เอกสารกำกับยาสำหรับแพทย์ฉบับภาษาอังกฤษ

Use an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter

(pore size 1.2 micrometer or less)

PRODUCT NAME

REMICADE® (infliximab)

DOSAGE FORMS AND STRENGTHS

REMICADE is available as a powder for concentrate for solution for infusion.

REMICADE is white lyophilized powder.

Each vial of the REMICADE contains 100 mg of infliximab, a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of tumor necrosis factor alpha (TNFα), but not to lymphotoxin α (TNFβ). Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα and when administered after disease onset allows eroded joints to heal. *In vivo*, infliximab rapidly forms stable complexes with human TNFα, a process that parallels the loss of TNFα bioactivity.

CLINICAL INFORMATION

Indications

Adult and Pediatric Crohn's disease

REMICADE is indicated for:

- reducing signs and symptoms,
- inducing and maintaining clinical remission,
- inducing and maintaining mucosal healing in adults
- reducing or eliminating corticosteroid use in adult
- improvement in quality of life

in patients with moderately to severely active Crohn's disease. REMICADE can be used alone or with conventional therapy.

Fistulizing Crohn’s disease

REMICADE is indicated for:

- reducing the number of draining enterocutaneous and rectovaginal fistulae and maintaining fistula closure
- reducing signs and symptoms
- improving quality of life

in patients with fistulizing Crohn's disease.

Adult and Pediatric Ulcerative colitis

REMICADE is indicated for:

- reducing signs and symptoms

- inducing and maintaining clinical remission
- inducing and maintaining mucosal healing
- reducing or discontinuing administration of corticosteroids
- improving quality of life
- reducing ulcerative colitis-related hospitalizations in adults
- reducing the incidence of colectomy in adults

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

REMICADE is also indicated for reducing the incidence of colectomy in adult patients with moderately to severely active ulcerative colitis refractory to IV corticosteroids.

Rheumatoid arthritis

REMICADE is a Disease Controlling Anti-Rheumatic Therapy (DCART); in combination with methotrexate, REMICADE is indicated for:

- reducing signs and symptoms,
- preventing structural joint damage,
- improving physical function and preventing disability

in patients with moderately to severely active rheumatoid arthritis.

Ankylosing spondylitis

REMICADE is indicated for:

- improving signs and symptoms, including range of motion
- improving in physical function
- improving quality of life

in patients with active ankylosing spondylitis.

Psoriatic arthritis

REMICADE is indicated for:

- reducing signs and symptoms of active arthritis
- inducing major clinical response in active arthritis
- inhibiting progression of structural damage of active arthritis
- improving dactylitis and enthesopathy
- improving psoriasis
- improving physical function
- improving quality of life

in patients with psoriatic arthritis when the response to non-steroidal anti-inflammatory or disease modifying drugs has been inadequate. REMICADE can be used with or without methotrexate.

Plaque Psoriasis

REMICADE is indicated for:

- improving psoriasis
- improving quality of life

in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy. For patients with moderate plaque psoriasis, REMICADE should be used after phototherapy has been shown to be ineffective or inappropriate.

Entero-Behçet's disease

REMICADE is indicated for the treatment of intestinal Behcet's disease in patients who had inadequate response to conventional therapy.

Dosage and Administration

REMICADE is administered by intravenous infusion.

REMICADE is for intravenous use in adults (≥ 18 years) across all approved indications and in pediatric patients, aged 6-17 years with Crohn's disease.

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

The recommended infusion time is 2 hours. All patients administered REMICADE are to be observed for at least 1 hour post infusion for side effects. Medications, an artificial airway and other appropriate materials must be available for the treatment of these effects. The infusion rate may be slowed in order to decrease the risk of infusion related reactions especially if infusion related reactions have occurred previously (see *Warnings and Precautions*).

Adult or pediatric Crohn's disease or adult Fistulizing Crohn's disease

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg.

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

Adult or pediatric Ulcerative colitis

5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. For adult patients who have an incomplete response or lose their response, consideration may be given to treatment 10 mg/kg. In patients with moderately to severely active ulcerative colitis refractory to IV corticosteroids, the recommended initial dose of REMICADE is 5 mg/kg.

Rheumatoid arthritis

3 mg/kg given as an intravenous infusion followed with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. REMICADE should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg and/or treating as often as every 4 weeks.

Ankylosing spondylitis

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

Psoriatic arthritis

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

Plaque Psoriasis

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

Shortened infusions across adult indications

In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of REMICADE (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses >6 mg/kg have not been studied.

Readministration for Crohn's disease and rheumatoid arthritis

If the signs and symptoms of disease recur, REMICADE can be readministered within 16-weeks following the last infusion. Readministration of an alternate formulation of infliximab with a drug free interval of 2 to 4 years following a previous infusion has been associated with a delayed hypersensitivity reaction in 10 patients with Crohn's disease (see *Warnings and Precautions* and *Adverse Reactions*). After a drug free interval of 16 weeks to 2 years, the risk of delayed hypersensitivity following readministration is not known. Therefore, after a drug free interval of 16 weeks, readministration can not be recommended.

Readministration for ulcerative colitis

Data supporting readministration, other than every 8 weeks, are not available at this time (see *Warnings and Precautions* and *Adverse Reactions*).

Readministration for ankylosing spondylitis

Data supporting readministration, other than every 6-8 weeks, are not available at this time (see *Warnings and Precautions* and *Adverse Reactions*).

Readministration for psoriatic arthritis

Data supporting readministration, other than every 8 weeks, are not available at this time (see *Warnings and Precautions* and *Adverse Reactions*).

Readministration for psoriasis

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

Entero-Behçet's disease

5 mg/kg/infusion of infliximab as an intravenous infusion, in general. An initial dose followed by additional doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter. After the additional dose at week 6, if inadequate or reduced efficacy is observed, a higher dose at 10 mg/kg/infusion can be given starting at week 14. Do not increase doses to 10 mg/kg, etc. as an initial dose and additional doses at weeks 2 and 6. When no improvement in symptoms or laboratory findings is observed after the dose increase, carefully reconsider the continuation of the current treatment plan.

Special populations

Pediatrics (6-17 years of age)

REMICADE has not been studied in children with Crohn's disease or ulcerative colitis < 6 years of age. The pharmacokinetics of REMICADE has been evaluated in pediatric patients with Crohn's disease and ulcerative colitis (see *Pharmacokinetic Properties*). The safety and effectiveness of

REMICADE in pediatric patients with Juvenile Rheumatoid Arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and Entero-Behcet's disease have not been established.

Renal Impairment

REMICADE has not been studied in patients with renal impairment. No dose recommendations can be made (see *Pharmacokinetic Properties*).

Hepatic Impairment

REMICADE has not been studied in patients with hepatic impairment. No dose recommendations can be made (see *Pharmacokinetic Properties*).

Administration

REMICADE infusions should be administered by qualified healthcare professionals.

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

Instructions for Use and Handling and Disposal

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 Sterile Water for Injections, using a syringe equipped with a 21-gauge (0.8 mm) or smaller needle. Upon reconstitution, each ml of reconstituted solution contains 10 mg of infliximab. Remove flip-top from the vial and wipe the top with a 70% alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injections to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. Check that the solution is colorless to light yellow and opalescent. The solution may develop a few fine translucent particles, as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 ml with 0.9% w/v sodium chloride solution for infusion. Do not dilute the reconstituted REMICADE solution with any other diluent. 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. For volumes greater than 250 mL, either use a larger infusion bag (e.g. 500 mL, 1000 mL) or use multiple 250 mL infusion bags to ensure that the concentration of the infusion solution does not exceed 4 mg/mL.
4. Administer the infusion solution over a period of not less than 2 hours (at not more than 2 ml/min). Use an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 1.2 micrometer or less). Since no preservative is present, it is recommended that the administration of the solution for infusion be started as soon as possible and within 3 hours of reconstitution and dilution. If reconstitution and dilution are performed under strict aseptic conditions, REMICADE infusion solution can be used within 24 hours if stored at 2ºC 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.

Interactions

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

Concurrent Use of REMICADE with other Biological Therapeutics

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

Live Vaccines/Therapeutic Infectious Agents

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

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (*see Warnings and Precautions and Pregnancy and Breast-feeding*).

It is recommended that therapeutic infectious agents not be given concurrently with REMICADE (see *Warnings and Precautions*).

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of infliximab based on the comprehensive assessment of the available adverse event information. A causal relationship with infliximab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

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

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

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

Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (> 1/100, < 1/10); uncommon (> 1/1000, < 1/100); rare (> 1/10,000, < 1/1000)); very rare (<1/10000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. ARs in Clinical Trials and from post marketing experience

Infections and Infestations	
Very Common:	Viral infection (e.g. influenza, herpes virus infection).
Common:	Bacterial infections (e.g. sepsis, cellulitis, abscess).
Uncommon:	Tuberculosis, fungal infections (e.g. candidiasis, onychomycosis).
Rare:	Meningitis, opportunistic infections (such as invasive fungal infections [pneumocystosis, histoplasmosis, aspergillosis, coccidioidomycosis, cryptococcosis, blastomycosis], bacterial infections [atypical mycobacterial, listeriosis, salmonellosis], and viral infections [cytomegalovirus]), parasitic infections, hepatitis B reactivation.
Not known:	Vaccine breakthrough infection (after *in utero* exposure to infliximab)*.
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Rare:	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukaemia, melanoma, cervical cancer.
Not known:	Hepatosplenic T-cell lymphoma (primarily in adolescents and young adult males with Crohn's disease or ulcerative colitis), Merkel cell carcinoma, Kaposi's sarcoma.
Blood and lymphatic system disorders	
Common:	Neutropenia, leucopenia, anemia, lymphadenopathy.
Uncommon:	Thrombocytopenia, lymphopenia, lymphocytosis.
Rare:	Agranulocytosis (including infants exposed in utero to infliximab), thrombotic thrombocytopenic purpura, pancytopenia, hemolytic anemia, idiopathic thrombocytopenic purpura.
Immune system disorders	

Common:	Allergic respiratory symptom.
Uncommon	Anaphylactic reactions, Lupus-like syndrome, serum sickness or serum sickness like reaction.
Rare:	Anaphylactic shock, vasculitis, Sarcoid-like reaction.
Metabolism and nutrition disorders	
Uncommon	Dyslipidaemia.
Psychiatric disorders	
Common:	Depression, insomnia.
Uncommon:	Amnesia, agitation, confusion, somnolence, nervousness.
Rare:	Apathy.
Nervous system disorders	
Very Common:	Headache.
Common:	Vertigo, dizziness, hypoaesthesia, paraesthesia.
Uncommon:	Seizure, neuropathy.
Rare:	Transverse myelitis, central nervous system demyelinating disorders (multiple sclerosis-like disease and optic neuritis), peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy).
Very rare:	Orbital apex syndrome
Not known:	Cerebrovascular accidents in close temporal association with infusion.
Eye disorders	
Common:	Conjunctivitis.
Uncommon:	Keratitis, periorbital edema, hordeolum.
Rare:	Endophthalmitis.
Not known:	Transient visual loss occurring during or within two hours of infusion.
Cardiac disorders	
Common:	Tachycardia, palpitation.

Uncommon:	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia.
Rare:	Cyanosis, pericardial effusion.
Not known:	Myocardial ischaemia/myocardial infarction.
Vascular disorders	
Common:	Hypotension, hypertension, ecchymosis, hot flushes, flushing.
Uncommon:	Peripheral ischemia, thrombophlebitis, hematoma.
Rare:	Circulatory failure, petechia, vasospasm.
Respiratory thoracic and mediastinal disorders	
Very Common:	Upper respiratory tract infection, sinusitis.
Common:	Lower respiratory tract infection (e.g., bronchitis, pneumonia), dyspnea, epistaxis.
Uncommon:	Pulmonary edema, bronchospasm, pleurisy, pleural effusion.
Rare:	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis).
Gastrointestinal disorders	
Very Common:	Abdominal pain, nausea.
Common:	Gastrointestinal haemorrhage, diarrhea, dyspepsia, gastroesophageal reflux, constipation.
Uncommon:	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis.
Hepatobiliary system disorders	
Common:	Hepatic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.
Skin and subcutaneous tissue disorders	

Common:	New onset or worsening psoriasis including pustular psoriasis (primarily palm & soles), urticaria, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia.
Uncommon:	Bullous eruption, seborrhoea, rosacea, skin papilloma, hyperkeratosis, abnormal skin pigmentation.
Rare:	Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, furunculosis, linear IgA bullous dermatosis (LABD), acute generalised exanthematous pustulosis (AGEP), lichenoid reactions.
Not known:	Worsening of symptoms of dermatomyositis.
Musculo-skeletal and connective tissue disorders	
Common:	Arthralgia, myalgia, back pain.
Renal and urinary disorders	
Common:	Urinary tract infection.
Uncommon:	Pyelonephritis.
Reproductive system and breast disorders	
Uncommon:	Vaginitis.
General disorders and administration site conditions	
Very Common:	Infusion-related reactions, pain.
Common:	Chest pain, fatigue, fever, injection site reaction, chills, edema.
Uncommon:	Impaired healing.
Rare:	Granulomatous lesion.
Investigations	
Uncommon:	Autoantibody positive.
Rare:	Complement factor abnormal, weight increased[1].

* including bovine tuberculosis (disseminated BCG infection), see *Warnings and Precautions*.

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

Infusion-related Reactions

In Phase 3 clinical studies, 18% of REMICADE-treated patients compared with 5% of placebo treated patients experienced an infusion-related reaction during infusion or within 1 hour post infusion. Of infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

In clinical trials, approximately 3% of REMICADE infusion were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), <1% were accompanied by pruritis, urticaria, or the combined symptoms of pruritis/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in less than 1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued treatment due to infusion reactions and all patients recovered with or without medical therapy.

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

In a clinical study of patients with Crohn's disease (SONIC), infusion-related reactions occurred in 16.6% (27/163) of patients receiving REMICADE monotherapy, 5.0% (9/179) of patients receiving REMICADE in combination with azathioprine, and 5.6% (9/161) of patients receiving azathioprine monotherapy. One patient experienced a serious infusion reaction with REMICADE monotherapy.

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

Infusion Reactions Following Re-administration of REMICADE

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

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

Delayed Hypersensitivity/Reactions Following Re-administration

In a study where 37 of 41 patients with Crohn's disease were retreated with REMICADE following a 2 to 4 year period without REMICADE treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.

Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial REMICADE therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have been observed only infrequently in clinical studies and postmarketing surveillance with re-treatment intervals up to 1 year. In the 3 psoriasis studies, 1% (15/1373) of patients experienced symptoms of arthralgia, serum sickness, myalgia, fever and rash. When these occurred, they were often early in the treatment course following REMICADE infusions. REMICADE treatment was discontinued and/or other treatment instituted in most cases with improvement or resolution of signs and symptoms.

Immunogenicity

Patients who developed antibodies to REMICADE were more likely (approximately 2- to 3- fold) to develop infusion-related reactions. Antibodies to REMICADE occurred in approximately 10% of patients given a 3-dose induction regimen followed by maintenance dosing. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to REMICADE and infusion reactions.

In a Phase 3 study of Crohn's disease in patients who were immunomodulator-naive, antibodies occurred at Week 30 in 14% of patients receiving REMICADE monotherapy and 1% of patients receiving REMICADE in combination with azathioprine. A higher incidence of antibodies to REMICADE was observed in Crohn's disease patients receiving REMICADE after drug free intervals > 16 weeks. In the Phase 3 study of psoriatic arthritis, where patients received 5 mg/kg with and without concomitant methotrexate, antibodies occurred in 15% of patients. In the 2 Phase 3 studies of psoriasis, REMICADE was administered with induction followed by maintenance therapy without concomitant immunosuppressants. In these studies, antibodies occurred in approximately 25%-30% of patients, who received 5 mg/kg every 8 week maintenance for 1 year, and at higher rates (up to 1.6-fold) with other dosage regimens (3 mg/kg q8 week, 3 mg/kg dosed as needed, and 5 mg/kg dosed as needed). Despite the increase in antibody formation, the infusion reaction rates in the two psoriasis Phase 3 studies in patients treated with 5 mg/kg induction followed by every 8 week maintenance for one year (14.1%-23.0%) and serious infusion reaction rates (< 1%) were similar to those observed in other study populations.

Infections

In clinical studies, 36% of REMICADE-treated patients were treated for infections compared with 28% of placebo-treated patients. No increased risk of serious infections was observed with REMICADE compared with placebo in Crohn's disease studies and the Phase 3 study of psoriatic arthritis. In RA trials, the incidence of serious infections, including pneumonia, was higher in REMICADE plus MTX treated patients compared with methotrexate alone, especially at doses of 6 mg/kg or greater. In the psoriasis studies, 1.5% of patients (average of 41.9 weeks of follow-up) receiving REMICADE and 0.6% of patients (average of 18.1 weeks of follow-up) receiving placebo developed serious infections.

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

Hepatobiliary Events

In postmarketing surveillance, cases of jaundice and hepatitis, some with features of autoimmune hepatitis, have been reported in patients receiving REMICADE (see *Warnings and Precautions*).

In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury. Elevations of ALT > 5 x ULN have been observed (see Table 2). Elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls, both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents (see Table 2). Most aminotransferase abnormalities were transient; however, a small number of patients experienced more prolonged elevations. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications.

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

					Proportion of patients with increased ALT					
	Number of Patients[1]		**Median Follow-up (wks)[2]**		**>1 to <3 x ULN**		**≥3 x ULN**		**≥5 x ULN**	
	placebo	**REMICADE**	**placebo**	**REMICADE**	**placebo**	**REMICADE**	**placebo**	**REMICADE**	**placebo**	**REMICADE**
Rheumatoid arthritis[3]	375	1087	58.1	58.3	24.0%	34.4%	3.2%	3.9%	0.8%	0.9%
Crohn's disease[4]	324	1034	53.7	54.0	24.1%	34.9%	2.2%	4.9%	0.0%	1.5%
Pediatric Crohn's disease[5]	n/a	139	n/a	53.0	n/a	18.2%	n/a	4.4%	n/a	1.5%
Ulcerative colitis[6]	242	482	30.1	30.8	12.4%	17.4%	1.2%	2.5%	0.4%	0.6%
Pediatric Ulcerative colitis[7]	n/a	60	n/a	49.4	n/a	16.7%	n/a	6.7%	n/a	1.7%
Ankylosing spondylitis[8]	76	275	24.1	101.9	14.5%	51.1%	0.0%	9.5%	0.0%	3.6%
Psoriatic arthritis	98	191	18.1	39.1	16.3%	49.5%	0.0%	6.8%	0.0%	2.1%
Plaque Psoriasis[9]	281	1175	16.1	50.1	23.8%	49.4%	0.4%	7.7%	0.0%	3.4%

1 Number of patients evaluated for ALT.
2 Median follow-up is based on patients treated.
3 Placebo patients received methotrexate while infliximab patients received both infliximab and methotrexate.
4 Placebo patients in 2 of the 3 Phase 3 trials in Crohn's disease, C0168T21 and C0168T26, received an initial dose of 5 mg/kg infliximab at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to infliximab are included in the infliximab group in the ALT analysis. In the Phase 3b trial in Crohn's disease, C0168T67, placebo patients received azathioprine 2.5 mg/kg/day in addition to placebo infusions.
5 Patients from Pediatric Crohn's Disease trials T23, T55 and T47. Median follow-up was 53.0 weeks.
6 Patients from Ulcerative Colitis trials C0168T37 and C0168T46. Median follow-up 30 weeks for placebo and 31 weeks for combined infliximab group.
7 Data from C0168T72.
8 Data from C0168T51.
9 ALT values are obtained in 2 Phase 3 psoriasis studies, C0168T38, C0168T44.

Malignancies

During clinical trials of REMICADE, new or recurrent malignancies have been reported in REMICADE-treated patients. The incidence of lymphoma in REMICADE-treated patients was higher than expected in the general population. The observed incidences of non lymphoma malignancies were similar to what would be expected in the general population whereas the rate among control patients was lower than expected. In an exploratory clinical trial involving patients with moderate to severe COPD who were either current smokers or ex-smokers, more malignancies were reported in REMICADE-treated patients compared with control patients (*see Warnings and Precautions – Malignancies*). A population-based retrospective cohort study found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age (see *Warnings and Precautions*). The potential role of TNF-blocking therapy in the development of malignancies is not known.

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

Approximately half of REMICADE-treated patients in clinical trials who were ANA negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of REMICADE-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Congestive Heart Failure

In a Phase 2 study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV with a left ventricular ejection fraction ≤ 35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo. Higher incidences of mortality and hospitalization due to worsening heart failure were seen in patients receiving the 10 mg/kg REMICADE dose. At 28 weeks, 3 patients in the 10 mg/kg REMICADE group died compared with 1 death in the 5 mg/kg REMICADE group, and no deaths in the placebo group. At the same time point, 11 of 51 patients in the 10 mg/kg REMICADE group were hospitalized for worsening heart failure compared with 3 of 50 patients in the 5 mg/kg REMICADE group and 5 of 49 in the placebo group. In follow-up, at 1 year, 8 patients in the 10 mg/kg REMICADE group died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (*See Contraindications and Warnings and Precautions*) There have been postmarketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE.

There have also been postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age.

Adverse Reactions in JRA

The safety and efficacy of REMICADE were assessed in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. A total of 122 patients with active JRA between the ages of 4 and 17 years who had been treated with methotrexate for at least 3 months were enrolled; 120 subjects received study drug. Concurrent use of folic acid, oral corticosteroids (≤ 10 mg/day), non-steroidal anti-inflammatory drugs, and/or MTX was permitted.

Doses of 3 mg/kg REMICADE or placebo were administered intravenously at weeks 0, 2, 6, 14, 20 and then every 8 weeks through week 44. To maintain the treatment blind, the 3 mg/kg treatment group also received a single placebo infusion at week 16 while subjects randomized to placebo crossed-over to receive 6 mg/kg REMICADE at weeks 14, 16, and 20, and then every 8 weeks through week 44.

The safety and efficacy of REMICADE in the treatment of children with JRA have not been established. Forty-one of 60 children (68.3%) with JRA receiving REMICADE 3 mg/kg in combination with methotrexate experienced an infection over 52 weeks of observation compared with 37 of 57 (64.9%) children with JRA receiving REMICADE 6 mg/kg in combination with methotrexate over 38 weeks of observation and 28 of 60 (46.7%) receiving placebo in combination with methotrexate over 14 weeks of observation. The most commonly reported infections were upper respiratory tract infection and pharyngitis and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

The incidence of infusion reactions in pediatric patients with JRA receiving 3 mg/kg REMICADE was 35.0% compared with 17.5% in patients receiving 6 mg/kg. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious infusion reaction and three patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious infusion reaction, one of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received REMICADE by rapid infusion (duration time less than 2 hours).

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

Adverse Reactions in pediatric Crohn's disease

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

The following adverse events were reported more commonly in 103 randomized pediatric Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anemia (10.7%), blood in stool (9.7%), leukopenia (8.7%), flushing (8.7%), viral infection (7.8%), neutropenia (6.8%), bone fracture (6.8%), bacterial infection (5.8%), and respiratory tract allergic reaction (5.8%).

Infections were reported in 56.3% of randomized subjects in REACH, and in 50.3% of subjects receiving 5 mg/kg REMICADE in ACCENT 1. Within REACH, infections were reported more frequently for subjects who received q8 week as opposed to q12 week infusions (73.6% and 38.0%, respectively), while serious infections were reported for 3 subjects in the q8 week and 4 subjects in the q12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported in 3 patients, 2 in the q8 week and 1 in the q12 week maintenance treatment groups. Herpes zoster was reported in 2 patients in the q8 week maintenance treatment group.

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

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

Adverse Reactions in pediatric ulcerative colitis

Overall proportions of patients with adverse events and serious adverse events were generally consistent in the pediatric ulcerative colitis and adult ulcerative colitis (ACT 1 and ACT 2) studies. In the pediatric ulcerative colitis study (Study Peds UC), the most common adverse event was worsening of ulcerative colitis which was greater in patients on the q12 week vs. the q8 week dosing regimen. In the ACT 1 and ACT 2 studies, the most common adverse event was headache. The most common serious adverse event across these three studies was worsening of the disease under study.

Infections were reported in 31 (51.7%) of 60 treated patients in Study Peds UC and 22 (36.7%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in Study Peds UC was similar to that in the pediatric Crohn's disease study (REACH) but higher than the proportion in the adults ulcerative colitis studies (ACT 1 and ACT 2). Unlike REACH, in which infections were reported more frequently for patients who received q8 week as opposed to q12 week infusions; in Study Peds UC, the overall incidence of infections was similar in the q8 week (13/22 [59.1%]) and q12 week (14/23 [60.9%]) maintenance treatment groups. In Study Peds UC, serious infections were reported for 3 of 22 (13.6%) patients in the q8 week and 3 of 23 (13.0%) patients in the q12 week maintenance treatment group. Upper respiratory tract infection (7/60 [11.7%]) and pharyngitis (5/60 [8.3%]) were the most frequently reported respiratory system infections among all treated patients. The infections occurring in more than one patient in a treatment group that required antimicrobial treatment were pharyngitis (4/60 [6.7%]), urinary tract infection (4/60 [6.7%]), and bronchitis (2/60 [3.3%]).

Overall, 8 (13.3%) of 60 treated patients experienced one or more infusion reactions, with 4 of 22 (18.2%) in the q8 week and 3 of 23 (13.0%) in the q12 week treatment maintenance group. No serious infusion reactions were reported. All infusion reactions were mild or moderate in intensity.

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

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

Postmarketing data

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to REMICADE exposure.

The most common serious adverse events reported in the postmarketing experience in children were infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions and hypersensitivity reactions. Spontaneous serious adverse events in the postmarketing experience with REMICADE in the pediatric population have included malignancies, transient hepatic enzyme abnormalities, lupus-like syndromes, and positive autoantibodies.

Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with REMICADE with the vast majority of cases occurring in Crohn's disease and ulcerative colitis, and most of whom were adolescent or young adult males (see *Warnings and Precautions - Malignancies, Lymphoma*). Hemophagocytic lymphohistiocytosis (HLH) has been very rarely reported in patients treated with REMICADE.

Contraindications

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

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

REMICADE is contraindicated in patients with moderate or severe heart failure (NYHA class III/IV) (see *Warnings and Precautions* and *Adverse Reactions*).

Warnings and Precautions

Infections

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

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

Tuberculosis

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), has been observed in patients receiving REMICADE. Patients must be evaluated for the risk of tuberculosis (including close contact with a person with active tuberculosis) and tested for latent tuberculosis, prior to initiation of REMICADE. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin test and chest x-ray, should be performed in all patients. 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 *Contraindications*). If latent tuberculosis is diagnosed, treatment must be initiated prior to treatment with REMICADE, in accordance with local recommendations. Use of anti-tuberculosis therapy should also be considered before the initiation of REMICADE in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients must be monitored closely for infections, including miliary tuberculosis, while on and after treatment with REMICADE.
Use of anti-tuberculosis therapy should be considered before the initiation of REMICADE in patients who have several or highly significant risk factors for tuberculosis infection and have a negative test for latent tuberculosis.
The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a physician with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

Cases of active tuberculosis have occurred in patients treated with REMICADE during and after treatment for latent tuberculosis. Patients receiving REMICADE should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis. All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after REMICADE treatment.

Invasive Fungal Infections

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

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

Congestive Heart Failure

In patients with moderate to severe heart failure (NYHA Class III/IV), an increased incidence of death and hospitalization due to worsening heart failure has not been observed with the 5 mg/kg dose (see *Adverse Reactions*). However, an adverse effect at this or lower doses, or in mild heart failure (NYHA Class I/II), particularly during long term treatment, cannot be excluded. Therefore, REMICADE should only be used with extreme caution in patients with heart failure and after consideration of other treatment options for their indicated conditions; the dose of REMICADE should not exceed 5 mg/kg. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE must not be continued if new or worsening symptoms of heart failure appear (see *Contraindications* and *Adverse Reactions*).

Infusion-related Reactions/Hypersensitivity Reactions

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

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. Hypersensitivity reactions, which include urticaria, dyspnea, and/or bronchospasm, laryngeal edema, pharyngeal edema, and hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's disease patients 1 to 14 days after REMICADE therapy. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema, and/or dysphagia. REMICADE should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions should be available for immediate use in the event of a reaction.

Data from the ATTRACT trial indicates that prophylactic pretreatment (acetaminophen and/or antihistamines) of patients for infusion reactions reduced the occurrence of subsequent infusion reactions. The infusion rate may be slowed in order to decrease infusion reactions especially if infusion reactions have occurred previously.

Acute infusion reactions may develop immediately or within a few hours of infusion. If acute infusion reactions occur, the infusion must be interrupted immediately. Some of these effects have been described as anaphylaxis. Medications (e.g., antihistamines, corticosteroids, adrenaline and/or paracetamol), an artificial airway and other appropriate materials for the treatment of these effects must be available for immediate use. Patients may be pretreated with e.g., antihistamine, hydrocortisone and/or paracetamol to prevent mild and transient effects.

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

Infusion Reactions Following Re-administration of REMICADE

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

the benefit-risk of re-administration of REMICADE after a period of no treatment, especially as a re-induction regimen given at weeks 0, 2, and 6, should be carefully considered.

Autoimmune Processes

Treatment with REMICADE may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus like syndrome following treatment with REMICADE, treatment should be discontinued.

Neurological Events

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

Hepatobiliary Events

Cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the postmarketing experience of REMICADE. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A causal relationship between REMICADE and these events has not been established. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or ALT elevations ≥ 5 times the upper limit of normal develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. As also observed with the use of other immunosuppressive drugs, use of TNF-blockers, including REMICADE, has been associated with reactivation of hepatitis B virus in patients who are chronic carriers of this virus (i.e., surface antigen positive). Patients should be tested for Hepatitis B Virus (HBV) infection before initiating treatment with immunosuppressants, including REMICADE. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of, during treatment with, and for several months following discontinuation of REMICADE.

Malignancies

Lymphoma

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF-blocker compared with control patients. During clinical trials of REMICADE in patients with rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, the incidence of lymphoma in REMICADE-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blocking therapy.

Pediatric malignancy

Postmarketing cases of malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) who received TNF-blocking agents (initiation of therapy ≤ 18 years of age), including REMICADE, to treat Juvenile Idiopathic Arthritis (JIA), Crohn's disease or other conditions. Approximately half the reports were lymphomas. The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant

immunosuppressants, such as methotrexate, azathioprine or 6 mercaptopurine. The role of TNF-blockers in the development of malignancies in children and adolescents remains unclear.

Hepatosplenic T-cell lymphoma

Postmarketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with TNF-blockers including REMICADE. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with or immediately prior to a TNF-blocker. The vast majority of REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and most were reported in adolescent or young adult males. Cases of hepatosplenic T-cell lymphoma have also occurred in Crohn's disease and ulcerative colitis patients receiving azathioprine or 6-mercaptopurine who were not treated with REMICADE. Before initiating or continuing REMICADE therapy in a patient who is receiving an immunosuppressant such as azathioprine or 6-mercaptopurine, carefully assess the need for continuing the immunosuppressant therapy in light of the potential risks of concomitant treatment. The causal relationship of hepatosplenic T-cell lymphoma to REMICADE therapy remains unclear.

Leukemia

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

Non-lymphoma malignancy

In the controlled portions of some clinical trials of the TNF-blocking agents, more cases of non-lymphoma malignancy have been observed among patients receiving a TNF-blocker compared with control patients. The rate of non-lymphoma malignancies among REMICADE-treated patients was similar to that expected in the general population whereas the rate among control patients was lower than expected.

In an exploratory clinical trial evaluating the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking.

Skin cancers

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

Cervical cancer

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

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

Concurrent Administration of TNF-alpha Inhibitor and Anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFα-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of

anakinra and other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended.

Concurrent Administration of REMICADE with Abatacept

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

Concurrent Administration with other Biological Therapeutics

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

Switching between Biological Therapeutics

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

Hematologic reactions

There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including REMICADE. Caution should be exercised in patients treated with REMICADE who have a current or past history of significant cytopenias.

Vaccinations

It is recommended that all patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remicade therapy.

Live Vaccines/Therapeutic Infectious Agents

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

Infant exposure in utero

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

Infant exposure via breast milk

Administration of a live vaccine to a breastfed infant while the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable (*see Pregnancy and Breast-feeding*).

Therapeutic infectious agents

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

Non-live Vaccines

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

Geriatric Use

Specific studies of REMICADE in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies. The incidence of serious infections in REMICADE-treated patients 65 years and older was greater than in those under 65 years of age. In addition, there is a greater incidence of infections in the elderly population in general, therefore, caution should be used in treating the elderly.

Others

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

Pregnancy and Breast-feeding

Pregnancy

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

It is not known whether REMICADE can affect reproductive potential.

Since REMICADE does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with REMICADE. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα. Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been detected in the serum of infants up to 12 months following birth. The clinical significance of low serum levels of infliximab on the immune status in infants is unknown.

After *in utero* exposure to infliximab, infants may be at increased risk of infection, including disseminated infection that can become fatal (see *Warnings and Precautions*).

Breast-feeding

REMICADE has been detected at low levels in human milk and in infant serum via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Limited data from published literature reported that infants exposed to infliximab through breast

milk had no increase in rates of infections and developed normally. The consideration of REMICADE use during breast-feeding should take into account the importance of the drug to the mother and health benefits of breast-feeding for the infant.

Fertility

The effect of infliximab on human fertility has not been evaluated.

Overdose

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Tumor necrosis factor alpha (TNFα) inhibitors

ATC code: L04AB02.

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), and increased haemoglobin levels in rheumatoid arthritis patients with reduced haemoglobin levels, compared with baseline. Peripheral blood lymphocytes further showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared with untreated patients' cells. In psoriasis patients, treatment with infliximab resulted in decreases in epidermal inflammation and normalization of keratinocyte differentiation in psoriatic plaques. In psoriatic arthritis, short term treatment with REMICADE reduced the number of T-cells and blood vessels in the synovium and psoriatic skin.

Histological evaluation of colonic biopsies, obtained before and 4 weeks after administration of infliximab, revealed a substantial reduction in detectable TNF_{α}. Infliximab treatment of Crohn's disease patients was also associated with a substantial reduction of the commonly elevated serum inflammatory marker, CRP. Total peripheral white blood cell counts were minimally affected in infliximab-treated patients, although changes in lymphocytes, monocytes and neutrophils reflected shifts towards normal ranges. Peripheral blood mononuclear cells (PBMC) from infliximab-treated patients showed undiminished proliferative responsiveness to stimuli compared with untreated patients, and no substantial changes in cytokine production by stimulated PBMC were observed following treatment with infliximab. Analysis of lamina propria mononuclear cells obtained by biopsy of the intestinal mucosa showed that infliximab treatment caused a reduction in the number of cells capable of expressing TNF_{α} and 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 (≤ 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 analog 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 cannot 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]	4.0	0.5	0.1	0.5	-0.5	0.0
(Interquartile range)	(0.5,9.7)	(-1.5,3.0)	(-2.5,3.0)	(-1.5,2.0)	(-3.0,1.5)	(-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.

Data to support dose titration in rheumatoid arthritis come from ATTRACT, ASPIRE and the START study. START was a randomised, multicenter, double-blind, 3-arm, parallel-group safety study. In one of the study arms (group 2, n=329), patients with an inadequate response were allowed to dose titrate with 1.5 mg/kg increments from 3 up to 9 mg/kg. The majority (67%) of these patients did not require any dose titration. Of the patients who required a dose titration, 80% achieved clinical response and the majority (64%) of these required only one adjustment of 1.5 mg/kg.

Adult 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) $\geq 220 \leq 400$) 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 (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 $\geq 220 \leq 400$) 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 *Indications*). 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 *Indications*).

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 $\geq$ 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 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.

Pediatric Crohn's disease (6 to17 years)

In the REACH trial, 112 patients (6 to 17 years, median age 13.0 years) with moderate to severe, active Crohn's disease (median PCDAI of 40) and an inadequate response to conventional therapies were to receive 5 mg/kg infliximab at weeks 0, 2, and 6. All patients were required to be on a stable dose of 6-MP, AZA or MTX (35% were also receiving corticosteroids at baseline). Patients assessed by the investigator to be in clinical response at week 10 were randomized and received 5 mg/kg infliximab at either q8 weeks or q12 weeks as a maintenance treatment regimen. If response was lost during maintenance treatment, crossing over to a higher dose (10 mg/kg) and/or shorter dosing interval (q8 weeks) was allowed. Thirty-two (32) evaluable paediatric patients crossed over (9 subjects in the q8 weeks and 23 subjects in the q12 weeks

maintenance groups). Twenty-four of these patients (75.0%) regained clinical response after crossing over.

The proportion of subjects in clinical response at week 10 was 88.4% (99/112). The proportion of subjects achieving clinical remission at week 10 was 58.9% (66/112).

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

Data about fistulas were derived from PCDAI scores. Of the 22 subjects that had fistulas at baseline, 63.6% (14/22), 59.1% (13/22) and 68.2% (15/22) were in complete fistula response at week 10, 30 and 54, respectively, in the combined q8 weeks and q12 weeks maintenance groups.

In addition, statistically and clinically significant improvements in quality of life and height, as well as a significant reduction in corticosteroid use, were observed versus baseline.

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.

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

		Infliximab		
	Placebo	5 mg/kg	10 mg/kg	Combined
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 assessed in two multicenter, double-blind, placebo-controlled studies in patients with active psoriatic arthritis.

In the first study (IMPACT), efficacy and safety of infliximab were studied in 104 patients with active polyarticular psoriatic arthritis. During the 16-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, and 14 (52 patients in each group). Starting at week 16, placebo patients were switched to infliximab and all patients subsequently received 5 mg/kg infliximab every 8 weeks up to week 46. After the first year of the study, 78 patients continued into an open-label extension to week 98.

In the second trial (IMPACT 2), efficacy and safety of infliximab were studied in 200 patients with active psoriatic arthritis (≥ 5 swollen joints and ≥ 5 tender joints). Forty-six percent of patients continued on stable doses of methotrexate (≤25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg infliximab or placebo at weeks 0, 2, 6, 14, and 22 (100 patients in each group). At week 16, 47 placebo patients with < 10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction (early escape). At week 24, all placebo-treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46.

Key efficacy results for IMPACT and IMPACT 2 are shown in table 6 below:

Table 6. Effects on ACR and PASI in IMPACT and IMPACT 2

	IMPACT			IMPACT 2*		
	Placebo (Week 16)	Infliximab (Week 16)	Infliximab (Week 98)	Placebo (Week 24)	Infliximab (Week 24)	Infliximab (Week 54)
Patients randomized	52	52	N/A[a]	100	100	100

ACR response (% of patients)							
N		52	52	78	100	100	100
ACR response*	20	5(10%)	34 (65%)	48 (62%)	16 (16%)	54 (54%)	53 (53%)
ACR response*	50	0(0%)	24 (46%)	35 (45%)	4 (4%)	41(41%)	33 (33%)
ACR response*	70	0(0%)	15 (29%)	27 (35%)	2 (2%)	27 (27%)	20 (20%)
PASI response (% of patients)[b]							
N					87	83	82
PASI response**	75				1 (1%)	50 (60%)	40 (48.8%)

* ITT-analysis where subjects with missing data were included as non-responders

[a]Week 98 data for IMPACT includes combined placebo crossover and infliximab patients who entered the open-label extension

[b]Based on patients with PASI $\geq$2.5 at baseline for IMPACT, and patients with $\geq$3% BSA psoriasis skin involvement at baseline in IMPACT 2

** PASI 75 response for IMPACT not included due to low N; p<0.001 for infliximab vs. placebo at week 24 for IMPACT 2

In IMPACT and IMPACT 2, clinical responses were observed as early as week 2 and were maintained through week 98 and week 54 respectively. Efficacy has been demonstrated with or without concomitant use of methotrexate. 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 demonstrated significant improvement in physical function as assessed by HAQ. Significant improvements in health-related quality of life were also demonstrated as measured by the physical and mental component summary scores of the SF-36 in IMPACT 2.

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). Nail psoriasis was assessed using the Nail Psoriasis Severity Index (NAPSI). 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 7. 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 7. Summary of PASI response, PGA response and percent of patients with all nails cleared 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%)
All nails cleared [c]		
Week 10	1/65(1.5%)	16/235 (6.8%)
Week 24	3/65 (4.6%)	58/223 (26,0%) [a]
Week 50	27/64 (42.2%)	92/226 (40.7%)

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

b: N = 292

c: Analysis was based on subjects with nail psoriasis at baseline (81.8% of subjects). Mean baseline NAPSI scores were 4.6 and 4.3 in infliximab and placebo group.

Significant improvements from baseline were demonstrated in DLQI ($p<0.001$) and the physical and mental component scores of the SF 36 ($p<0.001$ for each component comparison).

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.

Overall, serum levels in paediatric patients with Crohn's disease (53 patients aged 6 to 17 years old; 8 patients aged 6 to 10 years old) were similar to those in adult Crohn's disease patients. The median terminal half-life for the 5 mg/kg dose in paediatric patients with Crohn's disease is 10.9 days.

NON-CLINICAL INFORMATION

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.

List of Excipients

Dibasic sodium phosphate, dihydrate, Monobasic sodium phosphate, monohydrate, Polysorbate 80, Sucrose.

Incompatibilities

Specific drug interaction studies have not been conducted.

Shelf Life

Do not use beyond the expiration date.

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

See expiry date on the outer pack.

Storage Conditions

Store at 2 °C to 8 °C.

For storage conditions of the reconstituted medicinal product, see *Shelf Life*.

REMICADE may be stored at temperatures up to a maximum of 30 °C for a single period of up to 6 months; but not exceeding the original expiration date. The new expiration date should be written on the carton. Upon removal from refrigerated storage, REMICADE cannot be returned to refrigerated storage.

Keep out of the sight and reach of children.

Nature and Contents of Container

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

Manufactured by

Cilag AG, Schaffhausen, Swiss Confederation

Marketing Authorization Number

1C 27/56 (NB)

Date of Authorization

27 December 2013

Date of revision of the text

13-Mar-2024 (EU SmPC v. 26-Oct-2023)

Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com