



The European Agency for the Evaluation of Medicinal Products
Post-authorisation Evaluation of Medicines for Human Use

London, 1 February 2002
CPMP/32/02

**EMEA PUBLIC STATEMENT ON INFLIXIMAB (REMICADE)
Update on safety concerns**

The following public statement from the European Agency for the Evaluation of Medicinal Products (EMEA) contains essential information for anyone prescribing or taking Remicade (infliximab)¹.

Further to the EMEA public statements on 20 December 2000 (EMEA/CPMP/4445/00) and 24 October 2001 (CPMP/3257/01), the Agency's scientific committee, the Committee for Proprietary Medicinal Products (CPMP), has continued to review clinical efficacy and safety information on Remicade.

The CPMP concluded in its meeting on 17 January 2002, that Remicade continues to have a positive benefit/ risk balance in both Crohn's disease and Rheumatoid arthritis, provided that specific changes to the Product Information restricting the indication in Crohn's disease and reinforcing the special precautions and warnings have been made.

Because of safety concerns, the indications for treatment of Crohn's disease have been restricted as follows:

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

The indication for rheumatoid arthritis remains unchanged [see attached Summary of Product Characteristics (SPC)].

To further guarantee the safe use of Remicade, the EMEA draws attention to the following important safety information:

Remicade should only be administered under the supervision and monitoring of specialised physicians experienced in the diagnosis and treatment of rheumatoid arthritis or inflammatory bowel diseases.

Information for Health Care Professionals:

- **Infections including tuberculosis:** Remicade is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses, or opportunistic infections. Patients must be closely monitored for infections including tuberculosis before, during and after Remicade treatment, in accordance with local recommendations. Treatment with Remicade must not be continued if a patient develops serious infections or sepsis.

¹ Remicade 100 mg powder for concentrate for solution for infusion contains infliximab, a monoclonal antibody that inhibits the biological activity of tumour necrosis factor alpha (TNF α). Remicade was authorised in the European Union in August 1999. The Marketing Authorisation Holder is Centocor B.V. Since Remicade was first licensed in 1998 in the USA, approximately 200,000 patients have received it worldwide.

In postmarketing spontaneous reporting, infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Up to the middle of 2001, 202 deaths have been reported. Nearly 50% of these have been associated with infections.

Up to 31 October 2001, approximately 130 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 is recorded on the patient's alert card, which will be provided with the Remicade packages. 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 treatment must not be initiated.

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.

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

- **Heart Failure:** Remicade is contraindicated in patients with moderate to severe heart failure (NYHA class III/IV). Caution should be exercised if treating patients with Remicade who have mild heart failure (NYHA class I/II). While being treated with Remicade, the patient's heart failure status should be closely monitored. Remicade treatment must not be continued if the patient develops symptoms of heart failure or experiences worsening heart failure (see SPC for further details).
- **Other safety concerns:** These include hypersensitivity reactions including anaphylactic shock, neurological events and malignancies (see SPC for further details).
- **Care should be taken in selecting appropriate patients while observing the above safety information in order to minimise the risks associated with Remicade therapy.**
- **All patients treated with Remicade should be given the package leaflet and a special patient's alert card.**
- **The safety and efficacy of Remicade for indications outside of Crohn's disease and rheumatoid arthritis have not been established.**

Information for Patients

- **Remicade continues to be an effective and safe medicine.** However, it is important that the patients are selected carefully and the warnings indicated below are respected.
- **Remicade increases the risk of getting infections.** Infections may progress more rapidly and be more severe. This includes tuberculosis (TB).
- **You should not be treated with Remicade, if you have a severe infection.**

- **You should be tested for TB** prior to Remicade treatment. Tell your doctor if you have ever had TB or if you have been in close contact with someone who has had TB.
- **Contact your doctor** if symptoms suggestive of infections appear, such as fever, persistent cough, weight loss, or listlessness.
- **Remicade should not be used if you have moderate or severe heart failure.**
- **Contact your doctor** if you experience symptoms like shortness of breath, especially with exertion or upon lying down, or swelling of your feet which might indicate heart failure.

As an urgent measure, the patient and prescribing information has been amended accordingly through a rapid procedure at the request of the marketing authorisation holder and a patient's alert card has been introduced.

The revised Summary of Product Characteristics and patient leaflet as well as the new patient's alert card are attached for more detailed information.

For further information contact:

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**PROVISIONAL CHANGES INTRODUCED
TO INFORMATION FOR PATIENTS AND PRESCRIBERS**

(Changes are highlighted)

Deletions appear as ~~striketrough~~ and additions appear as underlined

INFORMATION TO PATIENTS (PACKAGE LEAFLET):

Read all of this leaflet carefully before you start using this medicine. This package leaflet should be given to the patient.

You will also be given a patient alert card, which contains important safety information that you need to be aware of before you are given Remicade and during treatment with Remicade. Keep this alert card together with the package leaflet.

If you have further questions, please ask your doctor or your pharmacist.
This medicine has been prescribed for you personally.

In this leaflet:

1. What Remicade is and what it is used for
2. Before you use Remicade
3. How to use Remicade
4. Possible side effects
5. Storing Remicade

Remicade 100 mg powder for concentrate for solution for infusion

The active substance is infliximab.

The other ingredients are sucrose, polysorbate 80, monobasic sodium phosphate and dibasic sodium phosphate.

Marketing authorisation holder and manufacturer:

Centocor B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

1. WHAT REMICADE IS AND WHAT IT IS USED FOR

Remicade is supplied as a powder for concentrate for solution for infusion. It is available in packs of 1, 2 or 3 vials. Not all pack sizes may be marketed. Before Remicade can be given to you, it is to be mixed with water for injections and further mixed with 0.9% sodium chloride solution. The prepared solution will be infused through a vein in your arm over a 2-hour period. Each vial (glass bottle) contains 100 mg of infliximab.

Remicade can be used to treat two different diseases, namely Crohn's disease and rheumatoid arthritis.

~~Remicade is a type of medicine that interrupts the inflammation process.~~ The active ingredient, infliximab, is a human-mouse monoclonal antibody. Monoclonal antibodies are proteins that recognise and bind to other unique proteins.

Infliximab binds to a specific naturally occurring protein (tumour necrosis factor alpha) ~~that is thought to cause your rheumatoid arthritis if it collects in your joints or Crohn's disease if it attacks the bowel.~~ alpha or TNF α

~~The amount of the naturally occurring protein, tumour necrosis factor alpha (TNF α).~~ The amount of TNF α is increased in both rheumatoid arthritis and Crohn's disease. Remicade (infliximab) is an anti-TNF antibody that can prevent the harmful effects of TNF α and it will interrupt the inflammation process.

Rheumatoid arthritis:

Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will be first given other disease-modifying medicines. If you do not respond well enough to these medicines, you will be given Remicade to:

- reduce the signs and symptoms of your disease.
- slow down the damage to your joints
- improve your physical function

You will also be given methotrexate.

Crohn's Disease:

Crohn's disease is an inflammatory disease of the bowel. Remicade is used for patients with Crohn's disease to:

- treat severe, active disease not controlled ~~by a corticosteroids and/or immunosuppressant~~ and an immunosuppressant; or if you have not been able to tolerate these types of medicines;
- lower the number of draining enterocutaneous fistulae (abnormal openings through the skin from the bowel) that have not been controlled by other medicines or surgery.

2. BEFORE YOU USE REMICADE

Do not use Remicade:

- if you have a history of ~~a serious~~ hypersensitivity or allergy to any ingredient of the product or to mouse (murine) proteins.
- if you have a severe infection, including tuberculosis (see: "Take special care with Remicade"). It is important that you tell your doctor if you have symptoms of infection, e.g. fever, malaise, wounds, dental problems.
- if you have moderate or severe heart failure. It is important to tell your doctor if you have had or have a serious heart condition.

If you have any uncertainty you must discuss this with your doctor.

Take special care with Remicade:

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

Specific studies with Remicade have not been conducted in elderly patients, or in patients with hepatic or renal disease.

Some patients had allergic reactions within 2 hours of receiving Remicade. These reactions were generally mild to moderate; however, on rare occasions they were ~~more~~ severe. The symptoms of such reactions were most often skin rash, hives, fatigue, wheezing, difficulty in breathing and/or low blood pressure. The symptoms will most often occur the first and second time you get the medicine. If you notice these symptoms tell your doctor. If the symptoms occur during your infusion, your doctor may slow down the speed of the infusion ~~so that it will take longer for you to get your medicine~~. Your doctor may also stop giving the medicine until the symptoms go away and then begin giving the medicine again. Your doctor may also treat your symptoms with other medicines (paracetamol, antihistamines, corticosteroids, bronchodilators and/or adrenaline). Most of the time you can still get Remicade even if the symptoms occur. However, in some cases your doctor may decide that it is best not to give you Remicade anymore.

Taking Remicade again after a drug free period of more than 14 weeks is not recommended.

If your last Remicade dose was given to you 2 years ago or more and you are given Remicade again, it is possible that you might have an allergic ~~reaction 3 to~~reaction up to 12 days after your infusion. The reaction can be serious. Signs and symptoms are tenderness or pain in the muscles, rash, fever, joint or jaw pain, hand and face swelling, swallowing difficulties, itching, sore throat and/or headache. Contact your doctor immediately for treatment of these symptoms.

You might get infections more easily. It is important that you tell your doctor if you get any symptoms of infection, e.g. fever, malaise, wounds, dental problems.

As cases of tuberculosis have been reported in patients treated with Remicade, you will be screened for tuberculosis before starting Remicade. This includes a thorough medical history and it is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. It is also important to tell about other medicines you may take. In addition, you will have a tuberculin skin test and a chest x-ray. It is recommended that the conduct of these tests is recorded on your alert card.

If symptoms of tuberculosis (persistent cough, weight loss, listlessness, fever), or any other infection appear during therapy notify your doctor immediately.

If you are about to undergo surgery or dental procedures please inform your doctor that you are taking Remicade.

If you have mild heart failure and you are being treated with Remicade, your heart failure status must be closely monitored by your doctor. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet), you must contact your doctor immediately.

On rare occasions, you may develop signs and symptoms of a disease called lupus (persistent rash, fever, joint pain and tiredness). If these symptoms occur and blood tests indicate that this may be happening, Remicade treatment will be stopped. With the appropriate treatment, the symptoms will generally disappear.

Generally, patients who have rheumatoid arthritis or Crohn's disease take several medicines which themselves may cause side effects. If you get additional side effects or any new symptoms, please tell your doctor.

Pregnancy

Remicade is not recommended to be given if you are pregnant. If you are given Remicade you must avoid pregnancy by using adequate contraception during treatment and for at least 6 months after the last Remicade infusion.

Breast-feeding

It is not known if infliximab is excreted in human milk. If you are a nursing mother, your doctor will advise you to stop nursing after Remicade treatment.

Driving and using machines:

Not applicable.

Using other medicines:

Please inform your doctor if you are taking or have recently taken any other medicines, even those not prescribed. Remicade can be taken together with methotrexate, azathioprine or 6-mercaptopurine.

3. HOW TO USE REMICADE

Rheumatoid arthritis:

The recommended treatment to start with is an infusion of 3 mg/kg of body weight over a 2-hour period. You will get additional doses of 3 mg/kg at 2 and 6 weeks after your first infusion and then every 8 weeks thereafter. You will be also taking methotrexate as part of your treatment.

Crohn's Disease:

The recommended dose for severe, active Crohn's disease is an infusion of 5 mg/kg of body weight. The recommended dose for closure of enterocutaneous fistulae is also 5 mg/kg of body weight; you will be given ~~two~~ additional 5 mg/kg doses at 2 and 6 weeks following the first infusion.

If signs and symptoms of your disease return, you may be retreated. There is a risk of hypersensitivity reactions if you are retreated after an interval of more than 14 weeks. Your doctor will discuss this with you.

After dilution, Remicade is given in a vein. This usually will be in your arm.

~~**Rheumatoid arthritis:**~~~~Your initial dose will be followed by additional infusions of 3 mg/kg doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.~~~~**Crohn's Disease:**~~~~For severe, active disease, you will receive a single treatment of Remicade. If you have fistulising disease you will normally get additional doses at 2 and 6 weeks after the first dose. If signs and symptoms of your disease return, you may be retreated. There is a risk of hypersensitivity reactions if retreatment is given after an interval of more than 14 weeks. Your doctor will discuss this with you.~~

Each time you are treated, it will take at least 2 hours for Remicade to be given to you in your vein. You will also need to stay at least 1-2 hours after Remicade is given to you before you can go home. Your treatment will be supervised by a doctor who specialises in the treatment of rheumatoid arthritis or bowel diseases.

~~Your doctor will especially have experience in observing rheumatoid arthritis patients during their long treatment regimens.~~**If you use more Remicade than you should:**

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Remicade can have side effects. Most side effects are mild to moderate. However some may be serious and may require treatment. Side effects may appear up to six months after the last infusion.

Tell your doctor immediately if you notice any of the following:

- pain or tenderness in chest, muscles, joints or jaw
- swelling of the hands, feet, ankles, face, lips, mouth or throat which may cause difficulty in swallowing or breathing
- fever
- rash

- itching
- shortness of breath with exertion or upon lying down and/or swelling of the feet

Tell your doctor as soon as possible if you notice any of the following:

- signs of infection
- shortness of breath
- problems with urination
- changes in the way your heart beats, for example, if you notice it beating faster
- light-headedness
- fatigue
- hoarseness
- coughing
- headache
- tingling
- numbness
- double vision
- arm or leg weakness

If you notice any side effects not mentioned in this leaflet, please tell your doctor.

5. STORING REMICADE

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label and the carton.

Store at 2°C – 8°C (in a refrigerator).

Do not freeze.

The reconstituted diluted infusion solution is stable for 24 hours at room temperature (25°C), but for bacteriological reasons it is recommended to use it as soon as possible. The infusion is to be started 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 .

Remicade will not be given to you if there are opaque particles, discoloration or other foreign particles present.

This leaflet was last approved on

Further information

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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INSTRUCTIONS FOR PROPER USE FOR THE HEALTHCARE PROFESSIONAL

Instructions for use and handling – reconstitution, dilution and administration

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. 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, 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 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 discoloration prior to administration. Do not use if visibly opaque particles, discoloration or foreign particulates are observed.
7. Discard any unused portion of the solution.

NEW PATIENT'S ALERT CARD:

<p><u>Remicade Patient's Alert Card</u></p> <p>This alert card contains important safety information that you need to be aware of before you are given Remicade and during treatment with Remicade.</p> <ul style="list-style-type: none">• Show this card to any doctor involved in your treatment.• Infections Remicade increases the risk of getting infections. Infections may progress more rapidly and be more severe. This includes tuberculosis (TB).<ul style="list-style-type: none">• You should not be treated with Remicade if you have a severe infection.• You should be screened for TB prior to Remicade treatment. It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had TB. Please record the dates of the last screening for TB below: Tuberculin test: _____ Chest x-ray: _____• If you develop symptoms suggestive of infections, such as fever, persistent cough, weight loss, or listlessness, seek medical attention immediately.	<p>Heart Failure</p> <ul style="list-style-type: none">• Remicade should not be used if you have moderate to severe heart failure.• If you develop symptoms of heart failure (shortness of breath or swelling of the feet) seek medical attention immediately. <p>Dates of Remicade treatment: Start: _____ Most recent: _____</p> <ul style="list-style-type: none">• See the Remicade package leaflet for more information.• Please make sure you also have a list of all your other medicines with you at any visit to a health care professional. <p>Patient's Name: _____ Doctor's Name: _____ Doctor's Phone: _____</p> <ul style="list-style-type: none">• Keep this card with you for 6 months after the last Remicade dose, since side effects may occur a long time after your last dose of Remicade.
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INFORMATION TO PRESCRIBERS (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. Upon 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 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. In this patient population, a reduction in the rate of the progression of joint damage, as measured by x-ray, has been demonstrated (see section 5.1). Efficacy and safety have been demonstrated only in combination with methotrexate.

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

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 or inflammatory bowel diseases. ~~Patients treated with Remicade should be given the package leaflet and the special Alert card which is provided by the local representative of the Marketing Authorisation Holder.~~

All patients administered Remicade are to be observed for at least 1-2 hours post infusion for ~~side effects—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 to decrease the risk of infusion related reactions~~ (see section 4.4: "Special warnings and special precautions for use").

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.

Severe, active Crohn's disease

5 mg/kg given as an intravenous infusion over a 2-hour period.

Fistulising Crohn's disease

An initial 5 mg/kg infusion given over a 2-hour period is to be followed with additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion.

Repeated administration for Crohn's disease and rheumatoid arthritis

In rheumatoid arthritis, the safety and efficacy of repeated administration given every eight weeks have been established.

In Crohn's disease, long-term efficacy of repeated administration has not been established. Available data do not support further infliximab treatment, if the patient does not respond to the initial infusion.

Readministration for Crohn's disease and rheumatoid arthritis

If the signs and symptoms of disease recur, Remicade can be readministered within 14 weeks following the last infusion. Readministration of Remicade with a drug free interval of 2 to 4 years following a previous infusion has been associated with a delayed hypersensitivity reaction in a significant number of patients with Crohn's disease (see section 4.4, and section 4.8: "Delayed hypersensitivity"). After a drug free interval of 15 weeks to 2 years, the risk of delayed hypersensitivity following readministration is not known. Therefore, readministration after a drug free interval of 15 weeks can not be recommended. This applies to both Crohn's disease patients and rheumatoid arthritis patients.

For preparation and administration instructions, see section 6.6.

4.3 Contraindications

Remicade is contraindicated in patients with tuberculosis or other severe infections such as sepsis, abscesses, tuberculosis and opportunistic infections (see section 4.4).

Remicade is contraindicated in 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 ~~rarely~~ 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 and are most likely to occur during the first and second 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 ~~directed towards infliximab (previously referred to as human antichimeric antibodies, HACA) will develop in some patients and rarely against infliximab may develop and~~ may cause serious allergic reactions. Patients who ~~are intolerant to methotrexate or other non-corticosteroid immunosuppressants (such as azathioprine, 6-mercaptopurine) and~~ discontinue immunosuppressants prior to or during Remicade treatment ~~potentially~~ are at greater risk of developing these antibodies (see section 4.8: “Immunogenicity”). These antibodies can not always be detected in serum samples. If serious reactions occur, symptomatic treatment must be given and further Remicade must be discontinued ~~infusions must not be administered.~~

A delayed hypersensitivity reaction has been observed in a significant number of patients with Crohn’s disease (25%) who were retreated with infliximab following a 2 to 4 year period without infliximab treatment. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash within ~~3–~~ 12 days following retreatment. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. 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. Opportunistic infections have been reported in patients treated with infliximab, suggesting that host defence against infections is compromised. It should be noted that suppression of TNF α may also mask symptoms of infection such as fever.

~~Patients must be monitored closely for infections while on and after treatment with Remicade. Opportunistic infections and other infections including sepsis have been reported in patients treated with infliximab, some of these infections have been fatal.~~

~~**Because the elimination of infliximab may take up to six months, a close monitoring of the patients throughout this period is important. Treatment with Remicade must be stopped if a patient develops a serious infection or sepsis.**~~

Cases of active tuberculosis including miliary tuberculosis and ~~some with unusual tuberculosis with~~ extrapulmonary location have been reported in patients treated with Remicade. ~~If active tuberculosis is suspected, Remicade treatment should be stopped until the diagnosis is ruled out or the infection has been treated in accordance with current guidelines. Some of these cases had a fatal outcome.~~

Before starting treatment with Remicade, all patients should must be evaluated for both active and inactive (‘latent’) ~~tuberculosis, by way of~~ tuberculosis. This evaluation should include a detailed medical history that includes with personal history of tuberculosis or possible previous contact with tuberculosis and ~~consideration of appropriate~~ previous and/or current immunosuppressive therapy. Appropriate screening tests, ~~(chest x-ray, i.e. tuberculin test)-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 ~~that~~ of the risk of false negative tuberculin skin test results ~~may be obtained especially~~ in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, Remicade therapy must not be initiated (see 4.3)

If inactive (‘latent’) tuberculosis is diagnosed, ~~measures should be taken to prevent the activation of tuberculosis and the risk /~~ 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.
~~benefit for the patient should be considered before starting Remicade therapy.~~

~~When on Remicade treatment,~~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.

~~If a patient requires surgery while on infliximab therapy, appropriate precautions must be taken as necessary.~~

Autoimmune processes

The relative deficiency of TNF α 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, further treatment must be discontinued 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 alpha have been associated with rare cases of exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease suggestive of multiple sclerosis or localised demyelination conditions such as optic neuritis (see Section 4.8). A careful risk/benefit evaluation is recommended when prescribing Remicade to patients with preexisting or recent onset of symptoms that may be consistent with a diagnosis of demyelinating disorders.

Malignancies and lymphoproliferative disorders:

It is unknown if exposure to infliximab can increase the risk of developing these disorders (see section 4.8).

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 Pharmacokinetic properties).

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 Remicade 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.

4.5 Interaction with other medicinal products and other forms of interaction

In rheumatoid arthritis patients, there are indications that concomitant use of methotrexate reduces the formation of antibodies against infliximab and increases the plasma concentrations of infliximab. The

changes were mainly observed at a subtherapeutic dose level (1 mg/kg). However, the results are uncertain due to shortcomings 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. Nothing is known regarding possible interactions between infliximab and other drugs.

4.6 Pregnancy and lactation

For infliximab, there is no experience in pregnant women. Due to its inhibition of TNF α , 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 TNF α , there was no indication of maternal toxicity, embryotoxicity or teratogenicity (see section 5.3).

Administration of infliximab is not recommended during pregnancy. 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.

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

Not applicable

4.8 Undesirable effects

In clinical studies with infliximab, adverse drug reactions (ADRs) ~~reasonably attributable to treatment~~ were observed in 57% of infliximab-treated patients and 36% of placebo-treated patients. ~~Reasonably-related~~ ADRs are listed in Table 1 by system organ class and frequency (common > 1/100, < 1/10; uncommon > 1/1000, < 1/100). Frequency is based on the excess incidence of the ADR compared with placebo in pooled data from clinical studies involving 192 patients receiving placebo and 771 patients receiving infliximab (primarily rheumatoid arthritis and Crohn's disease patients). 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

Resistance mechanism	Common: Viral infection (e.g. influenza, herpes infections), fever Uncommon: Abscess, cellulitis, moniliasis, sepsis, impaired healing, bacterial infection, tuberculosis, fungal infection
Immune	Uncommon: Autoantibodies, lupus-like syndrome, complement factor abnormality
Blood	Uncommon: Anaemia, leukopenia, lymphadenopathy, lymphocytosis, lymphopenia, neutropenia, thrombocytopenia
Psychiatric	Uncommon: Depression, confusion, agitation, amnesia, apathy, nervousness, somnolence
Central and peripheral nervous system	Common: Headache, vertigo/dizziness Uncommon: Exacerbation of demyelinating disease suggestive of multiple sclerosis
Vision and hearing	Uncommon: Conjunctivitis, endophthalmitis, keratoconjunctivitis
Cardiovascular	Common: Flushing Uncommon: Ecchymosis/haematoma, hypertension, hypotension, syncope, petechia, thrombophlebitis, bradycardia, palpitation, vasospasm, cyanosis, peripheral ischaemia, arrhythmia, <u>worsening heart failure</u>
Respiratory system	Common: Upper respiratory tract infection, lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, sinusitis Uncommon: Epistaxis, bronchospasm, pleurisy, respiratory tract allergic reaction, pulmonary oedema
Gastro-intestinal system	Common: Nausea, diarrhoea, abdominal pain, dyspepsia Uncommon: Constipation, gastroesophageal reflux, cheilitis, diverticulitis
Liver and biliary system	Common: Abnormal hepatic function Uncommon: Cholecystitis
Skin and appendages	Common: Rash, pruritus, urticaria, increased sweating, dry skin Uncommon: Fungal dermatitis/ onychomycosis, eczema/ seborrhoea, hordeolum, bullous eruption, furunculosis, periorbital oedema, hyperkeratosis, rosacea, verruca, abnormal skin pigmentation/coloration, alopecia
Musculo-skeletal system	Uncommon: Myalgia, arthralgia
Urinary system	Uncommon: Urinary tract infection, pyelonephritis
Reproductive	Uncommon: Vaginitis
Body as a whole-general	Common: Fatigue, chest pain, infusion-related reactions Uncommon: Oedema, hot flushes, pain, chills/rigors, anaphylactic reactions
Administration/application site	Uncommon: Injection site reactions

The following table of suspected undesirable effects is based on post-marketing reports.

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

Neurological events	Rare: Exacerbation of CNS demyelination suggestive of multiple sclerosis, localised demyelinating conditions such as optic neuritis, polyneuropathy, Guillain-Barre syndrome, numbness, tingling
Blood	Rare: Pancytopenia
Body as a whole-general	Common: Infusion-related reactions Uncommon: Anaphylactic reactions Rare: Anaphylactic shock
Resistance mechanism	Rare: opportunistic infections such as tuberculosis, pneumocystis carinii pneumonia (PCP), histoplasmosis, coccidioidomycosis, aspergillosis, listeriosis and oesophageal candidiasis

Infusion-related reactions: In clinical studies, 19% of infliximab-treated patients compared with 8% of placebo-treated patients experienced an infusion-related effect during infusion or within 2 hours post infusion. Approximately 3% of infliximab infusions were accompanied by non-specific symptoms such as fever or chills, 0.7% were accompanied by pruritus or urticaria, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnoea), and 0.1% were accompanied by combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Discontinuation of treatment resulted in 1.9% of patients, and all patients recovered with or without medical therapy. Infusion-related effects in patients were more likely to occur during the first (8%) and less likely on subsequent infusions (second, 7%; third, 6%; and fourth, 4%; etc.).

Delayed hypersensitivity: In a clinical study of 40 patients retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced undesirable effects manifesting 3 to 12 days following infusion. In 6 of these patients the effects were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash. Some patients also experienced pruritus, facial, hand or lip oedema, dysphagia, urticaria, sore throat and/or headache. No similar set of delayed adverse events has been observed in any other clinical study involving a total of 771 patients receiving 4797 infusions with intervals predominantly of 14 weeks or less, but ranging from 1 to 55 weeks. In ongoing studies and post-marketing reports, these events have been rare and have occurred at intervals of less than 1 year.

Immunogenicity: Patients who developed antibodies to infliximab were more likely to develop infusion-related reactions. In clinical studies using single and multiple infliximab doses ranging from 1 to 20 mg/kg, antibodies to infliximab were detected in 47 of 199 (24%) patients with any immunosuppressant therapy, and in 33 of 90 (37%) patients without immunosuppressant therapy. In rheumatoid arthritis patients who received the recommended repeated treatment dose regimens with methotrexate, 6 of 77 (8%) patients developed antibodies to infliximab. Due to methodological shortcomings, 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.

Infections:

In clinical studies 32% of infliximab-treated patients experienced infections compared with 22% of placebo-treated patients. Serious infections, such as pneumonia, were reported in 5% of both infliximab-treated patients and placebo-treated patients (see section 4.4).

In postmarketing spontaneous reporting, infections are the most common serious adverse event. Some of the cases have resulted in fatal outcome. Nearly 50% of reported deaths have been associated with

infection. Cases of tuberculosis, sometimes fatal, including miliary tuberculosis and tuberculosis with extrapulmonary location have been reported (see 4.4).

Lymphoproliferative Malignancies and lymphoproliferative disorders: In clinical studies with infliximab and during long-term follow-up of three years, representing 1385 patient years, four cases of lymphomas and 10 other malignancies were detected as compared with one malignancy in placebo-treated patients observed during 189 patient years. These observed rates and incidences were similar to those expected for the populations studied. From August 1998 to August 2001, 139 cases of suspected malignancies have been reported, 47 in Crohn's disease patients, 71 in rheumatoid arthritis patients and 21 in patients with other diseases. During this period, it is estimated that approximately 200,000 patients have been exposed to infliximab. It is unknown if ~~chronic~~ exposure to infliximab can increase the incidence of these disorders. The long-term immunosuppressive effects of concomitant use of methotrexate and infliximab are ~~to be considered unknown~~.

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 trial 150 patients with NYHA Class III-IV CHF (left ventricular ejection fraction $\leq 35\%$) were treated with 3 infusions of Remicade 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 38 weeks, 8 of 101 patients treated with Remicade (2 at 5 mg/kg and 6 at 10 mg/kg) died compared to one death among the 49 patients on placebo.

Antinuclear antibodies (ANA)/Double-stranded DNA (dsDNA) antibodies: In clinical studies infliximab-treated patients positive for ANA increased from 43% pre-treatment to 57% at the last evaluation. Anti-dsDNA antibodies developed in approximately 17% of patients treated with infliximab. Clinical signs consistent with a lupus-like syndrome have developed rarely. Normalisation of anti-dsDNA levels occurred after discontinuation of infliximab therapy.

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: LO4AA12.

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.

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

Clinical Efficacy

Rheumatoid arthritis

The safety and efficacy of infliximab were assessed at 30, 54 and 102 weeks in a multicenter, randomised, double-blind, placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with methotrexate (ATTRACT trial). 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. 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.

The primary endpoints were the reduction of signs and symptoms as assessed by the American College of Rheumatology criteria, 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: evaluator's global assessment, patient's global assessment, functional/disability measure, visual analogue pain scale and erythrocyte sedimentation rate or C-reactive protein. 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.

Results from week 54 (ACR20, HAQ and total van der Heijde-modified Sharp score) are shown in Table 3. At week 54, a higher percentage of patients in all infliximab treated groups had a significant reduction in signs and symptoms compared with methotrexate alone. This response was seen from 2 weeks, and was maintained through 102 weeks of treatment. 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

	Control ^a	infliximab ^b				All infliximab ^b
		3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks	
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 \pm SD ^e)	7.0 \pm 10.3	1.3 \pm 6.0	1.6 \pm 8.5	0.2 \pm 3.6	-0.7 \pm 3.8	0.6 \pm 5.9
Median ^e (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 \pm SD ^e	0.2 \pm 0.3	0.4 \pm 0.3	0.5 \pm 0.4	0.5 \pm 0.5	0.4 \pm 0.4	0.4 \pm 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.

Crohn's disease

The safety and efficacy of infliximab were assessed in 108 patients with moderate to severe, active Crohn's disease (Crohn's Disease Activity Index (CDAI) $\geq 220 \leq 400$) 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 (17%) 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.

The safety and efficacy were also assessed in a randomised, double-blinded, placebo-controlled study in 94 patients with fistulising Crohn's disease who had fistulae that were of at least 3 months'

duration. Thirty-one of these patients were treated with infliximab 5 mg/kg. Approximately 93% of the patients had previously received antibiotic or immunosuppressive therapy.

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

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

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 $\text{TNF}\alpha$ 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 $\text{TNF}\alpha$, 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. Long-term studies have not been performed to evaluate the carcinogenic potential of infliximab. Studies in mice deficient in $\text{TNF}\alpha$ 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 incompatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months.

Chemical and physical stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (25°C). 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.

6.4 Special precautions for storage

Store at 2°C - 8°C. Do not freeze.

6.5 Nature and contents of container

Remicade is supplied as a lyophilised powder (infliximab 100 mg) 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. 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, 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 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 discoloration prior to administration. Do not use if visibly opaque particles, discoloration or foreign particulates are observed.
7. Discard any unused portion of the solution.

7. MARKETING AUTHORISATION HOLDER

Centocor B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/99/116/001
EU/1/99/116/002
EU/1/99/116/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 August 1999.

10. DATE OF REVISION OF THE TEXT