



Remicade

INFLIXIMAB

RECOMBINANT

for IV Injection

WARNING

RISK OF INFECTIONS

TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS).

PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.¹ TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

DESCRIPTION

REMICADE is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 10¹⁰ M⁻¹. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.

CLINICAL PHARMACOLOGY

General

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.^{2,3} Infliximab does not neutralize TNFβ (lymphotoxin α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro*³ or *in vivo*.⁴ Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. 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.

Pharmacodynamics

Elevated concentrations of TNFα have been found in the joints of rheumatoid arthritis patients and the stools of Crohn's disease patients and correlate with elevated disease activity. In rheumatoid arthritis, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemotaxis [IL-8 and monocyte chemoattractant protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with REMICADE, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients.

Pharmacokinetics

Single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Median pharmacokinetic results for doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the terminal half-life of infliximab is 8.0 to 9.5 days.

Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-week intervals. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

A pediatric Crohn's disease pharmacokinetic study was conducted in 21 patients aged 11 to 17 years old. No notable differences in single-dose pharmacokinetic parameters were observed between pediatric and adult Crohn's disease patients (see **PRECAUTIONS, Pediatric Use**).

CLINICAL STUDIES

Rheumatoid Arthritis

The safety and efficacy of REMICADE when given in conjunction with methotrexate (MTX) were assessed in a multicenter, randomized, double-blind, placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX (the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy or ATTRACT). Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX. Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or nonsteroidal anti-inflammatory drugs was also permitted.

Data on use of REMICADE without concurrent MTX are limited (see **ADVERSE REACTIONS, Immunogenicity**).^{5,6}

Clinical response

All doses/schedules of REMICADE + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 1). This improvement was observed at week 2 and maintained through week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with REMICADE + MTX compared to placebo + MTX (Table 2). Approximately 10% of patients treated with REMICADE achieved a major clinical response, defined as maintenance of an ACR 70 response over a 6-month period compared to 0% of placebo-treated patients (p<0.018).

Table 1
PERCENTAGE OF PATIENTS WHO ACHIEVED AN ACR RESPONSE AT WEEKS 30 AND 54

Response	Placebo + MTX (n=88)	REMICADE + MTX			
		3 mg/kg ^a		10 mg/kg ^a	
		q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)
ACR 20					
Week 30	20%	50%	50%	52%	58%
Week 54	17%	42%	48%	59%	59%
ACR 50					
Week 30	5%	27%	29%	31%	26%
Week 54	9%	21%	34%	40%	38%
ACR 70					
Week 30	0%	8%	11%	18%	11%
Week 54	2%	11%	18%	26%	19%

^a p<0.05 for each outcome compared to placebo

Table 2
COMPONENTS OF ACR 20 AT BASELINE AND 54 WEEKS

Parameter (medians)	Placebo + MTX (n=88)		REMICADE + MTX ^a (n=340)	
	Baseline	Week 54	Baseline	Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain ^b	6.7	6.1	6.8	3.3
Physician's Global Assessment ^b	6.5	5.2	6.2	2.1
Patient's Global Assessment ^b	6.2	6.2	6.3	3.2
Disability Index (HAQ) ^c	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

^a All doses/schedules of REMICADE + MTX

^b Visual Analog Scale (0=best, 10=worst)

^c Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic response

Structural damage in both hands and feet was assessed radiographically at week 54 by the change from baseline in the van der Heijde-modified Sharp score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.⁷ Approximately 80% of patients had paired x-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 3) and maintained through 102 weeks.

Table 3
RADIOGRAPHIC CHANGE FROM BASELINE TO WEEK 54

Median (10, 90 percentiles)	Placebo + MTX (n=64)	REMICADE + MTX				p-value ^a
		3 mg/kg		10 mg/kg		
		q 8 wks (n=71)	q 4 wks (n=71)	q 8 wks (n=77)	q 4 wks (n=66)	
Total Score						
Baseline	55 (14, 188)	57 (15, 187)	45 (8, 162)	56 (6, 143)	43 (7, 178)	
Change from baseline	4.0 (-1.0, 19.0)	0.5 (-3.0, 5.5)	0.1 (-5.2, 9.0)	0.5 (-4.8, 5.0)	-0.5 (-5.7, 4.0)	p<0.001
Erosion Score						
Baseline	25 (8, 110)	29 (9, 100)	22 (3, 91)	22 (3, 80)	26 (4, 104)	
Change from baseline	2.0 (-1.0, 9.7)	0.0 (-3.0, 4.3)	-0.3 (-3.1, 2.5)	0.5 (-3.0, 2.5)	-0.5 (-2.7, 2.5)	p<0.001
JSN Score						
Baseline	26 (3, 88)	29 (4, 80)	20 (3, 83)	24 (1, 79)	25 (3, 77)	
Change from baseline	1.5 (-0.8, 8.0)	0.0 (-2.5, 4.5)	0.0 (-3.4, 5.0)	0.0 (-3.0, 2.5)	0.0 (-3.0, 3.5)	p<0.001

^a For comparisons of each dose against placebo

Physical function response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ) and the general health-related quality of life questionnaire SF-36. All doses/schedules of REMICADE + MTX showed significantly greater improvement from baseline in HAQ and SF-36 physical component summary score averaged over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score.

The median (interquartile range) improvement from baseline to week 54 in HAQ was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for REMICADE + MTX (p<0.001). Both HAQ and SF-36 effects were maintained through week 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in the trial through 102 weeks.

Active Crohn's Disease

The safety and efficacy of single and multiple doses of REMICADE were assessed in two randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥220 and ≤400) with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial⁸ of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg REMICADE (p<0.001, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission (CDAI <150) at week 4.

In a multidose trial (ACCENT I),⁹ 545 patients received 5 mg/kg at week 0 and were then randomized to one of three treatment groups: the placebo maintenance group received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at week 2 were randomized and analyzed separately from those not in response at week 2. Corticosteroid taper was permitted after week 6.

At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 4).

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg infliximab maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

	Single 5 mg/kg Dose ^a Placebo Maintenance	Three Dose Induction ^b REMICADE Maintenance q 8 wks	
		5 mg/kg	10 mg/kg
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
p-value ^c		0.022	0.001
Week 54	6/54	14/56	18/53
Patients in remission able to discontinue corticosteroid use ^d	11%	25%	34%
p-value ^c		0.059	0.005

^a REMICADE at week 0

^b REMICADE 5 mg/kg administered at weeks 0, 2 and 6

^c p-values represent pairwise comparisons to placebo

^d Of those receiving corticosteroids at baseline

Patients in the infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg infliximab-treated groups compared to the placebo group in the disease specific inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical component summary score of the general health-related quality of life questionnaire SF-36.

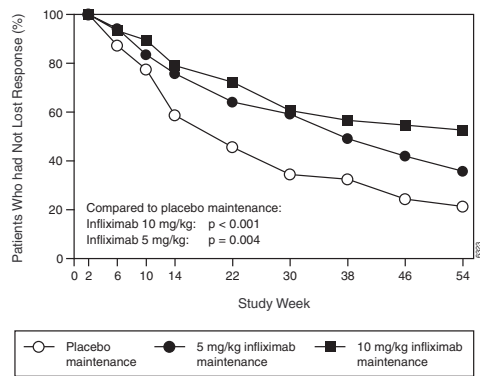


Figure 1

Kaplan-Meier estimate of the proportion of patients who had not lost response through week 54

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in the infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at week 10. Of the infliximab-treated patients showing mucosal healing at week 10, 9 of 12 patients also showed mucosal healing at week 54.

Patients who achieved a response and subsequently lost response were eligible to receive infliximab on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at week 2, 59% (192/157) of infliximab maintenance patients responded by week 14 compared to 51% (39/77) of placebo maintenance patients. Among patients who did not respond by week 14, additional therapy did not result in significantly more responses (see *DOSAGE AND ADMINISTRATION*).

Fistulizing Crohn's Disease

The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, MTX, 6-MP and/or AZA was permitted.

In the first trial,¹⁰ 94 patients received three doses of either placebo or REMICADE at weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least two consecutive visits without an increase in medication or surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE group (p=0.002) and 56% (18/32) of patients in the 10 mg/kg REMICADE group (p=0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of placebo-treated patients (p<0.001).

In the second trial (ACCENT II), patients who were enrolled had to have at least one draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg REMICADE at weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE maintenance at week 14. Patients received maintenance doses at week 14 and then every eight weeks through week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the patients had received previous immunosuppressive and antibiotic therapy.

At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to REMICADE maintenance had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no draining fistulas compared with 22% (20/90) of placebo-treated patients (p=0.02). Compared to placebo maintenance, patients on REMICADE maintenance had a trend toward fewer hospitalizations.

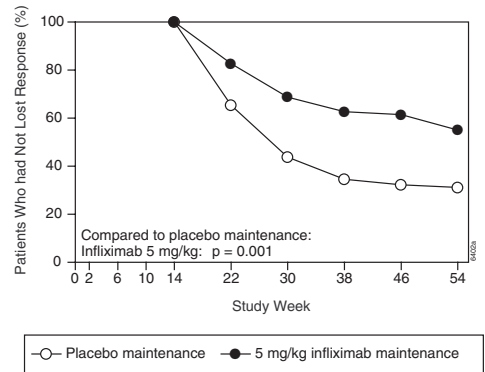


Figure 2

Life table estimates of the proportion of patients who had not lost fistula response through week 54

Patients who achieved a fistula response and subsequently lost response were eligible to receive REMICADE maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg REMICADE, and 57% (12/21) of REMICADE maintenance patients responded to 10 mg/kg.

Patients who had not achieved a response by week 14 were unlikely to respond to additional doses of REMICADE.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

INDICATIONS AND USAGE

Rheumatoid Arthritis

REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate.

Crohn's Disease

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.

REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

CONTRAINDICATIONS

REMICADE is contraindicated in patients with moderate or severe (NYHA Class III/IV) congestive heart failure (see *WARNINGS, Congestive Heart Failure*).

REMICADE should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS

RISK OF INFECTIONS

(See boxed WARNING)

SERIOUS INFECTIONS, INCLUDING SEPSIS HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS.

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 MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*).

CASES OF HISTOPLASMOIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, TUBERCULOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

Congestive Heart Failure

Doses greater than 5 mg/kg should not be administered to patients with congestive heart failure (CHF). REMICADE should be used with caution in patients with mild heart failure (NYHA Class I/II). Patients should be closely monitored, and REMICADE must not be continued in patients who develop new or worsening symptoms of heart failure (see *CONTRAINDICATIONS* and *ADVERSE REACTIONS, Congestive Heart Failure*).

Hypersensitivity

REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. Most hypersensitivity reactions, which include urticaria, dyspnea, and/or 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 3 to 12 days after REMICADE therapy was reinstated following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*).

Neurologic Events

Infliximab and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders.

PRECAUTIONS

Autoimmunity

Treatment with REMICADE may result in the formation of autoantibodies and, rarely, 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 (see *ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome*).

Malignancy

Patients with long duration of Crohn's disease or rheumatoid arthritis and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas (see *ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease*). The impact of treatment with REMICADE on these phenomena is unknown.

Vaccinations

No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently.

Information for Patients

Patients should be provided the REMICADE Patient Information Sheet and provided an opportunity to read it prior to each treatment infusion session. Because caution should be exercised in administering REMICADE to patients with clinically important active infections, it is important that the patient's overall health be assessed at each treatment visit and any questions resulting from the patient's reading of the Patient Information Sheet be discussed.

Drug Interactions

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicilates. Patients with Crohn's disease who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see *ADVERSE REACTIONS, Immunogenicity and Infusion-related Reactions*).

Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicilates.

Carcinogenesis, Mutagenesis and Impairment of Fertility

A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF α to evaluate tumorigenicity. cV1q is an analog of antibody that inhibits the function of TNF α in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

Pregnancy Category B

Since infliximab does not cross-react with TNF α 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 TNF α . 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. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed.

Nursing Mothers

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

Pediatric Use

Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease have not been established.

Geriatric Use

In the ATTRACT study, no overall differences were observed in effectiveness or safety in 72 patients aged 65 or older compared to younger patients. In Crohn's disease studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see *ADVERSE REACTIONS, Infections*).

ADVERSE REACTIONS

The data described herein reflect exposure to REMICADE in 1678 patients, including 842 patients exposed beyond 30 weeks and 295 exposed beyond one year. The most common reason for discontinuation of treatment was infusion-related reactions (e.g. dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease.

Infusion-related Reactions

Acute infusion reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions.

Patients who became positive for antibodies to infliximab were more likely (approximately 2- to 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and infusion reactions (see *ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug Interactions*).

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

Reactions following readministration

In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following a 2 to 4 year period without infliximab 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 infliximab 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 post-marketing surveillance with retreatment intervals up to 1 year.

Infections

In REMICADE clinical studies, treated infections were reported in 35% of REMICADE-treated patients (average of 53 weeks of follow-up) and in 26% of placebo-treated patients (average of 41 weeks of follow-up). When longer observation of patients on REMICADE was accounted for, the event rate was similar for both groups. The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis was observed with REMICADE compared with placebo in clinical studies. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. Three opportunistic infections were reported; coccidioidomycosis (which resulted in death), nocardiosis and cytomegalovirus. Tuberculosis was reported in two patients, one of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF INFECTIONS*). During the 54 week ACCENT II trial, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess.

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

Autoantibodies/Lupus-like Syndrome

Approximately 52% of 1261 infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately 19% of 129 placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of 1507 infliximab-treated patients compared with 0% of 162 placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

Malignancies/Lymphoproliferative Disease

In completed clinical studies of REMICADE for up to 102 weeks, 18 of 1678 patients developed 19 new or recurrent malignancies of various types, such as non-Hodgkin's B-cell lymphoma, breast, melanoma, squamous, rectal and basal cell. There are insufficient data to determine whether REMICADE contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied^{11,12} (see *PRECAUTIONS, Malignancy*).

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab. The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*). Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to infliximab with the incidence of antibodies to other products may be misleading.

Congestive Heart Failure

In a phase II study evaluating REMICADE in NYHA Class III/IV CHF patients (left ventricular ejection fraction \leq 35%), higher incidences of mortality and hospitalization due to worsening heart failure were seen in REMICADE-treated patients, especially those treated with 10 mg/kg. One hundred and fifty patients were treated with 3 infusions of REMICADE 5 mg/kg, 10 mg/kg, or placebo over 6 weeks. At 28 weeks, 4 of 101 patients treated with REMICADE (1 at 5 mg/kg and 3 at 10 mg/kg) died compared with no deaths among the 49 placebo-treated patients. In follow-up, at 38 weeks, 9 patients treated with REMICADE (2 at 5 mg/kg and 7 at 10 mg/kg) died compared with one death among the placebo-treated patients. At 28 weeks, 14 of 101 patients treated with REMICADE (3 at 5 mg/kg and 11 at 10 mg/kg) were hospitalized for worsening CHF compared with 5 of the 49 placebo-treated patients (see *CONTRAINDICATIONS and WARNINGS, Congestive Heart Failure*).

Other Adverse Reactions

Safety data are available from 1678 REMICADE-treated patients, including 555 with rheumatoid arthritis, 1106 with Crohn's disease and 17 with conditions other than rheumatoid arthritis or Crohn's disease. Adverse events reported in \geq 5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 5. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis and Crohn's disease patients except for abdominal pain which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

Table 5
ADVERSE EVENTS OCCURRING IN 5% OR MORE OF PATIENTS
RECEIVING 4 OR MORE INFUSIONS FOR RHEUMATOID ARTHRITIS

	Placebo (n=81)	REMICADE (n=430)
Average weeks of follow-up	73	82
Gastrointestinal		
Abdominal pain	12%	17%
Nausea	23%	24%
Diarrhea	19%	19%
Dyspepsia	9%	10%
Respiratory		
Upper respiratory tract infection	35%	40%
Pharyngitis	12%	17%
Sinusitis	7%	20%
Coughing	9%	18%
Rhinitis	14%	14%
Dyspnea	2%	6%
Skin and appendages disorders		
Rash	7%	18%
Pruritis	2%	9%
Body as a whole—general disorders		
Fatigue	9%	13%
Chest pain	6%	7%
Resistance mechanism disorders		
Fever	11%	13%
Abscess	5%	6%
Moniliasis	2%	8%
Central and peripheral nervous system disorders		
Headache	21%	29%
Musculoskeletal system disorders		
Arthralgia	7%	13%
Back pain	5%	13%
Psychiatric disorders		
Insomnia	4%	6%
Depression	2%	8%
Urinary system disorders		
Urinary tract infection	12%	14%
Cardiovascular disorders, general		
Hypertension	6%	10%

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice.

The most common serious adverse events observed in clinical trials were infections (see **ADVERSE REACTIONS, Infections**). Other serious, medically relevant adverse events $\geq 0.2\%$ or clinically significant adverse events by body system were as follows:

- Body as a whole:** allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
- Blood:** pancytopenia
- Cardiovascular:** circulatory failure, hypotension, syncope
- Gastrointestinal:** constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
- Central & Peripheral Nervous:** meningitis, neuritis, peripheral neuropathy, dizziness
- Heart Rate and Rhythm:** arrhythmia, bradycardia, cardiac arrest, tachycardia
- Liver and Biliary:** biliary pain, cholecystitis, cholelithiasis, hepatitis
- Metabolic and Nutritional:** dehydration
- Musculoskeletal:** intervertebral disk herniation, tendon disorder
- Myo-, Endo-, Pericardial and Coronary Valve:** myocardial infarction
- Platelet, Bleeding and Clotting:** thrombocytopenia
- Neoplasms:** basal cell, breast, lymphoma
- Psychiatric:** confusion, suicide attempt
- Red Blood Cell:** anemia, hemolytic anemia
- Reproductive:** menstrual irregularity
- Resistance Mechanism:** cellulitis, sepsis, serum sickness
- Respiratory:** adult respiratory distress syndrome, lower respiratory tract infection, pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
- Skin and Appendages:** increased sweating, ulceration
- Urinary:** renal calculus, renal failure
- Vascular (Extracardiac):** brain infarction, pulmonary embolism, thrombophlebitis
- White Cell and Reticuloendothelial:** leukopenia, lymphadenopathy

A greater proportion of patients enrolled into the ATTRACT study who received REMICADE + MTX experienced transient mild (< 2 times the upper limit of normal) or moderate (≥ 2 but < 3 times the upper limit of normal) elevations in AST or ALT (49% and 47%, respectively) compared to patients treated with placebo + MTX (27% and 35%, respectively). Six (1.8%) patients treated with REMICADE + MTX experienced more prolonged elevations in their ALT.

The following adverse events have been reported during post-approval use of REMICADE: demyelinating disorders (see **WARNINGS, Neurologic Events**) (such as multiple sclerosis and optic neuritis), Guillain-Barré syndrome, hemolytic anemia, idiopathic thrombocytopenic purpura, interstitial pneumonitis/fibrosis, neuropathies, thrombotic thrombocytopenic purpura, and transverse myelitis. 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.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis

The recommended dose of REMICADE is 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 or treating as often as every 4 weeks.

Crohn's Disease or Fistulizing Crohn's Disease

The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease or fistulizing disease. For patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue REMICADE in these patients.

Preparation and administration instructions

Use aseptic technique.

REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE infusion should begin within 3 hours of preparation.

- Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE solution required.
- Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the 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. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.
- The infusion solution must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 μ m or less). Any unused portion of the infusion solution should not be stored for reuse.
- No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE with other agents. REMICADE should not be infused concomitantly in the same intravenous line with other agents.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.

Storage

Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservative.

HOW SUPPLIED

REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-use vials in the following strength:

NDC 57894-030-01 100 mg infliximab in a 20 mL vial

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Revised April 1, 2003