



Our STN: BL 103772/5020

**SEP 03 2003**

Centocor Incorporated  
Attention: Stella Jones, Ph.D.  
Vice President, Worldwide Regulatory Affairs  
200 Great Valley Parkway  
Malvern, PA 19355-1307

Dear Dr. Jones:

Your request to supplement your biologics license application for Infliximab to revise the package insert to include a contraindication for patients with congestive heart failure, update the Warnings and Adverse Reactions sections, and update the patient information sheet has been approved.

Pursuant to 21 CFR 201.57(f)(2), patient labeling must be reprinted at the end of the package insert. We request that the text of information distributed to patients be printed in a minimum of 10-point font.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see <http://www.fda.gov/cber/transfer/transfer.htm> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html>. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center  
Attn: Office of Therapeutics Research and Review  
Suite 200N (HFM-99)  
1401 Rockville Pike  
Rockville, Maryland 20852-1448

This information will be included in your biologics license application file.

Sincerely,

(b)(6)

Patricia Keegan, M.D.  
Acting Director  
Division of Clinical Trials Design and Analysis  
Office of Therapeutics Research and Review  
Center for Drug Evaluation and Research

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**REMICADE®**  
**(infliximab)**  
**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.<sup>1</sup> 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  $10^{10} \text{ M}^{-1}$ . 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 TNF $\alpha$  by binding with high affinity to the soluble and transmembrane forms of TNF $\alpha$  and inhibits binding of TNF $\alpha$  with its receptors.<sup>2,3</sup> Infliximab does not neutralize TNF $\beta$  (lymphotoxin  $\alpha$ ), a related cytokine that utilizes the same receptors as TNF $\alpha$ . Biological activities attributed to TNF $\alpha$  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 TNF $\alpha$  bound by infliximab can be lysed *in vitro*<sup>3</sup> or *in vivo*.<sup>4</sup> Infliximab inhibits the functional activity of TNF $\alpha$  in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNF $\alpha$  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 TNF $\alpha$ , and when administered after disease onset, allows eroded joints to heal.

### Pharmacodynamics

Elevated concentrations of TNF $\alpha$  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)], chemoattraction [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 TNF $\alpha$  production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNF $\alpha$  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 ( $\leq 10$  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).<sup>5,6</sup>

#### *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 ( $p \leq 0.018$ ).

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

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

<sup>a</sup>p<0.05 for each outcome compared to placebo



**Table 2**  
**COMPONENTS OF ACR 20**  
**AT BASELINE AND 54 WEEKS**

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

<sup>a</sup>All doses/schedules of REMICADE + MTX

<sup>b</sup>Visual Analog Scale (0=best, 10=worst)

<sup>c</sup>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.<sup>7</sup> 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)	REMICADE + MTX					p-value <sup>a</sup>
	Placebo + MTX (n=64)	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)	
<i>Total Score</i>						
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
<i>Erosion Score</i>						
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
<i>JSN Score</i>						
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

<sup>a</sup>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]  $\geq 220$  and  $\leq 400$ ) 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 trial<sup>8</sup> of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI  $\geq 70$  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 D)<sup>9</sup>, 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 <sup>a</sup>	Three Dose Induction <sup>b</sup>	
	<u>Placebo Maintenance</u>	<u>REMICADE Maintenance q 8 wks</u>	
		<u>5 mg/kg</u>	<u>10 mg/kg</u>
Week 30			
Clinical remission	25/102 25%	41/104 39%	48/105 46%
p-value <sup>c</sup>		0.022	0.001
Week 54			
Patients in remission able to discontinue corticosteroid use <sup>d</sup>	6/54 11%	14/56 25%	18/53 34%
p-value <sup>c</sup>		0.059	0.005

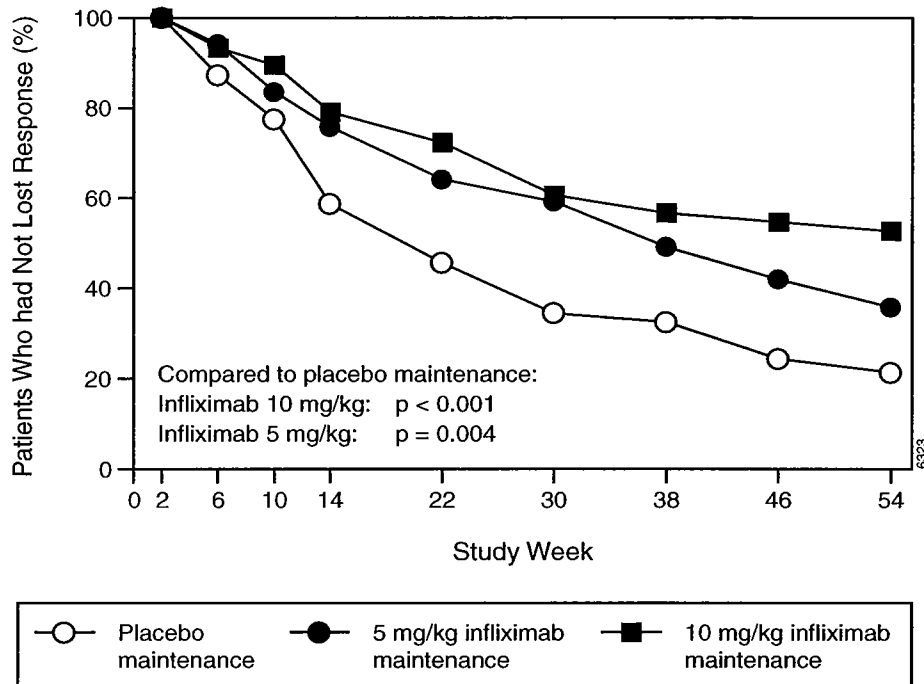
<sup>a</sup>REMICADE at week 0

<sup>b</sup>REMICADE 5 mg/kg administered at weeks 0, 2 and 6

<sup>c</sup>p-values represent pairwise comparisons to placebo

<sup>d</sup>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% (92/157) 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

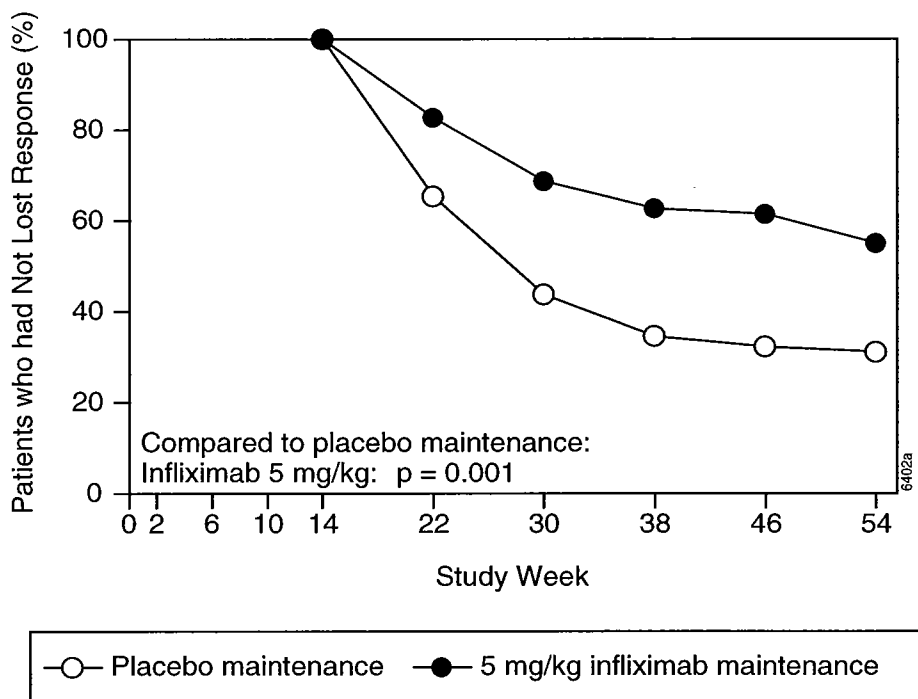
The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, MTX, 6-MP and/or AZA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

In the first trial<sup>10</sup>, 94 patients received three doses of either placebo or REMICADE at weeks 0, 2 and 6. Fistula response ( $\geq 50\%$  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 (see 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 at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure (see WARNINGS and ADVERSE REACTIONS, Patients with 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 HISTOPLASMOSIS, 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 HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.**

### **Patients with Heart Failure**

REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Patients with 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 aminosalicylates. 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 aminosalicylates.

## **Carcinogenesis, Mutagenesis and Impairment of Fertility**

A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF $\alpha$  to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNF $\alpha$  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 $\alpha$  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 $\alpha$ . 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 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<sup>11,12</sup> (see PRECAUTIONS, Malignancy).

### **Patients with Heart Failure**

In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction  $\leq 35\%$ ), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends towards increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See CONTRAINDICATIONS and WARNINGS, Patients with Heart Failure.)

### **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.

## **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 adverse events of abdominal pain that 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
<b>Gastrointestinal</b>		
Abdominal Pain	12%	17%
Nausea	23%	24%
Diarrhea	19%	19%
Vomiting	16%	12%
Dyspepsia	9%	10%
<b>Respiratory</b>		
Upper respiratory tract infection	35%	40%
Pharyngitis	12%	17%
Sinusitis	7%	20%
Coughing	9%	18%
Rhinitis	14%	14%
Dyspnea	2%	6%
<b>Skin and appendages disorders</b>		
Rash	7%	18%
Pruritis	2%	9%
<b>Body as a whole-general disorders</b>		
Pain	17%	15%
Fatigue	9%	13%
Peripheral edema	10%	8%
Chest pain	6%	7%
<b>Resistance mechanism disorders</b>		
Fever	11%	13%
Abscess	5%	6%
Flu Syndrome	7%	6%
Moniliasis	2%	8%
<b>Central and peripheral nervous system disorders</b>		
Headache	21%	29%

Musculoskeletal system disorders		
Arthralgia	7%	13%
Back pain	5%	13%
Myalgia	6%	5%
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 ( $\geq 2$  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: interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Guillain-Barré syndrome, transverse myelitis and neuropathies (additional neurologic events have also been observed, see WARNINGS, Neurologic Events). 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.

1. 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.
2. 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.
3. 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.
4. 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  $\mu$ m or less). Any unused portion of the infusion solution should not be stored for reuse.

5. 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.
6. 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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## **Rx Only**

### **REMICADE® (infliximab) Patient Information Sheet**

You should read this information sheet before you start using REMICADE (pronounced rem-eh-kaid) and before each time you are scheduled to receive REMICADE. This information sheet does not take the place of talking with your doctor. You and your doctor should talk about your health and how you are feeling before you start taking REMICADE, while you are taking it and at regular checkups. If you do not understand any of the information in this sheet, you should ask your doctor to explain what it means.

#### **What is REMICADE?**

REMICADE is a medicine that is used to treat adults with moderate to severely active rheumatoid arthritis and Crohn's disease. Your doctor has decided to treat you with REMICADE because your disease is still active even though you have tried other treatments.

#### **How does REMICADE work?**

The medicine REMICADE is a type of protein that recognizes, attaches to and blocks the action of a substance in your body called tumor necrosis factor. Tumor necrosis factor (TNF) is made by certain blood cells in your body. REMICADE will not cure rheumatoid arthritis or Crohn's disease, but blocking TNF with REMICADE may reduce the inflammation caused by too much TNF in your body. You should also know that REMICADE may help you feel better but can also cause serious side effects and can reduce your body's ability to fight infections (see below).

#### **What should I know about the immune system, and taking REMICADE for Rheumatoid Arthritis or Crohn's Disease?**

The immune system protects the body by responding to "invaders" like bacteria, viruses and other foreign matter that enter your body by producing antibodies and putting them into action to fight off the "invaders." In diseases like rheumatoid arthritis and Crohn's disease, your body's immune system produces too much TNF. Too much TNF can cause your immune system to attack healthy tissues in your body and cause inflammation. If this condition is left untreated, it can cause permanent damage to the body's bones, cartilage and tissue.

While taking REMICADE can block the TNF that causes inflammation, it can also lower your body's ability to fight infections. So, taking REMICADE can make you more prone to getting infections or it can make an infection that you already have worse. You should call your doctor right away if you think you have an infection.

#### **What important information should I know about treatment with REMICADE?**

REMICADE, like other medicines that affect your immune system, is a strong medicine that can cause serious side effects. Possible serious side effects include:

##### Serious Infections:

- Some patients have had serious infections while receiving REMICADE. Some of the patients have died from these infections. Serious infections include TB (tuberculosis), and infections

caused by viruses, fungi or bacteria that have spread throughout the body. If you develop a fever, feel very tired, have a cough, or have flu-like symptoms, these could be signs that you may be getting an infection. If you have any of these symptoms while you are taking or after you have taken REMICADE, you should tell your doctor right away.

#### Heart Failure:

- If you have been told that you have a heart problem called congestive heart failure and you are currently being treated with REMICADE, you will need to be closely monitored by your doctor. If you develop new or worse symptoms that are related to your heart condition, such as shortness of breath or swelling of your ankles or feet, you must contact your doctor immediately.

#### Allergic Reactions:

- Some patients have had severe allergic reactions to REMICADE. These reactions can happen while you are getting your REMICADE infusion or shortly afterwards. The symptoms of an allergic reaction may include hives (red, raised, itchy patches of skin), difficulty breathing, chest pain and high or low blood pressure. Your doctor may decide to stop REMICADE treatment and give you medicines to treat the allergic reaction.
- Some patients who have been taking REMICADE for Crohn's disease have had allergic reactions 3 to 12 days after receiving their REMICADE treatment. The symptoms of this type of delayed reaction may include fever, rash, headache and muscle or joint pain. Call your doctor right away if you develop any of these symptoms or any other unusual symptoms such as difficulty swallowing.

#### Nervous System Disorders:

- There have been rare cases where people taking REMICADE or other TNF blockers have developed disorders that affected their nervous system. Signs that you could be having a problem include: changes in your vision, weakness in your arms and/or legs, and numbness or tingling in any part of your body.

#### **Other Important Information:**

People who have been treated for rheumatoid arthritis or Crohn's disease for a long time tend to be more prone to a type of blood cancer called lymphoma. There have been some patients that while taking REMICADE developed other types of cancer, but, the number of people taking REMICADE that developed cancer does not seem to be much different from what you would expect to see in people who are not taking REMICADE.

Some patients have developed symptoms that can resemble a disease called lupus. Lupus-like symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint pain, or a rash on the cheeks or arms that gets worse in the sun. If you develop any of these symptoms your doctor may decide to stop your treatment with REMICADE.

#### **What are the more common side effects of REMICADE?**

The more common side effects with REMICADE are respiratory infections (that may include sinus infections and sore throat), coughing and stomach pain.



### **Who should not take REMICADE?**

YOU SHOULD NOT take REMICADE if you have:

- Heart failure, unless your doctor has talked to you and decided that you are able to take REMICADE.
- Had an allergic reaction to REMICADE or any other product that was made with murine (mouse) proteins.

### **What health concerns should I talk to my doctor about?**

Before receiving your first treatment with REMICADE you should tell your doctor if you:

- Have or think you may have any kind of infection. The infection could be in only one place in your body (such as an open cut or sore), or an infection that affects your whole body (such as the flu). Having an infection could put you at risk for serious side effects from REMICADE.
- Have an infection that won't go away or a history of infection that keeps coming back.
- Have had TB (tuberculosis), or if you have recently been with anyone who might have TB. Your doctor will examine you for TB and perform a skin test. If your doctor feels that you are at risk for TB, he or she may start treating you for TB before you begin REMICADE therapy.
- Have lived in or visited an area of the country where an infection called histoplasmosis or coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common. If you don't know if the area you live in is one where histoplasmosis or coccidioidomycosis is common, ask your doctor.
- Have or have previously had heart failure or other heart conditions.
- Have or have had a condition that affects your nervous system, like multiple sclerosis, or Guillain-Barré syndrome, or if you experience any numbness, or tingling, or have had a seizure.
- Are pregnant or nursing.
- Have recently received or are scheduled to receive a vaccine.

### **Can I take REMICADE while I am on other medicines?**

Tell your doctor if you are taking any other medicines including over the counter medicines, supplements or herbal products before you are treated with REMICADE. If you start taking or plan to start taking any new medicine while you are taking REMICADE, tell your doctor.

### **How will REMICADE be given to me?**

REMICADE will be given to you by a healthcare professional. REMICADE will be given to you by an IV. This means that the medicine will be given to you through a needle placed in a vein in your arm. It will take about 2 hours to give you the full dose of medicine. During that time and for a period after you receive REMICADE, you will be monitored by a healthcare professional. Your doctor may ask you to take other medicines along with REMICADE.

Only a health care professional should prepare the medicine and administer it to you.

**How often will I receive REMICADE?****Rheumatoid Arthritis**

If you are receiving REMICADE for rheumatoid arthritis you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE and may change your dose or dose you more frequently (as often as every 4 weeks).

**Crohn's Disease or Fistulizing Crohn's Disease**

If you are receiving REMICADE for active Crohn's disease or fistulizing Crohn's disease, you will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE and may change your dose.

**What if I still have questions?**

If you have any questions, or problems, always talk first with your doctor. You can also visit the REMICADE internet site at [www.remicade.com](http://www.remicade.com).

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