions, oedema, pain, chills/rigors, impaired healing
Rare:	Granulomatous lesion
Investigations	
Common:	Elevated hepatic transaminases
Uncommon:	Autoantibodies, complement factor abnormality

Table 2
Undesirable effects in Post-marketing reports
(common > 1/100, < 1/10; uncommon > 1/1000, < 1/100; rare > 1/10,000, < 1/1000; very rare < 1/10,000, including isolated reports).

Infections and infestations		
	Rare:	Opportunistic infections (such as tuberculosis, atypical mycobacteria, pneumocystosis, histoplasmosis, coccidioidomycosis, cryptococcosis, aspergillosis, listeriosis and candidiasis)
	Very Rare:	Salmonellosis, reactivation of hepatitis B
Blood and lymphatic system disorders		
	Rare:	Pancytopenia
	Very Rare:	Haemolytic anaemia, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, agranulocytosis
Immune system disorders		
	Uncommon:	Anaphylactic reactions
	Rare:	Anaphylactic shock, serum sickness, vasculitis
Nervous system disorders		
	Rare:	Demyelinating disorders (such as multiple sclerosis and optic neuritis), Guillain-Barré syndrome, neuropathies, numbness, tingling, seizure
	Very Rare:	Transverse myelitis
Cardiac disorders		
	Rare:	Worsening heart failure, new onset heart failure
	Very rare:	Pericardial effusion
Respiratory, thoracic and mediastinal disorders		
	Rare:	Interstitial pneumonitis/fibrosis
Gastrointestinal disorders		
	Rare:	Pancreatitis
Hepatobiliary disorders		
	Rare:	Hepatitis
	Very rare:	Hepatocellular damage, jaundice, liver failure, autoimmune hepatitis
Skin and subcutaneous tissue disorders		
	Rare:	Vasculitis (primarily cutaneous)
General disorders and administration site conditions		
	Common:	Infusion-related reactions

Infusion-related reactions: An infusion-related reaction was defined in clinical studies as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. In clinical studies, approximately 20% of infliximab-treated patients compared with approximately 10% of placebo-treated patients experienced an infusion-related effect. Approximately 3% of patients discontinued treatment due to infusions reactions and all patients recovered with or without medical therapy

In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal oedema and severe bronchospasm, and seizure have been associated with Remicade administration.

Delayed hypersensitivity: In clinical studies delayed hypersensitivity reactions have been uncommon and have occurred after drug free intervals of less than 1 year. In the psoriasis studies, delayed

hypersensitivity reactions occurred early in the treatment course. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat and headache.

There are insufficient data on the incidence of delayed hypersensitivity reactions after drug free intervals of more than 1 year but limited data from clinical trials suggest an increased risk for delayed hypersensitivity with increasing drug free interval.

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

Immunogenicity: Patients who developed antibodies to infliximab were more likely (approximately 2-3 fold) to develop infusion-related reactions. Use of concomitant immunosuppressant agents appeared to reduce the frequency of 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 14% of patients with any immunosuppressant therapy, and in 24% of patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 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 limitations, a negative assay did not exclude the presence of antibodies to infliximab. Some patients who developed high titres of antibodies to infliximab had evidence of reduced efficacy (see section 4.4: "Infusion reactions and hypersensitivity"). In psoriasis patients treated with infliximab as a maintenance regimen in the absence of concomitant immunomodulators, approximately 28% developed antibodies to infliximab.

Infections: In clinical studies 36% of infliximab-treated patients were treated for infections compared with 25% of placebo-treated patients.

In RA trials, the incidence of serious infections including pneumonia was higher in infliximab plus MTX treated patients compared with methotrexate alone especially at doses of 6 mg/kg or greater (see section 4.4).

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

Malignancies and lymphoproliferative disorders: In clinical studies with infliximab and during long-term follow-up of 4 years, representing 8800 patient years, 8 cases of lymphomas and 43 other malignancies were detected as compared with 9 malignancies and 0 lymphoma in placebo-treated patients observed during 1274 patient years. The overall rate of malignancies in these patients was similar to that expected for an age-, gender- and race-matched general population. From August 1998 to August 2004, 1367 cases of suspected malignancies have been reported from post-marketing, clinical trials and registries (229 in Crohn's disease patients, 942 in rheumatoid arthritis patients and 196 in patients with other or unknown indications). Among those there were 242 lymphoma cases. During this period, the estimated exposure is 1,350,000 patient years (see section 4.4: Special Warnings and Special Precautions for Use - "Malignancies").

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

Six cases of a rare type of hepatosplenic T-cell lymphoma have been reported in adolescent and young adult patients with Crohn's disease treated with Remicade in the United States (see section 4.4). It is estimated that approximately 270,000 Crohn' disease patients have been exposed to infliximab, and in the United States, approximately 10,000 patients with Crohn's disease below 18 years of age.

Heart failure: In a phase II study aimed at evaluating Remicade in congestive heart failure (CHF), higher incidence of mortality due to worsening of heart failure were seen in patients treated with Remicade, especially those treated with the higher dose of 10 mg/kg (i.e. twice the maximum approved dose). In this study 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction ≤35%) were treated with 3 infusions of Remicade 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 9 of 101 patients treated with Remicade (2 at 5 mg/kg and 7 at 10 mg/kg) died compared to one death among the 49 patients on placebo.
There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking 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.

Hepatobiliary events: 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 aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving Remicade than in controls, both when Remicade was given as monotherapy and when it was used in combination with other immunosuppressive agents. Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of Remicade, or modification of concomitant medications. ALT elevations ≥ 5 times the upper limit of normal were observed in 1% of patients receiving Remicade. ALT elevations ≥ 3 times the upper limit of normal were observed across all approved indications at the following frequencies (placebo/infliximab): rheumatoid arthritis 3.2%/3.9%; Crohn's disease 3.5%/5.1%; ankylosing spondylitis 0.0%/5.9%; psoriatic arthritis 0.0%/5.4%; psoriasis 0.0%/10.4%. 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 section 4.4)

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective immunosuppressive agents, ATC code: L04A A12.

Pharmacodynamic properties: Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF_{α} but not to lymphotoxin α (TNF_{β}). Infliximab inhibits the functional activity of TNF_{α} in a wide variety of *in vitro* bioassays. Infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive

expression of human TNF_α and when administered after disease onset, it allowed eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNF_α, a process that parallels the loss of TNF_α bioactivity.

Elevated concentrations of TNF_α have been found in the joints of rheumatoid arthritis patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemoattraction and tissue degradation. After infliximab treatment, patients exhibited decreased levels of serum interleukin 6 (IL-6) and C-reactive protein (CRP) compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalization of keratinocyte differentiation in psoriatic plaques.

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

Clinical Efficacy

Rheumatoid arthritis

The efficacy of infliximab was assessed in two multicentre, randomised, double-blind, pivotal trials: ATTRACT and ASPIRE. In both studies concurrent use of stable doses of folic acid, oral corticosteroids ($\leq$ 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 criteria (ACR20 for ATTRACT, landmark ACR-N for ASPIRE), the prevention of structural joint damage, and the improvement in physical function. A reduction in signs and symptoms was defined to be at least a 20% improvement (ACR20) in both tender and swollen joint counts, and in 3 of the following 5 criteria: (1) evaluator's global assessment, (2) patient's global assessment, (3) functional/disability measure, (4) visual analogue pain scale and (5) erythrocyte sedimentation rate or C-reactive protein. ACR-N uses the same criteria as the ACR20, calculated by taking the lowest percent improvement in swollen joint count, tender joint count, and the median of the remaining 5 components of the ACR response. Structural joint damage (erosions and joint space narrowing) in both hands and feet was measured by the change from baseline in the total van der Heijde-modified Sharp score (0-440). The Health Assessment Questionnaire (HAQ; scale 0-3) was used to measure patients' average change from baseline scores over time, in physical function.

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

Results from week 54 (ACR20, total van der Heijde-modified Sharp score and HAQ) are shown in Table 3. Higher degrees of clinical response (ACR50 and ACR70) were observed in all infliximab groups at 30 and 54 weeks compared with methotrexate alone.

A reduction in the rate of the progression of structural joint damage (erosions and joint space narrowing) was observed in all infliximab groups at 54 weeks (Table 3).

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

Table 3
Effects on ACR20, Structural Joint Damage and Physical Function at week 54, ATTRACT

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

a: control = All patients had active RA despite treatment with stable methotrexate doses for 6 months prior to enrolment and were to remain on stable doses throughout the study. Concurrent use of stable doses of oral corticosteroids (≤ 10 mg/day) and/or non-steroidal anti-inflammatory drugs was permitted, and folate supplementation was given.
b: all infliximab doses given in combination with methotrexate and folate with some on corticosteroids and/or non-steroidal anti-inflammatory drugs
c: $p < 0.001$, for each infliximab treatment group vs. control
d: greater values indicate more joint damage.
e: HAQ = Health Assessment Questionnaire; greater values indicate less disability.

The ASPIRE trial evaluated responses at 54 weeks in 1004 methotrexate naive patients with early (≤3 years disease duration, median 0.6 years) active rheumatoid arthritis (median swollen and tender joint count of 19 and 31, respectively). All patients received methotrexate (optimised to 20 mg/wk by week 8) and either placebo, 3 mg/kg or 6 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. Results from week 54 are shown in Table 4.

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

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

Table 4
Effects on ACRn, Structural Joint Damage and Physical Function at week 54, ASPIRE

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

a: $p < 0.001$, for each infliximab treatment group vs. control
b: greater values indicate more joint damage.
c: HAQ = Health Assessment Questionnaire; greater values indicate less disability.
d: $p = 0.030$ and < 0.001 for the 3mg/kg and 6mg/kg treatment groups respectively vs. placebo + MTX.

Crohn's disease

Induction treatment in severe active Crohn's disease

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

The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥ 70 points from baseline at the 4-week evaluation and without an increase in Crohn's disease medications or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients in clinical remission at week 4 (CDAI < 150) and clinical response over time.

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

Maintenance treatment in severe active Crohn's disease

The efficacy of repeated infusions with infliximab was studied in a 1-year clinical study.

A total of 573 patients with active Crohn's disease (CDAI ≥ 220 ≤ 400) received a single infusion of 5 mg/kg at week 0. Sixty-eight of these patients (12%) belonged to the population defined in the indication (see section 4.1). Three hundred and thirty-five patients (58%) responding to the 5 mg/kg infusion at week 2 were randomised to one of three treatment groups; a placebo maintenance group, 5 mg/kg maintenance group and 10 mg/kg maintenance group, receiving repeated infusions at week 2, 6 and every eight weeks.

At week 30, a significantly greater proportion of patients in the combined infliximab maintenance treatment group (42%) achieved clinical remission, compared with patients in the placebo maintenance group (21%). Median time to loss of response was 46 weeks in the combined infliximab maintenance treatment group vs. 19 weeks in the placebo maintenance group ($p < 0.001$). Similar results were obtained in the subgroup analyses of the population defined in the indication (see section 4.1).

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

Induction treatment in fistulising active Crohn's disease
The efficacy was assessed in a randomised, double-blinded, placebo-controlled study in 94 patients with fistulising Crohn's disease who had fistulae that were of at least 3 months' duration. Thirty-one of these patients were treated with infliximab 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.
Concurrent use of stable doses of conventional therapies was permitted, and 83% of patients continued to receive at least one of these medications. Patients received three doses of either placebo or infliximab at weeks 0, 2 and 6. Patients were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥ 50% reduction from baseline in the number of fistulae draining upon gentle compression on at least two consecutive visits (4 weeks apart), without an increase in medication or surgery for Crohn's disease.
Sixty-eight percent (21/31) of infliximab-treated patients receiving a 5 mg/kg dose regimen achieved a clinical response vs. 26% (8/31) placebo-treated patients ($p = 0.002$). The median time to onset of response in the infliximab-treated group was 2 weeks. The median duration of response was 12 weeks. Additionally, closure of all fistulae was achieved in 55% of infliximab-treated patients compared with 13% of placebo-treated patients ($p = 0.001$).

Maintenance treatment in fistulising active Crohn's disease
The efficacy of repeated infusions with infliximab in patients with fistulising Crohn's disease was studied in a 1-year clinical study. A total of 306 patients received 3 doses of infliximab 5 mg/kg at week 0,2 and 6. At baseline, 87% of the patients had perianal fistulae, 14% had abdominal fistulae, 9% had rectovaginal fistulae. The median CDAI score was 180. One-hundred and ninety-five patients responding to the 3 doses (for definition of response see description of primary endpoint for the study above) were randomised at week 14 to receive either placebo or 5 mg/kg infliximab every 8 weeks through week 46. A significantly longer time to loss of response was seen in the infliximab maintenance group 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. Most patients had a loss of response due to increase in medication for Crohn's disease and not because of a < 50% reduction in number of draining fistulas. At week 54, the infliximab group showed greater improvement in CDAI score from baseline compared with placebo ($p = 0.04$). There was no significant difference between placebo and infliximab for the proportion of patients with sustained closure of all fistulas through week 54, for symptoms such as proctalgia, abscesses and urinary tract infection or for number of newly developed fistulas during treatment.

Ulcerative Colitis
The safety and efficacy of Remicade 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 Remicade, or 10 mg/kg Remicade at weeks 0, 2, 6, 14 and 22, and in ACT 1 at weeks 30, 38 and 46. Corticosteroid taper was permitted after week 8.

Table 5
Effects on clinical response, clinical remission and mucosal healing at Weeks 8 and 30.
Combined data from ACT1 & 2.

	Placebo	Infliximab 5 mg/kg	Infliximab 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 and sustained remission				
Clinical remission at Week 8[a]	10.2%	36.4%	29.8%	33.1%
Clinical remission at Week 30[a]	13.1%	29.8%	36.4%	33.1%
Sustained remission (in remission at both Week 8 and Week 30)[a]	5.3%	19.0%	24.4%	21.7%
Percentage of subjects with mucosal healing				
Mucosal healing at Week 8[a]	32.4%	61.2%	60.3%	60.7%
Mucosal healing at Week 30[a]	27.5%	48.3%	52.9%	50.6%

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

The efficacy of Remicade through week 54 was assessed in the ACT 1 trial.
At 54 weeks, 44.9% of patients in the combined infliximab treatment group were in clinical response compared to 19.8% in the placebo treatment group ($p<0.001$). Clinical remission and mucosal healing occurred in a greater proportion of patients in the combined infliximab treatment group compared to the placebo treatment group at week 54 (34.6% vs. 16.5%, $p<0.001$ and 46.1% vs. 18.2%, $p<0.001$, respectively). The proportions of patients in sustained response and sustained remission at week 54 were greater in the combined infliximab treatment group than in the placebo treatment group (37.9% vs. 14.0%, $p<0.001$; and 20.2% vs. 6.6%, $p<0.001$, respectively).

Infliximab improved Quality of Life, confirmed by statistically and clinically significant improvement in both a 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 lower in the combined infliximab treatment group than in the placebo treatment group (9 versus 18 hospitalizations per 100 subjects, $p = 0.005$). No notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab treatment groups.

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

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

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

Psoriatic Arthritis

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

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 ($p<0.01$). Improvement (ACR 20 and 50) was observed as early as week 2 and was maintained through week 50 (ACR 20, 50, and 70). Decreases in parameters of peripheral activity characteristic of psoriatic arthritis (such as number of swollen joints, number of painful/tender joints, dactylitis and presence of enthesopathy) were seen in the infliximab-treated patients.
Infliximab-treated patients also 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).

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] $\geq$10% and Psoriasis Area and Severity Index [PASI] score $\geq$12). The primary endpoint in both studies was the percent of patients who achieved $\geq$ 75% improvement in PASI from baseline at week 10.

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

In SPIRIT, the proportion of patients achieving PASI 75 at week 10 was 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p < 0.001$). By week 26, twenty weeks after the last induction dose, 30% of patients in the 5mg/kg group and 13.8% of patients in the 3mg/kg group were PASI 75 responders. Between weeks 6 and 26, symptoms of psoriasis gradually returned with a median time to disease relapse of > 20 weeks. No rebound was observed.

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

Table 6
Summary of PASI response and PGA score at Weeks 10, 24 and 50. EXPRESS.

	Placebo → Infliximab 5 mg/kg (at week 24)	Infliximab 5 mg/kg
Week 10		
n	77	301
≥ 90% improvement	1 (1.3%)	172 (57.1%)[a]
≥ 75% improvement	2 (2.6%)	242 (80.4%)[a]
≥ 50% improvement	6 (7.8%)	274 (91.0%)
PGA of cleared (0) or minimal (1)	3 (3.9%)	242 (82.9%)[ab]
PGA of cleared (0), minimal (1), or mild (2)	14 (18.2%)	275 (94.2%)[ab]
Week 24		
n	77	276
≥ 90% improvement	1 (1.3%)	161 (58.3%)[a]
≥ 75% improvement	3 (3.9%)	227 (82.2%)[a]
≥ 50% improvement	5 (6.5%)	248 (89.9%)
PGA of cleared (0) or minimal (1)	2 (2.6%)	203 (73.6%)[a]
PGA of cleared (0), minimal (1), or mild (2)	15 (19.5%)	246 (89.1%)[a]
Week 50		
n	68	281
≥ 90% improvement	34 (50.0%)	127 (45.2%)
≥ 75% improvement	52 (76.5%)	170 (60.5%)
≥ 50% improvement	61 (89.7%)	193 (68.7%)
PGA of cleared (0) or minimal (1)	46 (67.6%)	149 (53.0%)
PGA of cleared (0), minimal (1), or mild (2)	59 (86.8%)	189 (67.3%)

a: $p < 0.001$, for each infliximab treatment group vs. control
b: n = 292

5.2 Pharmacokinetic properties

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

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

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

fistulising Crohn's disease patients, infliximab was detected in serum for 12 weeks (range 4-28 weeks) after administration of the regimen.

5.3 Preclinical safety data

Infliximab does not cross react with TNF_α from species other than human and chimpanzees. Therefore, conventional preclinical safety data with infliximab are limited. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNF_α, there was no indication of maternal toxicity, embryotoxicity or teratogenicity. In a fertility and general reproductive function study, the number of pregnant mice was reduced following administration of the same analogous antibody. It is not known whether this finding was due to effects on the males and/or the females. In a 6-month repeated dose toxicity study in mice, using the same analogous antibody against mouse TNF_α, crystalline deposits were observed on the lens capsule of some of the treated male mice. No specific ophthalmologic examinations have been performed in patients to investigate the relevance of this finding for humans.
Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in TNF_α demonstrated no increase in tumours when challenged with known tumour initiators and/or promoters.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, polysorbate 80, monobasic sodium phosphate, dibasic sodium phosphate.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

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

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

6.5 Nature and contents of container

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

6.6 Instructions for use and handling

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

2. Under aseptic conditions, reconstitute each Remicade vial with 10 ml of water for injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. Remove flip-top from the vial and wipe the top with a 70% alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper and direct the stream of water for injections to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilised powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colourless 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, discolouration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted Remicade solution dose to 250 ml with sodium chloride 9 mg/ml (0.9%) solution for infusion. This can be accomplished by withdrawing a volume of the sodium chloride 9 mg/ml (0.9%) solution for infusion from the 250-ml glass bottle or infusion bag equal to the volume of reconstituted Remicade. 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 only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometer or less). Since no preservative is present, it is recommended that the administration of the solution for infusion is to be started as soon as possible and within 3 hours of reconstitution and dilution. When reconstitution and dilution are performed under aseptic conditions, Remicade infusion solution can be used within 24 hours if stored at 2°C to 8°C. Do not store any unused portion of the infusion solution for reuse.

5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of Remicade with other agents. Do not infuse Remicade concomitantly in the same intravenous line with other agents.

6. Visually inspect parenteral medicinal products for particulate matter or discolouration prior to administration. Do not use if visibly opaque particles, discolouration or foreign particulates are observed.

7. Discard any unused portion of the solution.

7. MARKETING AUTHORISATION HOLDER

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Einsteinweg 101
2333 CB Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT