

1 **REMICADE®**  
2 **(infliximab)**  
3 **for IV Injection**  
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6 **WARNING**  
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8 **RISK OF INFECTIONS**  
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10 **TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT**  
11 **CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER**  
12 **OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS**  
13 **RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE**  
14 **WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH A**  
15 **REACTIVE TUBERCULIN SKIN TEST REDUCES THE RISK OF TB**  
16 **REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH REMICADE.**  
17 **HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS**  
18 **RECEIVING REMICADE WHO WERE TUBERCULIN SKIN TEST NEGATIVE**  
19 **PRIOR TO RECEIVING REMICADE.**  
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21 **PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION**  
22 **WITH A TUBERCULIN SKIN TEST.<sup>1</sup> TREATMENT OF LATENT TUBERCULOSIS**  
23 **INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.**  
24 **PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING REMICADE FOR SIGNS**  
25 **AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE**  
26 **TUBERCULIN SKIN TEST NEGATIVE.**  
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30 **DESCRIPTION**  
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32 REMICADE® is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight  
33 of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab  
34 binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of  
35  $10^{10} \text{ M}^{-1}$ . Infliximab is produced by a recombinant cell line cultured by continuous perfusion and  
36 is purified by a series of steps that includes measures to inactivate and remove viruses.  
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38 REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion.  
39 Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is  
40 approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg  
41 polysorbate-80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium  
42 phosphate, dihydrate. No preservatives are present.

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## 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 involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, and ankylosing spondylitis and psoriatic arthritis. 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. In psoriatic arthritis, treatment with REMICADE resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin as well as a reduction of macrophages in the synovium. The relationship between these pharmacodynamic activities and the mechanism(s) by which REMICADE exerts its clinical effects is unknown.

### 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

90 steady state was independent of dose and indicated that infliximab was distributed primarily  
91 within the vascular compartment. Median pharmacokinetic results for doses of 3 mg/kg to  
92 10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the terminal half-  
93 life of infliximab is 8.0 to 9.5 days.

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95 Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in  
96 predictable concentration-time profiles following each treatment. No systemic accumulation of  
97 infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-  
98 week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8  
99 weeks after a maintenance dose of 3 to 10 mg/kg of REMICADE, median infliximab serum  
100 concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations  
101 were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab.  
102 No major differences in clearance or volume of distribution were observed in patient subgroups  
103 defined by age, weight, or gender. It is not known if there are differences in clearance or volume  
104 of distribution in patients with marked impairment of hepatic or renal function.

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

## 108 **CLINICAL STUDIES**

### 109 **Rheumatoid Arthritis**

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113 | The safety and efficacy of ~~infliximab~~ REMICADE were assessed in two multicenter,  
114 randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II).  
115 Concurrent use of stable doses of folic acid, oral corticosteroids ( $\leq 10$  mg/day) and/or non-  
116 steroidal anti-inflammatory drugs was permitted.

117  
118 Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis  
119 despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease  
120 duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were  
121 on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4  
122 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at  
123 weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.

124  
125 Study RA II was a placebo-controlled study of three active treatment arms in 1004 MTX naive  
126 patients of 3 or fewer years duration active rheumatoid arthritis. Patients enrolled had a median  
127 age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint  
128 count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At  
129 randomization, all patients received MTX (optimized to 20 mg/wk by week 8) and either  
130 placebo, 3mg/kg or 6 mg/kg REMICADE at weeks 0, 2, and 6 and every 8 weeks thereafter.

131  
132 ~~Data on use of REMICADE without concurrent MTX are limited (see ADVERSE REACTIONS,~~  
133 ~~Immunogenicity).~~<sup>5,6</sup>

134

135 *Clinical response*

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137 In Study RA I, all doses/schedules of REMICADE + MTX resulted in improvement in signs and  
138 symptoms as measured by the American College of Rheumatology response criteria (ACR 20)  
139 with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo +  
140 MTX (Table 1). This improvement was observed at week 2 and maintained through week 102.  
141 Greater effects on each component of the ACR 20 were observed in all patients treated with  
142 REMICADE + MTX compared to placebo + MTX (Table 2). More patients treated with  
143 REMICADE reached a major clinical response than placebo-treated patients (Table 1).

144

145 In Study RA II, after 54 weeks of treatment, both doses of REMICADE + MTX resulted in  
146 statistically significantly greater response in signs and symptoms compared to MTX alone as  
147 measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 1). More  
148 patients treated with REMICADE reached a major clinical response than placebo-treated patients  
149 (Table 1).

**Table 1**

**ACR RESPONSE (PERCENT OF PATIENTS)**

Response	Study RA I						Study RA II
	REMICADE + MTX						
	Placebo + MTX (n=88)	3 mg/kg		10 mg/kg		Placebo + MTX (n=274)	
		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% <sup>a</sup>	50% <sup>a</sup>	52% <sup>a</sup>	58% <sup>a</sup>	N/A	
Week 54	17%	42% <sup>a</sup>	48% <sup>a</sup>	59% <sup>a</sup>	59% <sup>a</sup>	54%	
ACR 50							
Week 30	5%	27% <sup>a</sup>	29% <sup>a</sup>	31% <sup>a</sup>	26% <sup>a</sup>	N/A	
Week 54	9%	21% <sup>c</sup>	34% <sup>a</sup>	40% <sup>a</sup>	38% <sup>a</sup>	32%	
ACR 70							
Week 30	0%	8% <sup>b</sup>	11% <sup>b</sup>	18% <sup>a</sup>	11% <sup>a</sup>	N/A	
Week 54	2%	11% <sup>c</sup>	18% <sup>a</sup>	26% <sup>a</sup>	19% <sup>a</sup>	21%	
Major clinical response <sup>#</sup>	0%	7% <sup>c</sup>	8% <sup>b</sup>	15% <sup>a</sup>	6% <sup>c</sup>	8%	

# A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through week 54 for Study RA II.

<sup>a</sup> p ≤ 0.001

<sup>b</sup> p < 0.01

<sup>c</sup> p < 0.05

**Table 2**  
**COMPONENTS OF ACR 20**  
**AT BASELINE AND 54 WEEKS (Study RA I)**

Parameter (medians)	Placebo + MTX (n=88)		REMICADE + MTX <sup>a</sup> (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 <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-DI) <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 (vdH-S) 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>

In Study RA I, 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.

In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of

172 to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving  
 173 REMICADE + MTX, 59% had no progression (vdH-S score  $\leq 0$  unit) of structural damage  
 174 compared to 45% patients receiving MTX alone. In a subset of patients who began the study  
 175 without erosions, REMICADE + MTX maintained an erosion free state at 1 year in a greater  
 176 proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively ( $p < 0.01$ ).  
 177 Fewer patients in the REMICADE + MTX groups (47%) developed erosions in uninvolved  
 178 joints compared to MTX alone (59%).  
 179

**Table 3**  
**RADIOGRAPHIC CHANGE**  
**FROM BASELINE TO WEEK 54**

	Study RA I			Study RA II		
	REMICADE + MTX			REMICADE + MTX		
	Placebo + MTX (n=64)	3 mg/kg q 8 wks (n=71)	10 mg/kg q 8 wks (n=77)	Placebo + MTX (n=282)	3 mg/kg q 8 wks (n=359)	6 mg/kg q 8 wks (n=363)
<i>Total Score</i>						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3 <sup>a</sup>	0.2 <sup>a</sup>	3.7	0.4 <sup>a</sup>	0.5 <sup>a</sup>
Median	4.0	0.5	0.5	0.4	0.0	0.0
<i>Erosion Score</i>						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8
Change from baseline						
Mean	4.1	0.2 <sup>a</sup>	0.2 <sup>a</sup>	3.0	0.3 <sup>a</sup>	0.1 <sup>a</sup>
Median	2.0	0.0	0.5	0.3	0.0	0.0
<i>JSN Score</i>						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1 <sup>a</sup>	0.0 <sup>a</sup>	0.6	0.1 <sup>a</sup>	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

<sup>a</sup> P < 0.001 for each outcome against placebo.

### Physical function response

Physical function and disability were assessed using the Health Assessment Questionnaire (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater improvement from baseline in HAQ-DI 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-DI 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-DI 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.

In Study RA II, both REMICADE treatment groups showed greater improvement in HAQ-DI from baseline averaged over time through week 54 compared to MTX alone; 0.7 for REMICADE + MTX vs. 0.6 for MTX alone ( $p < 0.001$ ). No worsening in the SF-36 mental component summary score was observed.

### 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 I [Study Crohn's I])<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.

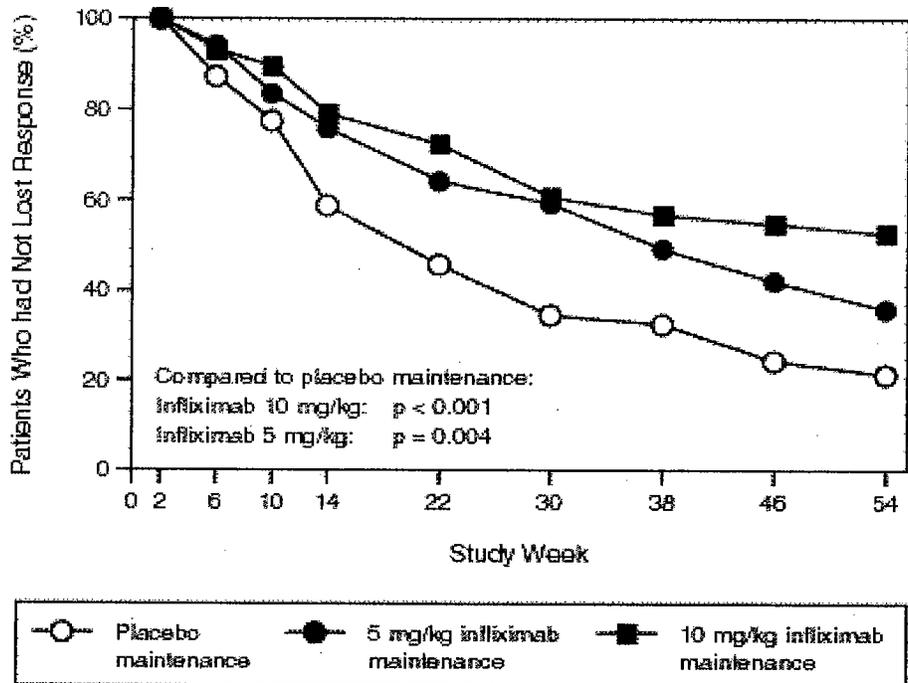
At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group (Table 4).

226 Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg  
 227 | ~~infiximab-REMICADE~~ maintenance groups were in clinical remission and were able to  
 228 discontinue corticosteroid use compared to patients in the placebo maintenance group at week 54  
 229 (Table 4).  
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**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>Infiximab-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

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 232 | <sup>a</sup>REMICADE at week 0  
 233 | <sup>b</sup>REMICADE 5 mg/kg administered at weeks 0, 2 and 6  
 234 | <sup>c</sup>p-values represent pairwise comparisons to placebo  
 235 | <sup>d</sup>Of those receiving corticosteroids at baseline  
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 237 | Patients in the ~~infiximab-REMICADE~~ maintenance groups (5 mg/kg and 10 mg/kg) had a longer  
 238 time to loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30  
 239 and 54, significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg  
 240 | ~~infiximab-REMICADE~~-treated groups compared to the placebo group in the disease specific  
 241 inflammatory bowel disease questionnaire (IBDQ), particularly the bowel and systemic  
 242 components, and in the physical component summary score of the general health-related quality  
 243 of life questionnaire SF-36.  
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**Figure 1**  
**Kaplan-Meier estimate of the proportion of patients**  
**who had not lost response through week 54**

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

256  
 257 Patients who achieved a response and subsequently lost response were eligible to receive  
 258 infliximab-REMICADE on an episodic basis at a dose that was 5 mg/kg higher than the dose to  
 259 which they were randomized. The majority of such patients responded to the higher dose.  
 260 Among patients who were not in response at week 2, 59% (92/157) of infliximab-REMICADE  
 261 REMICADE-maintenance patients responded by week 14 compared to 51% (39/77) of placebo  
 262 maintenance patients. Among patients who did not respond by week 14, additional therapy did  
 263 not result in significantly more responses (see DOSAGE AND ADMINISTRATION).

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265 **Fistulizing Crohn's Disease**

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267 The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-  
 268 controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least  
 269 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates,  
 270 antibiotics, MTX, 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

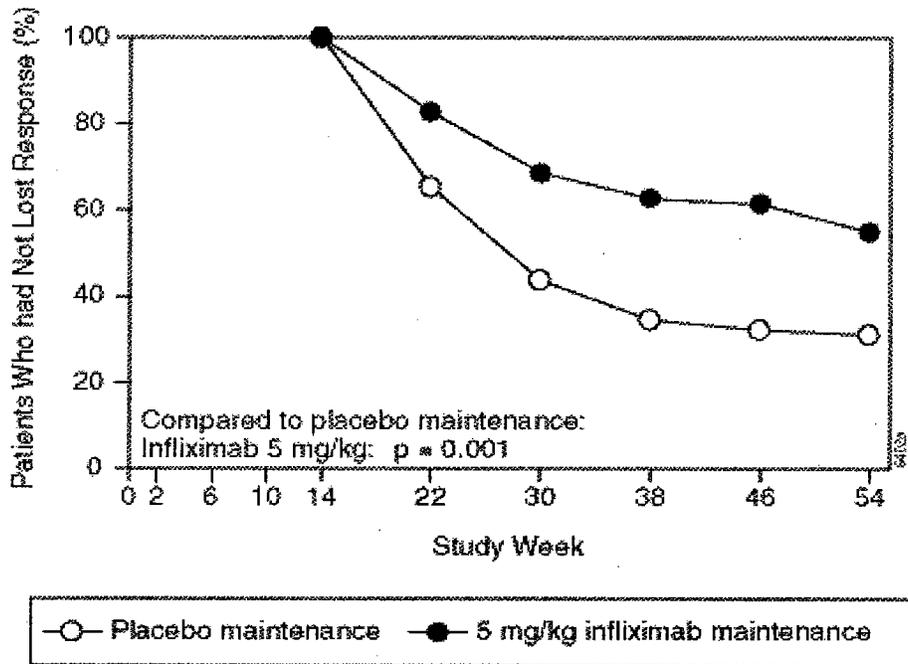
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272 In the first trial,<sup>10</sup> 94 patients received three doses of either placebo or REMICADE at weeks 0,  
273 2 and 6. Fistula response ( $\geq 50\%$  reduction in number of enterocutaneous fistulas draining upon  
274 gentle compression on at least two consecutive visits without an increase in medication or  
275 surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE  
276 group ( $p=0.002$ ) and 56% (18/32) of patients in the 10 mg/kg REMICADE group ( $p=0.021$ ) vs.  
277 26% (8/31) of patients in the placebo arm. The median time to onset of response and median  
278 duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure  
279 of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of  
280 placebo-treated patients ( $p<0.001$ ).

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

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291 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and  
292 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the  
293 patients had received previous immunosuppressive and antibiotic therapy.

294  
295 At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to  
296 REMICADE maintenance had a longer time to loss of fistula response compared to the placebo  
297 maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no  
298 draining fistulas compared with 22% (20/90) of placebo-treated patients ( $p=0.02$ ). Compared to  
299 placebo maintenance, patients on REMICADE maintenance had a trend toward fewer  
300 hospitalizations.



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**Figure 2**  
**Life table estimates of the proportion of patients**  
**who had not lost fistula response through week 54**

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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.

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

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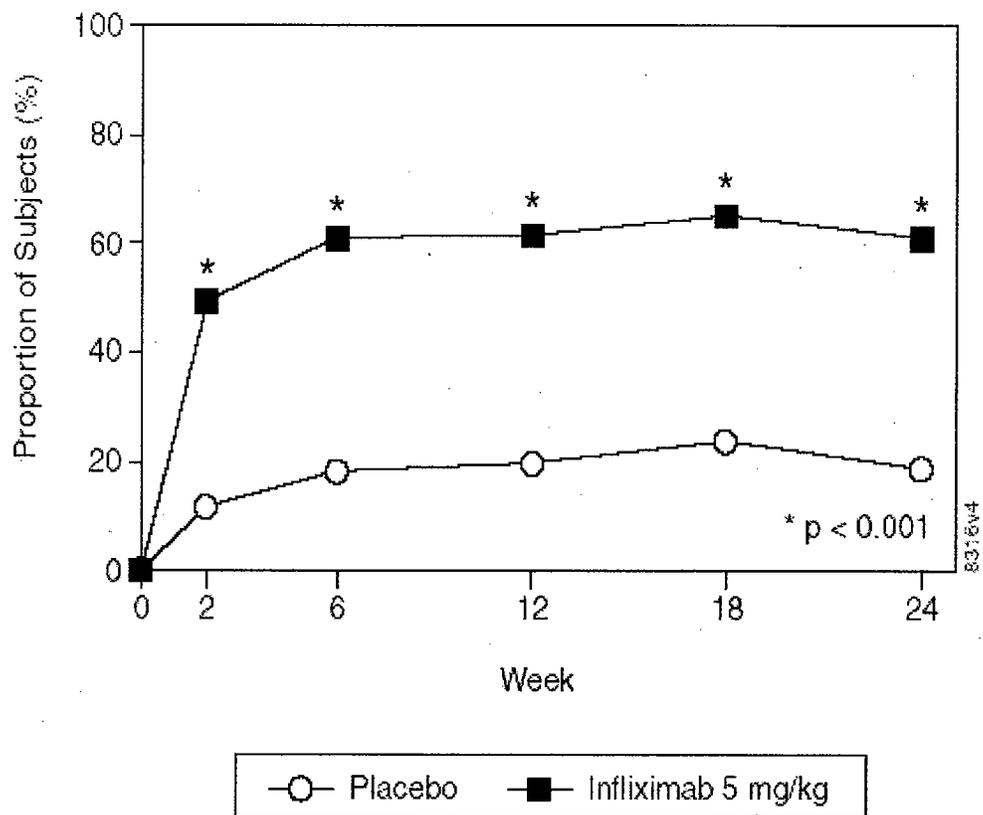
Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

**Ankylosing Spondylitis**

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The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New York criteria for Ankylosing Spondylitis.<sup>11</sup> Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18.

331 At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by  
 332 the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20),  
 333 was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo  
 334 group ( $p < 0.001$ ). Improvement was observed at week 2 and maintained through week 24 (Figure  
 335 3 and Table 5).  
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 340 **Figure 3**  
 341 **Proportion of patients achieving ASAS 20 response**  
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343 At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs  
 344 and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and  
 345 ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE,  
 346 compared to 9% and 4%, respectively, for patients receiving placebo ( $p < 0.001$ , REMICADE vs.  
 347 placebo). A low level of disease activity (defined as a value  $< 20$  [on a scale of 0-100 mm] in  
 348 each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated  
 349 patients vs. 1% in placebo-treated patients ( $p < 0.001$ ).  
 350  
 351  
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**Table 5**  
**Components of Ankylosing Spondylitis Disease Activity**

	Placebo (n=78)		REMICADE 5mg/kg (n=201)		p-value
	Baseline	24 Weeks	Baseline	24 Weeks	
ASAS 20 response Criteria (Mean)					
Patient global assessment <sup>a</sup>	6.6	6.0	6.8	3.8	<0.001
Spinal pain <sup>a</sup>	7.3	6.5	7.6	4.0	<0.001
BASFI <sup>b</sup>	5.8	5.6	5.7	3.6	<0.001
Inflammation <sup>c</sup>	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP <sup>d</sup> (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test <sup>e</sup>	4.0	5.0	4.3	4.4	0.75
Chest expansion <sup>e</sup>	3.6	3.7	3.3	3.9	0.04
Tragus to wall <sup>e</sup>	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion <sup>e</sup>	10.6	11.0	11.4	12.9	0.03

<sup>a</sup> measured on a VAS with 0="none" and 10="severe"

<sup>b</sup> Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions

<sup>c</sup> Inflammation, average of last 2 questions on the 6 question BASDAI

<sup>d</sup> CRP normal range 0-1.0 mg/dL

<sup>e</sup> Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion:>6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

356  
357 The median improvement from baseline in the general health-related quality of life questionnaire  
358 SF-36 physical component summary score at week 24 was 10.2 for the REMICADE group vs.  
359 0.8 for the placebo group (p<0.001). There was no change in the SF-36 mental component  
360 summary score in either the REMICADE group or the placebo group.

361  
362 Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled  
363 study of 70 patients with ankylosing spondylitis.

364  
365 **Psoriatic Arthritis**

366  
367 Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-  
368 controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID  
369 therapy (≥ 5 swollen joints and ≥ 5 tender joints) with one or more of the following subtypes:  
370 arthritis involving DIP joints (n = 49), arthritis mutilans (n = 3), asymmetric peripheral arthritis  
371 (n = 40), polyarticular arthritis (n = 100), and spondylitis with peripheral arthritis (n = 8).  
372 Patients also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Forty-six  
373 percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-  
374 week double-blind phase, patients received either 5 mg/kg REMICADE or placebo at weeks 0, 2,  
375 6, 14, and 22 (100 patients in each group). At week 16, placebo patients with < 10%  
376 improvement from baseline in both swollen and tender joint counts were switched to  
377 REMICADE induction (early escape).

378 Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the  
 379 ACR criteria, with 58% of REMICADE-treated patients achieving ACR 20 at week 14,  
 380 compared with 11% of placebo-treated patients ( $p < 0.001$ ). The response was similar regardless  
 381 of concomitant use of methotrexate. Improvement was observed as early as week 2. At 6 months,  
 382 the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients  
 383 receiving REMICADE compared to 16%, 4%, and 2%, respectively, of patients receiving  
 384 placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis,  
 385 although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral  
 386 arthritis subtypes.

387  
 388 Compared to placebo, treatment with REMICADE resulted in improvements in the components  
 389 of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 6).

390  
 391 The results of this study were similar to those seen in an earlier multicenter, randomized,  
 392 placebo-controlled study of 104 patients with psoriatic arthritis.  
 393

**Table 6**  
**COMPONENTS OF ACR 20 AND PERCENTAGE OF PATIENTS WITH 1 OR MORE JOINTS**  
**WITH DACTYLITIS AND PERCENTAGE OF PATIENTS WITH ENTHESOPATHY**  
**AT BASELINE and WEEK 24**

Parameter (medians)	Placebo (n=100)		REMICADE 5mg/kg <sup>a</sup> (n=100)	
	Baseline	Week 24	Baseline	Week 24
No of Tender Joints <sup>b</sup>	24	20	20	6
No. of Swollen Joints <sup>c</sup>	12	9	12	3
Pain <sup>d</sup>	6.4	5.6	5.9	2.6
Physician's Global Assessment <sup>d</sup>	6.0	4.5	5.6	1.5
Patient's Global Assessment <sup>d</sup>	6.1	5.0	5.9	2.5
Disability Index (HAQ- DI) <sup>e</sup>	1.1	1.1	1.1	0.5
CRP (mg/dL) <sup>f</sup>	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

<sup>a</sup>  $p < 0.001$  for percent change from baseline in all components of ACR 20 at week 24,  $p < 0.05$  for % of patients with dactylitis, and  $p = 0.004$  for % of patients with enthesopathy at week 24

<sup>b</sup> Scale 0-68

<sup>c</sup> Scale 0-66

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

<sup>e</sup> Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

<sup>f</sup> Normal range 0-0.6 mg/dL

396 Improvement in PASI in patients with baseline body surface area (BSA)  $\geq$  3% (n=87  
397 placebo, n=83 REMICADE) was achieved at week 14, regardless of concomitant  
398 methotrexate use, with 64% of REMICADE-treated patients achieving at least 75%  
399 improvement from baseline vs. 2% of placebo-treated patients; improvement was  
400 observed as early as week 2. At 6 months, the PASI 75 and PASI 90 responses were  
401 achieved by 60% and 39%, respectively, of patients receiving REMICADE compared to  
402 1% and 0%, respectively, of patients receiving placebo.

## 403 **INDICATIONS AND USAGE**

### 404 **Rheumatoid Arthritis**

405  
406  
407  
408 REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms,  
409 inhibiting the progression of structural damage, and improving physical function in patients with  
410 moderately to severely active rheumatoid arthritis.

### 411 **Crohn's Disease**

412  
413  
414 REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical  
415 remission in patients with moderately to severely active Crohn's disease who have had an  
416 inadequate response to conventional therapy.

417  
418 REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal  
419 fistulas and maintaining fistula closure in patients with fistulizing Crohn's disease.

### 420 **Ankylosing Spondylitis**

421  
422  
423 REMICADE is indicated for reducing signs and symptoms in patients with active ankylosing  
424 spondylitis.

### 425 **Psoriatic Arthritis**

426  
427  
428 REMICADE is indicated for reducing signs and symptoms of active arthritis in patients with  
429 psoriatic arthritis.

## 430 **CONTRAINDICATIONS**

431  
432  
433 REMICADE at doses  $>5$  mg/kg should not be administered to patients with moderate to severe  
434 heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe  
435 heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE  
436 treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization  
437 due to worsening heart failure (see WARNINGS and ADVERSE REACTIONS, Patients with  
438 Heart Failure).

439  
440 REMICADE should not be administered to patients with known hypersensitivity to any murine  
441 proteins or other component of the product.

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**WARNINGS**

**RISK OF INFECTIONS**  
(See boxed WARNING)

**SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, 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 TUBERCULOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, 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.**

**SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT USE OF ANAKINRA AND ANOTHER TNF $\alpha$ -BLOCKING AGENT, ETANERCEPT, WITH NO ADDED CLINICAL BENEFIT COMPARED TO ETANERCEPT ALONE. BECAUSE OF THE NATURE OF THE ADVERSE EVENTS SEEN WITH COMBINATION OF ETANERCEPT AND ANAKINRA THERAPY, SIMILAR TOXICITIES MAY ALSO RESULT FROM THE COMBINATION OF ANAKINRA AND OTHER TNF $\alpha$ -BLOCKING AGENTS. THEREFORE, THE COMBINATION OF REMICADE AND ANAKINRA IS NOT RECOMMENDED.**

**Hepatotoxicity**

484 Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have  
485 been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune  
486 hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between  
487 two weeks to more than a year after initiation of REMICADE; elevations in hepatic  
488 aminotransferase levels were not noted prior to discovery of the liver injury in many of these  
489 cases. Some of these cases were fatal or necessitated liver transplantation. Patients with  
490 symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If  
491 jaundice and/or marked liver enzyme elevations (e.g.,  $\geq 5$  times the upper limit of normal)  
492 develops, REMICADE should be discontinued, and a thorough investigation of the abnormality  
493 should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been  
494 associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e.,  
495 surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and  
496 monitored prior to the initiation of and during treatment with REMICADE. In clinical trials,  
497 mild or moderate elevations of ALT and AST have been observed in patients receiving  
498 REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS,  
499 Hepatotoxicity).

500

### 501 **Patients with Heart Failure**

502

503 REMICADE has been associated with adverse outcomes in patients with heart failure, and  
504 should be used in patients with heart failure only after consideration of other treatment options.  
505 The results of a randomized study evaluating the use of REMICADE in patients with heart  
506 failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10  
507 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and  
508 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without  
509 identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-  
510 marketing reports of new onset heart failure, including heart failure in patients without known  
511 pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a  
512 decision is made to administer REMICADE to patients with heart failure, they should be closely  
513 monitored during therapy, and REMICADE should be discontinued if new or worsening  
514 symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE  
515 REACTIONS, Patients with Heart Failure.)

516

### 517 **Hematologic Events**

518

519 Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal  
520 outcome, have been reported in patients receiving REMICADE. The causal relationship to  
521 REMICADE therapy remains unclear. Although no high-risk group(s) has been identified,  
522 caution should be exercised in patients being treated with REMICADE who have ongoing or a  
523 history of significant hematologic abnormalities. All patients should be advised to seek  
524 immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias  
525 or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE  
526 therapy should be considered in patients who develop significant hematologic abnormalities.

527

### 528 **Hypersensitivity**

529  
530 REMICADE has been associated with hypersensitivity reactions that vary in their time of onset  
531 and required hospitalization in some cases. Most hypersensitivity reactions, which include  
532 urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE  
533 infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's  
534 disease patients 3 to 12 days after REMICADE therapy was reinstated following an extended  
535 period without REMICADE treatment. Symptoms associated with these reactions include fever,  
536 rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia.  
537 These reactions were associated with marked increase in antibodies to infliximab, loss of  
538 detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE  
539 should be discontinued for severe reactions. Medications for the treatment of hypersensitivity  
540 reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be  
541 available for immediate use in the event of a reaction (see ADVERSE REACTIONS, Infusion-  
542 related Reactions).

### 543 544 **Neurologic Events**

545  
546 Infliximab-REMICADE and other agents that inhibit TNF have been associated in rare cases  
547 with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or  
548 radiographic evidence of central nervous system demyelinating disorders, including multiple  
549 sclerosis, and CNS manifestation of systemic vasculitis. Prescribers should exercise caution in  
550 considering the use of REMICADE in patients with pre-existing or recent onset of central  
551 nervous system demyelinating or seizure disorders. Discontinuation of REMICADE should be  
552 considered in patients who develop significant central nervous system adverse reactions.

### 553 554 **Malignancies**

555  
556 In the controlled portions of clinical trials of all the TNF $\alpha$ -blocking agents, more cases of  
557 lymphoma have been observed among patients receiving a TNF blocker compared with control  
558 patients. During the controlled portions of REMICADE trials in patients with moderately to  
559 severely active rheumatoid arthritis and Crohn's disease, 2 patients developed lymphoma among  
560 1964 REMICADE-treated patients versus 0 among 483 control patients (median duration of  
561 follow-up 0.9 years). In the controlled and open-label portions of these clinical trials of  
562 REMICADE, 4 patients developed lymphomas (2 patients with rheumatoid arthritis and 2  
563 patients with Crohn's disease) among 3469 patients (median duration of follow-up 1.0 years). In  
564 rheumatoid arthritis patients, this is approximately 3-fold higher than expected in the general  
565 population. In the combined clinical trial population for rheumatoid arthritis and Crohn's  
566 disease, this is approximately 5-fold higher than expected in the general population. Rates in  
567 clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF  
568 blockers and may not predict rates observed in a broader patient population. Patients with  
569 Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or  
570 chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold)  
571 than the general population for the development of lymphoma. The potential role of TNF $\alpha$ -  
572 blocking therapy in the development of malignancies is not known (see ADVERSE  
573 REACTIONS, Malignancies). No studies have been conducted that include patients with a  
574 history of malignancy or that continue treatment in patients who develop malignancy while

575 receiving REMICADE; thus additional caution should be exercised in considering REMICADE  
576 treatment of these patients.

577

## 578 **PRECAUTIONS**

579

### 580 **Autoimmunity**

581

582 Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the  
583 development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like  
584 syndrome following treatment with REMICADE, treatment should be discontinued (see  
585 ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome).

586

### 587 **Vaccinations**

588

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

592

### 593 **Information for Patients**

594

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

600

### 601 **Drug Interactions**

602

603 Concurrent administration of etanercept (another TNF $\alpha$ -blocking agent) and anakinra (an  
604 interleukin-1 antagonist) has been associated with an increased risk of serious infections, and  
605 increased risk of neutropenia and no additional benefit compared to these medicinal products  
606 alone. Other TNF $\alpha$ -blocking agents (including REMICADE) used in combination with anakinra  
607 may also result in similar toxicities (see WARNINGS, RISK OF INFECTIONS).

608

609 Specific drug interaction studies, including interactions with MTX, have not been conducted.  
610 The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one  
611 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides  
612 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.  
613 Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids,  
614 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications  
615 included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory  
616 agents, folic acid and corticosteroids.

617

618 Patients with Crohn's disease who received immunosuppressants tended to experience fewer  
619 infusion reactions compared to patients on no immunosuppressants (see ADVERSE  
620 REACTIONS, Immunogenicity and Infusion-related Reactions). Serum infliximab  
621 concentrations appeared to be unaffected by baseline use of medications for the treatment of  
622 Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and  
623 aminosalicylates.

624

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

626

627 A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF $\alpha$  to evaluate  
628 tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNF $\alpha$  in mice.  
629 Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly  
630 for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the  
631 human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause  
632 tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the  
633 *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.  
634 Chromosomal aberrations were not observed in an assay performed using human lymphocytes.  
635 The significance of these findings for human risk is unknown. It is not known whether infliximab  
636 can impair fertility in humans. No impairment of fertility was observed in a fertility and general  
637 reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic  
638 toxicity study.

639

#### 640 **Pregnancy Category B**

641

642 Since infliximab does not cross-react with TNF $\alpha$  in species other than humans and chimpanzees,  
643 animal reproduction studies have not been conducted with REMICADE. No evidence of  
644 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity  
645 study conducted in mice using an analogous antibody that selectively inhibits the functional  
646 activity of mouse TNF $\alpha$ . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the  
647 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to  
648 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not  
649 known whether REMICADE can cause fetal harm when administered to a pregnant woman or  
650 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if  
651 clearly needed.

652

#### 653 **Nursing Mothers**

654

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

660

661 **Pediatric Use**

662

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

665

666 **Geriatric Use**

667

668 In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or  
669 safety in 181 patients aged 65 or older compared to younger patients although the incidence of  
670 serious adverse events in patients aged 65 or older was higher in both ~~infliximab~~ REMICADE  
671 and control groups compared to younger patients. In Crohn's disease, ~~and~~ ankylosing spondylitis  
672 and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to  
673 determine whether they respond differently from patients aged 18 to 65. Because there is a  
674 higher incidence of infections in the elderly population in general, caution should be used in  
675 treating the elderly (see ADVERSE REACTIONS, Infections).

676

677 **ADVERSE REACTIONS**

678

679 The data described herein reflect exposure to REMICADE in ~~2629-2779~~ patients, including 1484  
680 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most common reason  
681 for discontinuation of treatment was infusion-related reactions (e.g. dyspnea, flushing, headache  
682 and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis  
683 patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were  
684 observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in  
685 patients with Crohn's disease.

686

687 **Infusion-related Reactions**

688

689 *Acute infusion reactions*

690

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

703

704 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to  
705 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant  
706 immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and

707 infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug  
708 Interactions).

709  
710 In post-marketing experience, cases of anaphylactic-like reactions, including  
711 laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with  
712 REMICADE administration.

713  
714 *Reactions following readministration*

715  
716 In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following  
717 a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events  
718 manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and  
719 symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also  
720 experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.  
721 Patients experiencing these adverse events had not experienced infusion-related adverse events  
722 associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of  
723 patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients  
724 who received lyophilized formulation. The clinical data are not adequate to determine if  
725 occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms  
726 improved substantially or resolved with treatment in all cases. There are insufficient data on the  
727 incidence of these events after drug-free intervals of 1 to 2 years. These events have been  
728 observed only infrequently in clinical studies and post-marketing surveillance with retreatment  
729 intervals up to 1 year.

730  
731 **Infections**

732  
733 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated  
734 patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of  
735 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections  
736 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among  
737 REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin  
738 ulceration, sepsis, and bacterial infection. In all clinical trials, six opportunistic infections were  
739 reported; two cases of coccidioidomycosis (one of which resulted in death), and one case each of  
740 histoplasmosis, pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in  
741 thirteen patients, four of whom died due to miliary tuberculosis. Other cases of tuberculosis,  
742 including disseminated tuberculosis, also have been reported post-marketing. Most of these cases  
743 of tuberculosis occurred within the first two months after initiation of therapy with ~~infliximab~~  
744 REMICADE and may reflect recrudescence of latent disease (see WARNINGS, RISK OF  
745 INFECTIONS). In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients  
746 receiving ~~infliximab-REMICADE~~ every 8 weeks with MTX developed serious infections as  
747 compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving ~~infliximab~~  
748 REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and  
749 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082  
750 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2,  
751 and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the  
752 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During

753 the 54 weeks Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new  
754 fistula-related abscess.

755  
756 In post-marketing experience, infections have been observed with various pathogens including  
757 viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems  
758 and have been reported in patients receiving REMICADE alone or in combination with  
759 immunosuppressive agents.

#### 760 761 **Autoantibodies/Lupus-like Syndrome**

762  
763 | Approximately half of ~~infliximab-REMICADE~~-treated patients in clinical trials who were  
764 antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial  
765 compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were  
766 | newly detected in approximately one-fifth of ~~infliximab-REMICADE~~-treated patients compared  
767 with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however,  
768 remain uncommon.

#### 769 770 **Malignancies**

771  
772 Among 3469 patients with moderately to severely active rheumatoid arthritis and Crohn's disease  
773 treated with REMICADE in clinical trials with a median of 1.0 years of follow-up, 4 patients  
774 developed lymphomas, for a rate of 0.08 cases per 100 patient-years of follow-up in patients with  
775 rheumatoid arthritis and 0.12 cases per 100 patient-years of follow up in the combined clinical  
776 trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold  
777 higher in the RA clinical trial population and 5-fold higher in the overall clinical trial population  
778 than expected in an age-, gender-, and race-matched general population based on the  
779 Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE  
780 cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates  
781 observed in a broader patient population. An increased rate of lymphoma up to several fold has  
782 been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be  
783 further increased in patients with more severe disease activity. Other than lymphoma, 23 patients  
784 developed noncutaneous malignancies, which was similar in number to what would be expected  
785 in the general population. Of these, the most common malignancies were breast, colorectal, and  
786 melanoma. (See WARNINGS, Malignancies.)

787  
788 Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been  
789 reported in patients receiving REMICADE during post-approval use.

#### 790 791 **Patients with Heart Failure**

792  
793 In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class  
794 III/IV; left ventricular ejection fraction  $\leq 35\%$ ), 150 patients were randomized to receive  
795 treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks.  
796 Higher incidences of mortality and hospitalization due to worsening heart failure were observed  
797 in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg  
798 REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the  
799 placebo groups. There were trends towards increased dyspnea, hypotension, angina, and

800 dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo.  
801 REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See  
802 CONTRAINDICATIONS and WARNINGS, Patients with Heart Failure.)

803

#### 804 **Immunogenicity**

805

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

816

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

823

#### 824 **Hepatotoxicity**

825

826 Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported  
827 rarely in patients receiving REMICADE (see WARNINGS, Hepatotoxicity). Reactivation of  
828 hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus  
829 (i.e., surface antigen positive) (see WARNINGS, Hepatotoxicity).

830

831 In clinical trials in RA, Crohn's disease, ~~and~~ ankylosing spondylitis and psoriatic arthritis,  
832 elevations of aminotransferases were observed (ALT more common than AST) in a greater  
833 proportion of patients receiving REMICADE than in controls, both when REMICADE was  
834 given as monotherapy and when it was used in combination with other immunosuppressive  
835 agents. In general, patients who developed ALT and AST elevations were asymptomatic, and  
836 the abnormalities decreased or resolved with either continuation or discontinuation of  
837 REMICADE, or modification of concomitant medications. ALT elevations  $\geq 5$  times the upper  
838 limit of normal were observed in 1% of patients receiving REMICADE.

839

840 In rheumatoid arthritis clinical trials, 34% of patients who received REMICADE + MTX  
841 experienced transient mild ( $< 2$  times the upper limit of normal) or moderate ( $\geq 2$  but  $< 3$  times the  
842 upper limit of normal) elevations in ALT compared to 24% of patients treated with placebo +  
843 MTX. ALT elevations  $\geq 3$  times the upper limit of normal were observed in 3.9% of patients  
844 who received REMICADE + MTX compared with 3.2% of patients who received MTX alone  
845 (median follow up approximately 1 year).

846

847 In Crohn's disease clinical trials (median follow up 54 weeks), 39% of patients receiving  
848 REMICADE-maintenance experienced mild to moderate elevations in ALT, compared to 34% of  
849 patients treated with placebo-maintenance. ALT elevations  $\geq 3$  times the upper limit of normal  
850 were observed in 5.0% of patients who received REMICADE-maintenance compared with 4.0%  
851 of patients who received placebo-maintenance.

852  
853 In an ankylosing spondylitis clinical trial in which patients were not receiving MTX, 40% of  
854 patients who received REMICADE experienced mild to moderate elevations in ALT compared  
855 to 13% of patients treated with placebo. ALT elevations  $\geq 3$  times the upper limit of normal were  
856 observed in 12 (6%) REMICADE-treated patients compared to none in placebo-treated patients.  
857 Similar rates of mild to moderate ALT elevations and elevations  $\geq 3$  times the upper limit of  
858 normal were observed in a psoriatic arthritis clinical trial.

859

### 860 **Other Adverse Reactions**

861

862 Safety data are available from 2629-2779 REMICADE-treated patients, including 1304 with  
863 rheumatoid arthritis, 1106 with Crohn's disease, 202 with ankylosing spondylitis, 150 with  
864 psoriatic arthritis, and 17 with other conditions. Adverse events reported in  $\geq 5\%$  of all patients  
865 with rheumatoid arthritis receiving 4 or more infusions are in Table 67. The types and  
866 frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid  
867 arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease patients except for  
868 abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In  
869 the Crohn's disease studies, there were insufficient numbers and duration of follow-up for  
870 patients who never received REMICADE to provide meaningful comparisons.

871  
872  
873  
874

**Table 6-7**  
**ADVERSE EVENTS OCCURRING IN 5% OR MORE OF PATIENTS**  
**RECEIVING 4 OR MORE INFUSIONS FOR RHEUMATOID ARTHRITIS**

	Placebo (n=350)	REMICADE (n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal Pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Rhinitis	5%	8%
Skin and appendages disorders		
Rash	5%	10%
Pruritis	2%	7%
Body as a whole-general disorders		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Back pain	5%	8%
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

875  
876 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
877 ~~observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of~~  
878 ~~another drug and may not predict the rates observed in broader patient populations in clinical~~  
879 ~~practice.~~  
880

881 The most common serious adverse events observed in clinical trials were infections (see  
882 ADVERSE REACTIONS, Infections). Other serious, medically relevant adverse events  $\geq 0.2\%$   
883 or clinically significant adverse events by body system were as follows:  
884

885 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela  
886 *Blood:* pancytopenia  
887 *Cardiovascular:* circulatory failure, hypotension, syncope  
888 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,  
889 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia  
890 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness  
891 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia  
892 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis  
893 *Metabolic and Nutritional:* dehydration  
894 *Musculoskeletal:* intervertebral disk herniation, tendon disorder  
895 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction  
896 *Platelet, Bleeding and Clotting:* thrombocytopenia  
897 *Neoplasms:* basal cell, breast, lymphoma  
898 *Psychiatric:* confusion, suicide attempt  
899 *Red Blood Cell:* anemia, hemolytic anemia  
900 *Reproductive:* menstrual irregularity  
901 *Resistance Mechanism:* cellulitis, sepsis, serum sickness  
902 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including  
903 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency  
904 *Skin and Appendages:* increased sweating, ulceration  
905 *Urinary:* renal calculus, renal failure  
906 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis  
907 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy  
908

909 The following adverse events have been reported during post-approval use of REMICADE:  
910 neutropenia (see WARNINGS, Hematologic Events), interstitial pneumonitis/fibrosis, idiopathic  
911 thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic  
912 and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies  
913 (additional neurologic events have also been observed, see WARNINGS, Neurologic Events).  
914 Because these events are reported voluntarily from a population of uncertain size, it is not always  
915 possible to reliably estimate their frequency or establish a causal relationship to REMICADE  
916 exposure.  
917

## 918 **OVERDOSAGE**

919  
920 Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of  
921 overdose, it is recommended that the patient be monitored for any signs or symptoms of  
922 adverse reactions or effects and appropriate symptomatic treatment instituted immediately.  
923

924 **DOSAGE AND ADMINISTRATION**

925  
926 **Rheumatoid Arthritis**

927  
928 The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed  
929 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks  
930 thereafter. REMICADE should be given in combination with methotrexate. For patients who  
931 have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or  
932 treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at  
933 higher doses (see ADVERSE REACTIONS, Infections).

934  
935 **Crohn's Disease or Fistulizing Crohn's Disease**

936  
937 The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6  
938 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment  
939 of moderately to severely active Crohn's disease or fistulizing disease. For patients who respond  
940 and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients  
941 who do not respond by week 14 are unlikely to respond with continued dosing and consideration  
942 should be given to discontinue REMICADE in these patients.

943  
944 **Ankylosing Spondylitis**

945  
946 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed  
947 with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks  
948 thereafter.

949  
950 **Psoriatic Arthritis**

951  
952 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed  
953 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks  
954 thereafter. REMICADE can be used with or without methotrexate.

955  
956 **Preparation and Administration Instructions**

957 **Use aseptic technique.**

958  
959 REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after  
960 reconstitution should be used immediately, not re-entered or stored. The diluent to be used for  
961 reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted  
962 product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The  
963 infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE  
964 infusion should begin within 3 hours of preparation.

- 965  
966 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial  
967 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE  
968 solution required.  
969

- 970 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a  
971 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and  
972 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center  
973 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass  
974 wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution  
975 by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous  
976 agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.  
977 Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to  
978 light yellow and opalescent, and the solution may develop a few translucent particles as  
979 infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign  
980 particles are present.  
981
- 982 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with  
983 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride  
984 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium  
985 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted  
986 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.  
987
- 988 4. The infusion solution must be administered over a period of not less than 2 hours and must  
989 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore  
990 size of 1.2  $\mu\text{m}$  or less). Any unused portion of the infusion solution should not be stored for  
991 reuse.  
992
- 993 5. No physical biochemical compatibility studies have been conducted to evaluate the co-  
994 administration of REMICADE with other agents. REMICADE should not be infused  
995 concomitantly in the same intravenous line with other agents.  
996
- 997 6. Parenteral drug products should be inspected visually for particulate matter and  
998 discoloration prior to administration, whenever solution and container permit. If visibly  
999 opaque particles, discoloration or other foreign particulates are observed, the solution  
1000 should not be used.  
1001

## 1002 **Storage**

1003  
1004 Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do  
1005 not use beyond the expiration date. This product contains no preservative.  
1006

## 1007 **HOW SUPPLIED**

1008  
1009 REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-  
1010 use vials in the following strength:

1011  
1012 ~~NDC 57894-030-01~~ 100 mg infliximab in a 20 mL vial

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1056

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1060 1-800-457-6399  
1061

License #1242  
Revised April 2005

1062 **Rx Only**

1063 **REMICADE® (infliximab)**  
1064 **Patient Information Sheet**

1065  
1066 You should read this information sheet before you start using REMICADE® (pronounced rem-  
1067 eh-kaid) and before each time you are scheduled to receive REMICADE. This information sheet  
1068 does not take the place of talking with your doctor. You and your doctor should talk about your  
1069 health and how you are feeling before you start taking REMICADE, while you are taking it and  
1070 at regular checkups. If you do not understand any of the information in this sheet, you should ask  
1071 your doctor to explain what it means.

1072  
1073 **What is REMICADE?**

1074 REMICADE is a medicine that is used to treat adults with moderately to severely active  
1075 rheumatoid arthritis, and Crohn's disease ~~and ankylosing spondylitis~~. In Crohn's disease,  
1076 REMICADE is for people who have not responded well enough to other medicines. REMICADE  
1077 is also used to treat active ankylosing spondylitis and psoriatic arthritis.

1078  
1079 **How does REMICADE work?**

1080 The medicine REMICADE is a type of protein that recognizes, attaches to and blocks the action  
1081 of a substance in your body called tumor necrosis factor. Tumor necrosis factor (TNF) is made  
1082 by certain blood cells in your body. REMICADE will not cure rheumatoid arthritis, Crohn's  
1083 disease, ~~or ankylosing spondylitis or psoriatic arthritis~~, but blocking TNF with REMICADE may  
1084 reduce the inflammation caused by ~~too much~~ TNF in your body. You should also know that  
1085 REMICADE may help you feel better but can also cause serious side effects and can reduce your  
1086 body's ability to fight infections (see below).

1087  
1088 **What should I know about the immune system, and taking REMICADE for Rheumatoid**  
1089 **Arthritis, Crohn's Disease, ~~or Ankylosing Spondylitis or Psoriatic Arthritis?~~**

1090 The immune system protects the body by responding to "invaders" like bacteria, viruses and  
1091 other foreign matter that enter your body by producing antibodies and putting them into action to  
1092 fight off the "invaders." In diseases like rheumatoid arthritis, Crohn's disease, ~~and ankylosing~~  
1093 ~~spondylitis and psoriatic arthritis~~, your body's immune system produces ~~too much~~ TNF. ~~Too~~  
1094 ~~much~~ TNF can cause your immune system to attack healthy tissues in your body and cause  
1095 inflammation and damage. If these diseases are ~~this condition is left untreated~~, it can cause  
1096 permanent damage to the body's bones, cartilage and tissue.

1097  
1098 While taking REMICADE can block the TNF that causes inflammation, it can also lower your  
1099 body's ability to fight infections. So, taking REMICADE can make you more prone to getting  
1100 infections or it can make an infection that you already have worse. You should call your doctor  
1101 right away if you think you have an infection.

1102  
1103 **What important information should I know about treatment with REMICADE?**

1104 REMICADE, like other medicines that affect your immune system, is a strong medicine that can  
1105 cause serious side effects. Possible serious side effects include:

1106  
1107 Serious Infections:

- 1108 • Some patients have had serious infections while receiving REMICADE. Some of the patients  
1109 have died from these infections. Serious infections include TB (tuberculosis), and infections  
1110 caused by viruses, fungi or bacteria that have spread throughout the body. If you develop a  
1111 fever, feel very tired, have a cough, or have flu-like symptoms, these could be signs that you  
1112 may be getting an infection. If you have any of these symptoms while you are taking or after  
1113 you have taken REMICADE, you should tell your doctor right away.

- 1114  
1115 Heart Failure:  
1116 • If you have been told that you have a heart problem called congestive heart failure and you  
1117 are currently being treated with REMICADE, you will need to be closely monitored by your  
1118 doctor. If you develop new or worse symptoms that are related to your heart condition, such  
1119 as shortness of breath or swelling of your ankles or feet, you must contact your doctor  
1120 immediately.

- 1121  
1122 Blood Problems:  
1123 • In some patients the body may fail to produce enough of the blood cells that help your body  
1124 fight infections or help you stop bleeding. Some of the patients have died from this failure to  
1125 produce blood cells. If you develop a fever that doesn't go away, bruise or bleed very easily  
1126 or look very pale, call your doctor right away. Your doctor may decide to stop your  
1127 treatment.

- 1128  
1129 Allergic Reactions:  
1130 • Some patients have had severe allergic reactions to REMICADE. These reactions can happen  
1131 while you are getting your REMICADE infusion or shortly afterwards. The symptoms of an  
1132 allergic reaction may include hives (red, raised, itchy patches of skin), difficulty breathing,  
1133 chest pain and high or low blood pressure. Your doctor may decide to stop REMICADE  
1134 treatment and give you medicines to treat the allergic reaction.  
1135 • Some patients who have been taking REMICADE for Crohn's disease have had allergic  
1136 reactions 3 to 12 days after receiving their REMICADE treatment. The symptoms of this  
1137 type of delayed reaction may include fever, rash, headache and muscle or joint pain. Call  
1138 your doctor right away if you develop any of these symptoms or any other unusual symptoms  
1139 such as difficulty swallowing.

- 1140  
1141 Nervous System Disorders:  
1142 • There have been rare cases where people taking REMICADE or other TNF blockers have  
1143 developed disorders that affected their nervous system. Signs that you could be having a  
1144 problem include: changes in your vision, weakness in your arms and/or legs, and numbness  
1145 or tingling in any part of your body.

- 1146  
1147 Malignancy  
1148 • Reports of a type of blood cancer called lymphoma in patients on REMICADE or other TNF  
1149 blockers are rare but occur more often than expected for people in general. People who have  
1150 been treated for rheumatoid arthritis, Crohn's disease, or ankylosing spondylitis or psoriatic  
1151 arthritis for a long time, particularly those with highly active disease may be more prone to  
1152 develop lymphoma. If you take REMICADE or other TNF blockers, your risk for  
1153 developing lymphoma may increase. You should also tell your doctor if you have had or  
1154 develop lymphoma or other cancers while you are taking REMICADE.

1155

1156 **Liver Injury**

- 1157 • There have been rare cases where people taking REMICADE have developed serious liver  
1158 problems, some fatal. Signs that you could be having a problem include: jaundice (skin and  
1159 eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever, and  
1160 severe fatigue (tiredness). You should contact your doctor immediately if you develop any  
1161 of these symptoms.

1162

1163 **Other Important Information**

1164

1165 Some patients have developed symptoms that can resemble a disease called lupus. Lupus-like  
1166 symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint  
1167 pain, or a rash on the cheeks or arms that gets worse in the sun. If you develop any of these  
1168 symptoms your doctor may decide to stop your treatment with REMICADE.

1169

1170 **What are the more common side effects of REMICADE?**

1171 The more common side effects with REMICADE are respiratory infections (that may include  
1172 sinus infections and sore throat), coughing and stomach pain.

1173

1174 **Who should not take REMICADE?**

1175 YOU SHOULD NOT take REMICADE if you have:

- 1176 • Heart failure, unless your doctor has talked to you and decided that you are able to take  
1177 REMICADE.
- 1178 • Had an allergic reaction to REMICADE or any other product that was made with murine  
1179 (mouse) proteins.

1180

1181 **What health concerns should I talk to my doctor about?**

1182 Before receiving your first treatment with REMICADE you should tell your doctor if you:

- 1183 • Have or think you may have any kind of infection. The infection could be in only one place  
1184 in your body (such as an open cut or sore), or an infection that affects your whole body (such  
1185 as the flu). Having an infection could put you at risk for serious side effects from  
1186 REMICADE.

- 1187 • Have an infection that won't go away or a history of infection that keeps coming back.

- 1188 • Have had TB (tuberculosis), or if you have recently been with anyone who might have TB.  
1189 Your doctor will examine you for TB and perform a skin test. If your doctor feels that you  
1190 are at risk for TB, he or she may start treating you for TB before you begin REMICADE  
1191 therapy.

- 1192 • Have lived in or visited an area of the country where an infection called histoplasmosis or  
1193 coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common. If  
1194 you don't know if the area you live in is one where histoplasmosis or coccidioidomycosis is  
1195 common, ask your doctor.

- 1196 • Have or have previously had heart failure or other heart conditions.

- 1197 • Have or have had a condition that affects your nervous system, like multiple sclerosis, or  
1198 Guillain-Barré syndrome, or if you experience any numbness, or tingling, or have had a  
1199 seizure.

- 1200 • Are pregnant or nursing.

- 1201 • Have recently received or are scheduled to receive a vaccine.

1202

1203 **Can I take REMICADE while I am on other medicines?**

1204 Tell your doctor if you are taking any other medicines including over the counter medicines,  
1205 supplements or herbal products before you are treated with REMICADE. If you start taking or  
1206 plan to start taking any new medicine while you are taking REMICADE, tell your doctor.

1207

1208 REMICADE and KINERET should not be taken together.

1209

1210 **How will REMICADE be given to me?**

1211 REMICADE will be given to you by a healthcare professional. REMICADE will be given to you  
1212 by an IV. This means that the medicine will be given to you through a needle placed in a vein in  
1213 your arm. It will take about 2 hours to give you the full dose of medicine. During that time and for  
1214 a period after you receive REMICADE, you will be monitored by a healthcare professional. Your  
1215 doctor may ask you to take other medicines along with REMICADE.

1216

1217 Only a health care professional should prepare the medicine and administer it to you.

1218

1219 **How often will I receive REMICADE?**

1220 Rheumatoid Arthritis

1221 If you are receiving REMICADE for rheumatoid arthritis you will receive your first dose  
1222 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose  
1223 every 8 weeks. Your doctor will monitor your response to REMICADE and may change your  
1224 dose or treat you more frequently (as often as every 4 weeks).

1225

1226 Crohn's Disease or Fistulizing Crohn's Disease

1227 If you are receiving REMICADE for active Crohn's disease or fistulizing Crohn's disease, you  
1228 will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You  
1229 will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE  
1230 and may change your dose.

1231

1232 Ankylosing Spondylitis

1233 If you are receiving REMICADE for ankylosing spondylitis you will receive your first dose  
1234 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose  
1235 every 6 weeks.

1236

1237 Psoriatic Arthritis

1238 If you are receiving REMICADE for psoriatic arthritis you will receive your first dose followed  
1239 by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8  
1240 weeks.

1241

1242 **What if I still have questions?**

1243 If you have any questions, or problems, always talk first with your doctor. You can also visit the  
1244 REMICADE internet site at [www.remicade.com](http://www.remicade.com).

1245

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1250  
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1252