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September 12, 2005

1 **REMICADE<sup>®</sup>**  
2 **(infliximab)**  
3 **for IV Injection**  
4  
5

6 **WARNING**  
7

8 **RISK OF INFECTIONS**  
9

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.**  
20

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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29  
30 **DESCRIPTION**  
31

32 REMICADE<sup>®</sup> 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<sup>10</sup> M<sup>-1</sup>. 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.  
37

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.

43

## 44 **CLINICAL PHARMACOLOGY**

45

### 46 **General**

47

48 Infliximab neutralizes the biological activity of TNF $\alpha$  by binding with high affinity to the  
49 soluble and transmembrane forms of TNF $\alpha$  and inhibits binding of TNF $\alpha$  with its receptors.<sup>2,3</sup>

50 Infliximab does not neutralize TNF $\beta$  (lymphotoxin  $\alpha$ ), a related cytokine that utilizes the same  
51 receptors as TNF $\alpha$ . Biological activities attributed to TNF $\alpha$  include: induction of pro-  
52 inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration  
53 by increasing endothelial layer permeability and expression of adhesion molecules by endothelial  
54 cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of  
55 acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by  
56 synoviocytes and/or chondrocytes. Cells expressing transmembrane TNF $\alpha$  bound by infliximab  
57 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  
58 variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T  
59 lymphocytes and epithelial cells. Anti-TNF $\alpha$  antibodies reduce disease activity in the cotton-top  
60 tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-  
61 induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a  
62 result of constitutive expression of human TNF $\alpha$ , and when administered after disease onset,  
63 allows eroded joints to heal.

64

### 65 **Pharmacodynamics**

66

67 Elevated concentrations of TNF $\alpha$  have been found in involved tissues and fluids of patients with  
68 rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic  
69 arthritis. In rheumatoid arthritis, treatment with REMICADE reduced infiltration of  
70 inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating  
71 cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell  
72 adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemoattractant protein  
73 (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease,  
74 treatment with REMICADE reduced infiltration of inflammatory cells and TNF $\alpha$  production in  
75 inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina  
76 propria able to express TNF $\alpha$  and interferon. After treatment with REMICADE, patients with  
77 rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive  
78 protein (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated  
79 patients showed no significant decrease in number or in proliferative responses to *in vitro*  
80 mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis,  
81 treatment with REMICADE resulted in a reduction in the number of T-cells and blood vessels in  
82 the synovium and psoriatic skin as well as a reduction of macrophages in the synovium. The  
83 relationship between these pharmacodynamic activities and the mechanism(s) by which  
84 REMICADE exerts its clinical effects is unknown.

85

86 **Pharmacokinetics**

87

88 Single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between  
89 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. Pharmacokinetic results for doses of 3 mg/kg to 10 mg/kg in  
92 rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the median terminal half-life of  
93 infliximab is 8.0 to 9.5 days.

94

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

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

109

110 **CLINICAL STUDIES**

111

112 **Rheumatoid Arthritis**

113

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

118

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

125

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

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

135

136 *Clinical response*

137

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

145

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

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**Table 1**  
**ACR RESPONSE (PERCENT OF PATIENTS)**

Response	Study RA I					Study RA II		
	Placebo + MTX (n=88)	REMICADE + MTX				Placebo + MTX (n=274)	REMICADE + MTX	
		3 mg/kg		10 mg/kg			3 mg/kg	6 mg/kg
		q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)	q 8 wks (n=351)	q 8 wks (n=355)	
ACR 20								
Week 30	20%	50% <sup>a</sup>	50% <sup>a</sup>	52% <sup>a</sup>	58% <sup>a</sup>	N/A	N/A	N/A
Week 54	17%	42% <sup>a</sup>	48% <sup>a</sup>	59% <sup>a</sup>	59% <sup>a</sup>	54%	62% <sup>c</sup>	66% <sup>a</sup>
ACR 50								
Week 30	5%	27% <sup>a</sup>	29% <sup>a</sup>	31% <sup>a</sup>	26% <sup>a</sup>	N/A	N/A	N/A
Week 54	9%	21% <sup>c</sup>	34% <sup>a</sup>	40% <sup>a</sup>	38% <sup>a</sup>	32%	46% <sup>a</sup>	50% <sup>a</sup>
ACR 70								
Week 30	0%	8% <sup>b</sup>	11% <sup>b</sup>	18% <sup>a</sup>	11% <sup>a</sup>	N/A	N/A	N/A
Week 54	2%	11% <sup>c</sup>	18% <sup>a</sup>	26% <sup>a</sup>	19% <sup>a</sup>	21%	33% <sup>b</sup>	37% <sup>a</sup>
Major clinical response <sup>#</sup>	0%	7% <sup>c</sup>	8% <sup>b</sup>	15% <sup>a</sup>	6% <sup>c</sup>	8%	12%	17% <sup>a</sup>

# A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through week 102 for Study RA I and week 54 for Study RA II.

<sup>a</sup> p ≤ 0.001

<sup>b</sup> p < 0.01

<sup>c</sup> p < 0.05

151

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

<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-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)

152

153 *Radiographic response*

154

155 Structural damage in both hands and feet was assessed radiographically at week 54 by the  
 156 change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of  
 157 structural damage that measures the number and size of joint erosions and the degree of joint  
 158 space narrowing in hands/wrists and feet.<sup>7</sup>

159

160 In Study RA I, approximately 80% of patients had paired x-ray data at 54 weeks and  
 161 approximately 70% at 102 weeks. The inhibition of progression of structural damage was  
 162 observed at 54 weeks (Table 3) and maintained through 102 weeks.

163

164 In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of  
 165 structural damage was observed at weeks 30 and 54 (Table 3) in the REMICADE + MTX groups  
 166 compared to MTX alone. In an exploratory analysis of Study RA II, patients treated with  
 167 REMICADE + MTX demonstrated less progression of structural damage compared to MTX  
 168 alone, whether baseline acute phase reactants (ESR and CRP) were normal or elevated: patients  
 169 with elevated baseline acute phase reactants treated with MTX alone demonstrated a mean  
 170 progression in vdH-S score of 4.2 units compared to patients treated with REMICADE + MTX  
 171 who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants

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172 treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared  
173 to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving  
174 REMICADE + MTX, 59% had no progression (vdH-S score  $\leq$  0 unit) of structural damage  
175 compared to 45% patients receiving MTX alone. In a subset of patients who began the study  
176 without erosions, REMICADE + MTX maintained an erosion free state at 1 year in a greater  
177 proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively ( $p < 0.01$ ).  
178 Fewer patients in the REMICADE + MTX groups (47%) developed erosions in uninvolved  
179 joints compared to MTX alone (59%).  
180

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**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.

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182 *Physical function response*

183  
184 Physical function and disability were assessed using the Health Assessment Questionnaire  
185 (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

186  
187 In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater  
188 improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged  
189 over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental  
190 component summary score. The median (interquartile range) improvement from baseline to week  
191 54 in HAQ-DI was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for  
192 REMICADE + MTX ( $p < 0.001$ ). Both HAQ-DI and SF-36 effects were maintained through week  
193 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in  
194 the trial through 102 weeks.

195  
196 In Study RA II, both REMICADE treatment groups showed greater improvement in HAQ-DI  
197 from baseline averaged over time through week 54 compared to MTX alone; 0.7 for  
198 REMICADE + MTX vs. 0.6 for MTX alone ( $p \leq 0.001$ ). No worsening in the SF-36 mental  
199 component summary score was observed.

200  
201 **Active Crohn's Disease**

202  
203 The safety and efficacy of single and multiple doses of REMICADE were assessed in two  
204 randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to  
205 severely active Crohn's disease [Crohn's Disease Activity Index (CDAI)  $\geq 220$  and  $\leq 400$ ] with  
206 an inadequate response to prior conventional therapies. Concomitant stable doses of  
207 aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of  
208 patients continued to receive at least one of these medications.

209  
210 In the single-dose trial<sup>8</sup> of 108 patients, 16% (4/25) of placebo patients achieved a clinical  
211 response (decrease in CDAI  $\geq 70$  points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg  
212 REMICADE ( $p < 0.001$ , two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo  
213 patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission  
214 (CDAI  $< 150$ ) at week 4.

215  
216 In a multidose trial (ACCENT I [Study Crohn's I])<sup>9</sup>, 545 patients received 5 mg/kg at week 0  
217 and were then randomized to one of three treatment groups; the placebo maintenance group  
218 received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group  
219 received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance  
220 group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response  
221 at week 2 were randomized and analyzed separately from those not in response at week 2.  
222 Corticosteroid taper was permitted after week 6.

223  
224 At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly  
225 greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved  
226 clinical remission compared to patients in the placebo maintenance group (Table 4).

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227 Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg  
228 REMICADE maintenance groups were in clinical remission and were able to discontinue  
229 corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).  
230

**Table 4**  
**CLINICAL REMISSION AND STEROID WITHDRAWAL**

	Single 5 mg/kg Dose <sup>a</sup>	Three Dose Induction <sup>b</sup> <u>REMICADE Maintenance q 8</u>	
	<u>Placebo Maintenance</u>	<u>wks</u> <u>5 mg/kg</u>	<u>10 mg/kg</u>
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	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

231

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

232

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

233

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

234

<sup>d</sup> Of those receiving corticosteroids at baseline

235

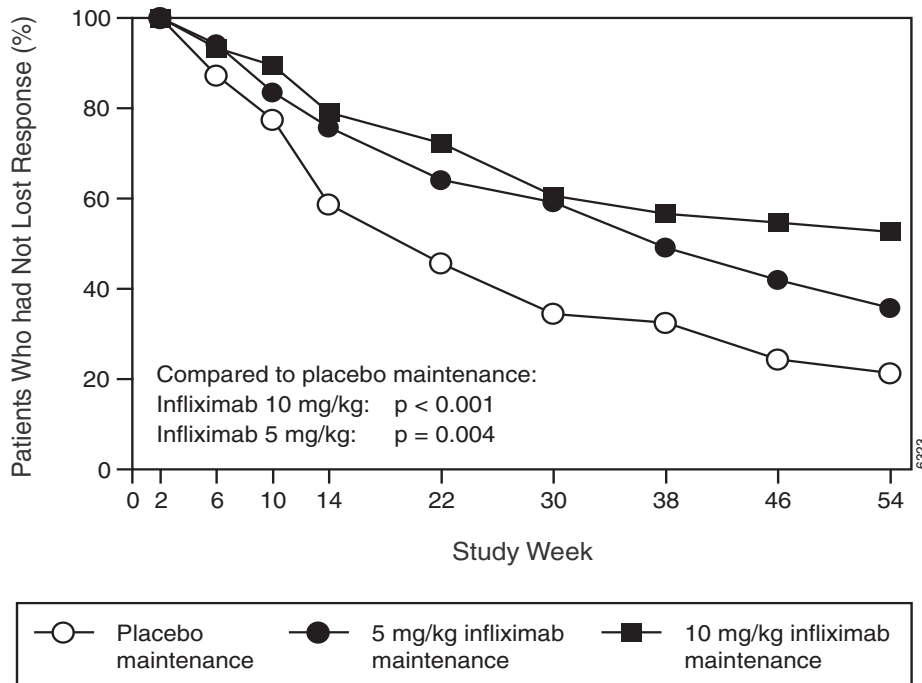
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237 Patients in the REMICADE maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to  
238 loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54,  
239 significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg REMICADE-  
240 treated groups compared to the placebo group in the disease specific inflammatory bowel disease  
241 questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical  
242 component summary score of the general health-related quality of life questionnaire SF-36.  
243

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**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 REMICADE maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at week 10. Of the REMICADE-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 REMICADE 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 REMICADE 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-aminosalicylates, antibiotics, MTX, 6-mercaptopurine (6-MP) and/or azathioprine (AZA) was permitted.

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

280

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

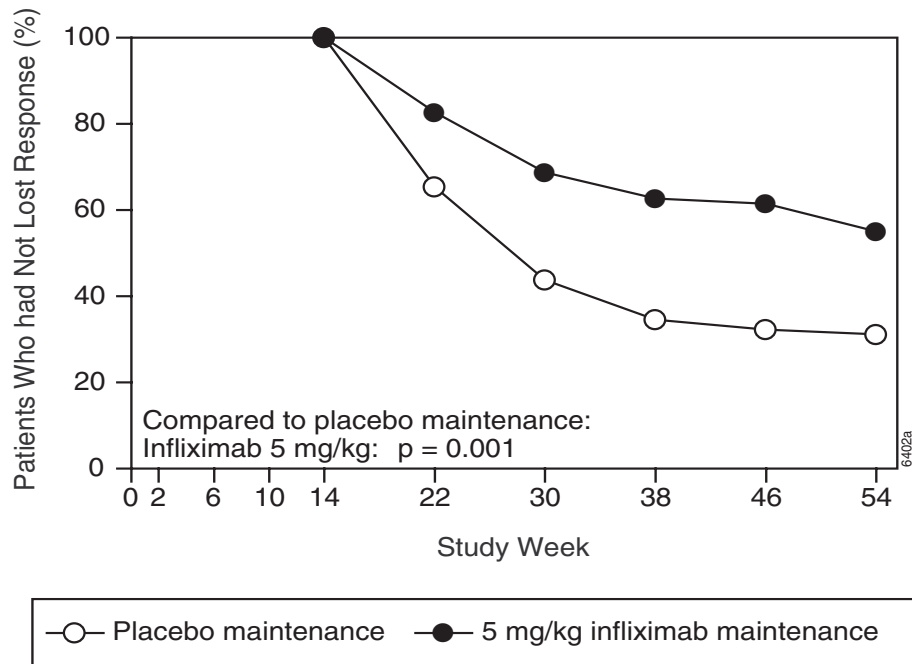
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290 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and  
291 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the  
292 patients had received previous immunosuppressive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

293

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

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**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).

### **Ankylosing Spondylitis**

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.

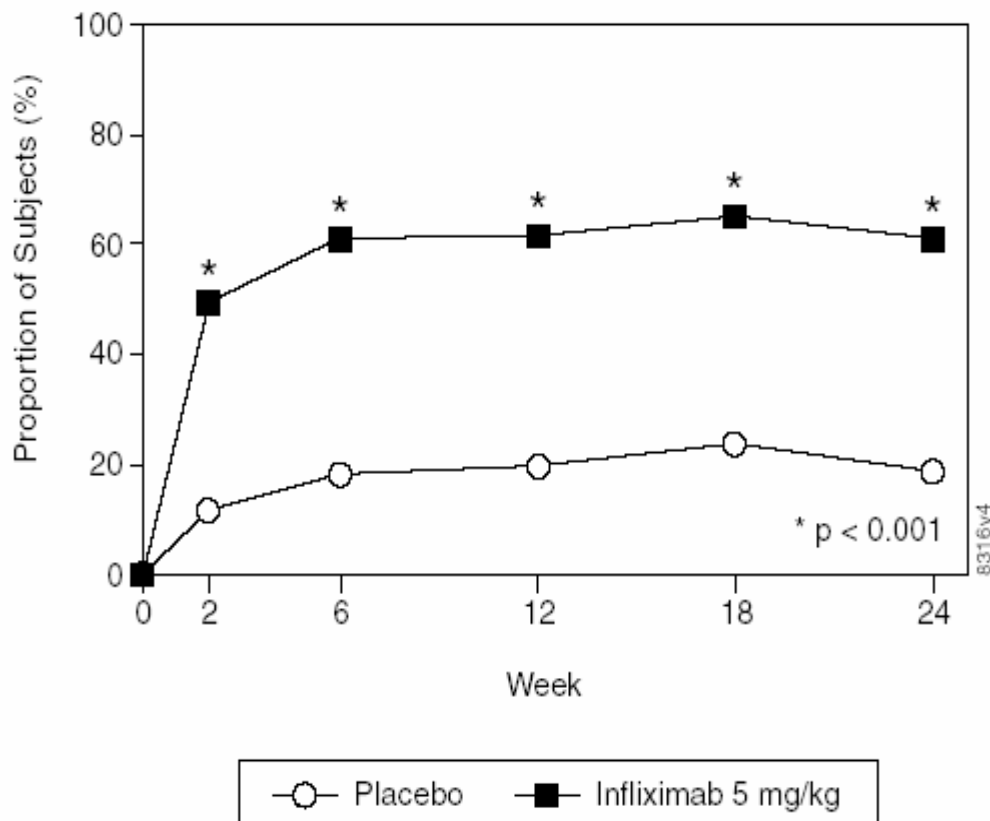
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328 Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12  
329 and 18.

330 At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by  
331 the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20),  
332 was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo  
333 group ( $p < 0.001$ ). Improvement was observed at week 2 and maintained through week 24 (Figure  
334 3 and Table 5).

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**Figure 3**  
**Proportion of patients achieving ASAS 20 response**

342 At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs  
343 and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and  
344 ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE,  
345 compared to 9% and 4%, respectively, for patients receiving placebo ( $p < 0.001$ , REMICADE vs.  
346 placebo). A low level of disease activity (defined as a value  $< 20$  [on a scale of 0-100 mm] in

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347 each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated  
348 patients vs. 1% in placebo-treated patients (p<0.001).  
349

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**Table 5**  
**Components of Ankylosing Spondylitis Disease Activity**

	<u>Placebo</u> (n=78)		<u>REMICADE 5mg/kg</u> (n=201)		<u>p-value</u>
	<u>Baseline</u>	<u>24 Weeks</u>	<u>Baseline</u>	<u>24 Weeks</u>	
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

355

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

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

### **Psoriatic Arthritis**

365

366 Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-  
367 controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID  
368 therapy (≥ 5 swollen joints and ≥ 5 tender joints) with one or more of the following subtypes:  
369 arthritis involving DIP joints (n = 49), arthritis mutilans (n = 3), asymmetric peripheral arthritis  
370 (n = 40), polyarticular arthritis (n = 100), and spondylitis with peripheral arthritis (n = 8).

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371 Patients also had plaque psoriasis with a qualifying target lesion  $\geq 2$  cm in diameter. Forty-six  
372 percent of patients continued on stable doses of methotrexate ( $\leq 25$  mg/week). During the 24-  
373 week double-blind phase, patients received either 5 mg/kg REMICADE or placebo at weeks 0, 2,  
374 6, 14, and 22 (100 patients in each group). At week 16, placebo patients with  $< 10\%$   
375 improvement from baseline in both swollen and tender joint counts were switched to  
376 REMICADE induction (early escape).

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

386

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

389

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

392

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

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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

394

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

401

## 402 **Ulcerative Colitis**

403

404 The safety and efficacy of REMICADE were assessed in two randomized, double-blind,  
405 placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative  
406 colitis (UC) (Mayo score<sup>12</sup> 6 to 12 [of possible range 0-12], Endoscopy subscore  $\geq$  2) with an  
407 inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant  
408 treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory  
409 agents was permitted. Corticosteroid taper was permitted after week 8. In both studies, patients  
410 were randomized to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE at  
411 weeks 0, 2, 6, 14 and 22.

412

413 Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-  
414 mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or  
415 were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients  
416 in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-  
417 MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More  
418 patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%,

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419 respectively). Clinical response was defined as a decrease from baseline in the Mayo score by  $\geq$   
420 30% and  $\geq$  3 points, accompanied by a decrease in the rectal bleeding subscore of  $\geq$  1 or a rectal  
421 bleeding subscore of 0 or 1.

422

423 In both studies, greater percentages of patients in both REMICADE groups achieved a clinical  
424 response, a sustained clinical response (response at both weeks 8 and 30), clinical remission and  
425 other assessed clinical outcomes than in the placebo group (Table 7). Of patients on  
426 corticosteroids at baseline, greater proportions of patients in the REMICADE treatment groups  
427 were in clinical remission and able to discontinue corticosteroids at week 30 compared with the  
428 patients in the placebo treatment groups (22% in REMICADE treatment groups vs. 10% in  
429 placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in placebo group in  
430 Study UC II). The REMICADE-associated response was generally similar in the 5 mg/kg and 10  
431 mg/kg dose groups.

432

Table 7

Response, Remission and Mucosal Healing in Ulcerative Colitis Studies

	Study UC I			Study UC II		
	Placebo	5 mg/kg REMICADE	10 mg/kg REMICADE	Placebo	5 mg/kg REMICADE	10 mg/kg REMICADE
Patients randomized	121	121	122	123	121	120
<hr/>						
Clinical Response <sup>1</sup>						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
<hr/>						
Sustained Response (both Week 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
<hr/>						
Clinical Remission <sup>2</sup>						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%*	37%*	11%	26%**	36%*
<hr/>						
Sustained Remission (both Week 8 and 30)	8%	23%*	26%*	2%	15%*	23%*

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<b>Mucosal Healing<sup>3</sup></b>						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%**	57%*

---

433

434

\* P < 0.001, \*\* P < 0.01

435

<sup>1</sup> Defined as a decrease from baseline in the Mayo score by  $\geq 30\%$  and  $\geq 3$  points, accompanied by a decrease in the rectal bleeding subscore of  $\geq 1$  or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings.)

436

437

438

<sup>2</sup> Defined as a Mayo score  $\leq 2$  points, no individual subscore  $>1$ .

439

<sup>3</sup> Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

440

441

442

The improvement with REMICADE was consistent across all Mayo subscores through week 30 (study UC I shown in Table 8; Study UC II was similar).

443

444

445

446

**Table 8**

**Proportion of patients in Study UC I with Mayo subscores indicating inactive or mild disease through week 30**

447

448

449

	<b>Study UC I</b>		
	<b>REMICADE</b>		
	<b>Placebo</b>	<b>5 mg/kg</b>	<b>10 mg/kg</b>
	(n=121)	(n=121)	(n=122)
<b>Stool frequency</b>			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
<b>Rectal Bleeding</b>			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
<b>Physician's global assessment</b>			
Baseline	4%	6%	3%
Week 8	44%	74%	64%
Week 30	36%	57%	55%
<b>Endoscopy findings</b>			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%

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451 **INDICATIONS AND USAGE**

452

453 **Rheumatoid Arthritis**

454

455 REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms,  
456 inhibiting the progression of structural damage, and improving physical function in patients with  
457 moderately to severely active rheumatoid arthritis.

458

459 **Crohn's Disease**

460

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

464

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

467

468 **Ankylosing Spondylitis**

469

470 REMICADE is indicated for reducing signs and symptoms in patients with active ankylosing  
471 spondylitis.

472

473 **Psoriatic Arthritis**

474

475 REMICADE is indicated for reducing signs and symptoms of active arthritis in patients with  
476 psoriatic arthritis.

477

478 **Ulcerative Colitis**

479

480 REMICADE is indicated for reducing signs and symptoms, achieving clinical remission and  
481 mucosal healing, and eliminating corticosteroid use in patients with moderately to severely  
482 active ulcerative colitis who have had an inadequate response to conventional therapy.

483

484 **CONTRAINDICATIONS**

485

486 REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe  
487 heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe  
488 heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE  
489 treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization  
490 due to worsening heart failure (see WARNINGS and ADVERSE REACTIONS, Patients with  
491 Heart Failure).

492

493 REMICADE should not be administered to patients with known hypersensitivity to any murine  
494 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 UNDERLYING DISEASE, 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**

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

552

#### 553 **Patients with Heart Failure**

554

555 REMICADE has been associated with adverse outcomes in patients with heart failure, and  
556 should be used in patients with heart failure only after consideration of other treatment options.  
557 The results of a randomized study evaluating the use of REMICADE in patients with heart  
558 failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10  
559 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and  
560 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without  
561 identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-  
562 marketing reports of new onset heart failure, including heart failure in patients without known  
563 pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If  
564 a decision is made to administer REMICADE to patients with heart failure, they should be closely  
565 monitored during therapy, and REMICADE should be discontinued if new or worsening  
566 symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE  
567 REACTIONS, Patients with Heart Failure.)

568

#### 569 **Hematologic Events**

570

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

579

#### 580 **Hypersensitivity**

581

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

595

### 596 **Neurologic Events**

597

598 REMICADE and other agents that inhibit TNF have been associated in rare cases with optic  
599 neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic  
600 evidence of central nervous system demyelinating disorders, including multiple sclerosis, and  
601 CNS manifestation of systemic vasculitis. Prescribers should exercise caution in considering the  
602 use of REMICADE in patients with pre-existing or recent onset of central nervous system  
603 demyelinating or seizure disorders. Discontinuation of REMICADE should be considered in  
604 patients who develop significant central nervous system adverse reactions.

605

### 606 **Malignancies**

607

608 In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE,  
609 more malignancies have been observed in patients receiving those TNF-blockers compared with  
610 control patients. During the controlled portions of REMICADE trials in patients with moderately  
611 to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis,  
612 and ulcerative colitis, 14 patients were diagnosed with malignancies among 2897 REMICADE-  
613 treated patients vs. 1 among 1262 control patients (at a rate of 0.65/100 patient-years among  
614 REMICADE-treated patients vs. a rate of 0.13/100 patient-years among control patients), with  
615 median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for  
616 control patients. Of these, the most common malignancies were breast, colorectal, and  
617 melanoma. The rate of malignancies among REMICADE-treated patients was similar to that  
618 expected in the general population whereas the rate in control patients was lower than expected.

619

620 In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of  
621 lymphoma have been observed among patients receiving a TNF blocker compared with control  
622 patients. In the controlled and open-label portions of REMICADE clinical trials, 4 patients  
623 developed lymphomas among 4292 patients treated with REMICADE (median duration of  
624 follow-up 1.0 years) vs. 0 lymphomas in 1265 control patients (median duration of follow-up 0.5  
625 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per

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626 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the  
627 general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's  
628 disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 4 lymphomas were  
629 observed for a rate of 0.11 cases per 100 patient-years of follow-up, which is approximately 5-  
630 fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid  
631 arthritis, particularly patients with highly active disease and/or chronic exposure to  
632 immunosuppressant therapies, may be at a higher risk (up to several fold) than the general  
633 population for the development of lymphoma, even in the absence of TNF-blocking therapy.

634  
635 The potential role of TNF-blocking therapy in the development of malignancies is not known  
636 (see ADVERSE REACTIONS, Malignancies). Rates in clinical trials for REMICADE cannot be  
637 compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a  
638 broader patient population. Caution should be exercised in considering REMICADE treatment in  
639 patients with a history of malignancy or in continuing treatment in patients who develop  
640 malignancy while receiving REMICADE.

641

## 642 **PRECAUTIONS**

643

### 644 **Autoimmunity**

645

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

650

### 651 **Vaccinations**

652

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

656

### 657 **Information for Patients**

658

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

664

### 665 **Drug Interactions**

666

667 Concurrent administration of etanercept (another TNF $\alpha$ -blocking agent) and anakinra (an  
668 interleukin-1 antagonist) has been associated with an increased risk of serious infections, and  
669 increased risk of neutropenia and no additional benefit compared to these medicinal products

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670 alone. Other TNF $\alpha$ -blocking agents (including REMICADE) used in combination with anakinra  
671 may also result in similar toxicities (see WARNINGS, RISK OF INFECTIONS).  
672

673 Specific drug interaction studies, including interactions with MTX, have not been conducted.  
674 The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one  
675 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides  
676 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.  
677 Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids,  
678 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications  
679 included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory  
680 agents, folic acid and corticosteroids.

681  
682 Patients with Crohn's disease who received immunosuppressants tended to experience fewer  
683 infusion reactions compared to patients on no immunosuppressants (see ADVERSE  
684 REACTIONS, Immunogenicity and Infusion-related Reactions). Serum infliximab  
685 concentrations appeared to be unaffected by baseline use of medications for the treatment of  
686 Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and  
687 aminosalicylates.

688

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

690

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

703

704 **Pregnancy Category B**

705

706 Since infliximab does not cross-react with TNF $\alpha$  in species other than humans and chimpanzees,  
707 animal reproduction studies have not been conducted with REMICADE. No evidence of  
708 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity  
709 study conducted in mice using an analogous antibody that selectively inhibits the functional  
710 activity of mouse TNF $\alpha$ . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the  
711 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to  
712 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not  
713 known whether REMICADE can cause fetal harm when administered to a pregnant woman or  
714 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if  
715 clearly needed.

716

717 **Nursing Mothers**

718

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

724

725 **Pediatric Use**

726

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

729

730 **Geriatric Use**

731

732 In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or  
733 safety in 181 patients aged 65 or older compared to younger patients although the incidence of  
734 serious adverse events in patients aged 65 or older was higher in both REMICADE and control  
735 groups compared to younger patients. In Crohn's disease, ulcerative colitis, ankylosing  
736 spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and  
737 over to determine whether they respond differently from patients aged 18 to 65. Because there is  
738 a higher incidence of infections in the elderly population in general, caution should be used in  
739 treating the elderly (see ADVERSE REACTIONS, Infections).

740

741 **ADVERSE REACTIONS**

742

743 The data described herein reflect exposure to REMICADE in 3263 patients (1304 patients with  
744 rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 150  
745 with psoriatic arthritis, 484 with ulcerative colitis and 17 patients with other conditions),  
746 including 1484 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most  
747 common reason for discontinuation of treatment was infusion-related reactions (e.g. dyspnea,  
748 flushing, headache and rash). Adverse events have been reported in a higher proportion of

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749 rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no  
750 differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10  
751 mg/kg dose in patients with Crohn’s disease.

752

### 753 **Infusion-related Reactions**

754

#### 755 *Acute infusion reactions*

756

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

769

770 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to  
771 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant  
772 immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and  
773 infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug  
774 Interactions).

775

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

779

#### 780 *Reactions following readministration*

781

782 In a study where 37 of 41 patients with Crohn’s disease were retreated with infliximab following  
783 a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events  
784 manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and  
785 symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also  
786 experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.  
787 Patients experiencing these adverse events had not experienced infusion-related adverse events  
788 associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of  
789 patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients  
790 who received lyophilized formulation. The clinical data are not adequate to determine if  
791 occurrence of these reactions is due to differences in formulation. Patients’ signs and symptoms  
792 improved substantially or resolved with treatment in all cases. There are insufficient data on the  
793 incidence of these events after drug-free intervals of 1 to 2 years. These events have been

794 observed only infrequently in clinical studies and post-marketing surveillance with retreatment  
795 intervals up to 1 year.

796

### 797 **Infections**

798

799 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated  
800 patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of  
801 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections  
802 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among  
803 REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin  
804 ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were  
805 reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was  
806 fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was  
807 reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis,  
808 including disseminated tuberculosis, also have been reported post-marketing. Most of these cases  
809 of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE  
810 and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). In  
811 the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE  
812 every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients  
813 receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4%  
814 developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter  
815 (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg  
816 or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX,  
817 serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3  
818 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients  
819 with fistulizing Crohn's disease developed a new fistula-related abscess.

820

821 In REMICADE clinical studies in patients with ulcerative colitis, infections treated with  
822 antimicrobials were reported in 19% of REMICADE-treated patients (average of 27 weeks of  
823 follow-up) and in 14% of placebo-treated patients (average 22 weeks of follow-up). The types of  
824 infections, including serious infections, reported in patients with ulcerative colitis were similar to  
825 those reported in other clinical studies.

826

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

831

### 832 **Autoantibodies/Lupus-like Syndrome**

833

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

839

840 **Malignancies**

841

842 In controlled trials, more REMICADE-treated patients developed malignancies than placebo-  
843 treated patients. (See WARNINGS, Malignancies.)

844

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

847

848 **Patients with Heart Failure**

849

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

860

861 **Immunogenicity**

862

863 Treatment with REMICADE can be associated with the development of antibodies to infliximab.  
864 The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed  
865 by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE  
866 treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease  
867 patients receiving REMICADE after drug free intervals  $>16$  weeks. The majority of antibody-  
868 positive patients had low titers. Patients who were antibody-positive were more likely to have  
869 higher rates of clearance, reduced efficacy and to experience an infusion reaction (see  
870 ADVERSE REACTIONS, Infusion-related Reactions) than were patients who were antibody  
871 negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease  
872 patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

873

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

880

881 **Hepatotoxicity**

882

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

887  
888 In clinical trials in rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis  
889 and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than  
890 AST) in a greater proportion of patients receiving REMICADE than in controls (Table 9), both  
891 when REMICADE was given as monotherapy and when it was used in combination with other  
892 immunosuppressive agents. In general, patients who developed ALT and AST elevations were  
893 asymptomatic, and the abnormalities decreased or resolved with either continuation or  
894 discontinuation of REMICADE, or modification of concomitant medications.

895  
896

**Table 9 Proportion of patients with elevated ALT in Clinical Trials**

	<u>Proportion of patients with elevated ALT</u>					
	<u>&gt;1 to &lt;3 x ULN</u>		<u>≥3 x ULN</u>		<u>≥5 x ULN</u>	
	Placebo	REMICADE	Placebo	REMICADE	Placebo	REMICADE
Rheumatoid arthritis <sup>1</sup>	24%	34%	3%	4%	<1%	<1%
Crohn’s disease <sup>2</sup>	34%	39%	4%	5%	0%	2%
Ulcerative colitis <sup>3</sup>	12%	15%	1%	2%	<1%	<1%
Ankylosing spondylitis <sup>4</sup>	13%	40%	0%	6%	0%	2%
Psoriatic arthritis <sup>5</sup>	16%	42%	0%	5%	0%	2%

897 <sup>1</sup> Placebo patients received methotrexate while REMICADE patients received both REMICADE and  
898 methotrexate. Median follow-up was 58 weeks.

899 <sup>2</sup> Placebo patients in the 2 Phase III trials in Crohn’s disease received an initial dose of 5 mg/kg REMICADE at  
900 study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo  
901 maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT  
902 analysis. Median follow-up was 54 weeks.

903 <sup>3</sup> Median follow-up was 30 weeks.

904 <sup>4</sup> Median follow-up was 24 weeks.

905 <sup>5</sup> Median follow-up was 24 weeks for REMICADE group and 18 weeks for placebo group.

906

907

908

909

**Other Adverse Reactions**

910

911  
912 Safety data are available from 3263 REMICADE-treated patients, including 1304 with  
913 rheumatoid arthritis, 1106 with Crohn’s disease, 484 with ulcerative colitis, 202 with ankylosing  
914 spondylitis, 150 with psoriatic arthritis, and 17 with other conditions. Adverse events reported in  
915 ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 10. The  
916 types and frequencies of adverse reactions observed were similar in REMICADE-treated

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917 rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease patients  
918 except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's  
919 disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up  
920 for patients who never received REMICADE to provide meaningful comparisons.

**Table 10**

**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
<b>Gastrointestinal</b>		
Nausea	20%	21%
Abdominal Pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
<b>Respiratory</b>		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Rhinitis	5%	8%
<b>Skin and appendages disorders</b>		
Rash	5%	10%
Pruritus	2%	7%
<b>Body as a whole-general disorders</b>		
Fatigue	7%	9%
Pain	7%	8%
<b>Resistance mechanism disorders</b>		
Fever	4%	7%
Moniliasis	3%	5%
<b>Central and peripheral nervous system disorders</b>		
Headache	14%	18%
<b>Musculoskeletal system disorders</b>		
Back pain	5%	8%
Arthralgia	7%	8%
<b>Urinary system disorders</b>		
Urinary tract infection	6%	8%
<b>Cardiovascular disorders, general</b>		
Hypertension	5%	7%

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

930

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

934

935 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela

936 *Blood:* pancytopenia

937 *Cardiovascular:* circulatory failure, hypotension, syncope

938 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,  
939 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia

940 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness

941 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia

942 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis

943 *Metabolic and Nutritional:* dehydration

944 *Musculoskeletal:* intervertebral disk herniation, tendon disorder

945 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction

946 *Platelet, Bleeding and Clotting:* thrombocytopenia

947 *Neoplasms:* basal cell, breast, lymphoma

948 *Psychiatric:* confusion, suicide attempt

949 *Red Blood Cell:* anemia, hemolytic anemia

950 *Reproductive:* menstrual irregularity

951 *Resistance Mechanism:* cellulitis, sepsis, serum sickness

952 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including  
953 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency

954 *Skin and Appendages:* increased sweating, ulceration

955 *Urinary:* renal calculus, renal failure

956 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis

957 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

958

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

967

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968 **OVERDOSAGE**

969

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

973

974 **DOSAGE AND ADMINISTRATION**

975

976 **Rheumatoid Arthritis**

977

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

984

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

986

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

993

994 **Ankylosing Spondylitis**

995

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

999

1000 **Psoriatic Arthritis**

1001

1002 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed  
1003 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks  
1004 thereafter. REMICADE can be used with or without methotrexate.

1005

1006 **Ulcerative Colitis**

1007

1008 The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6  
1009 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment  
1010 of moderately to severely active ulcerative colitis.

1011

1012

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1013 **Preparation and Administration Instructions**

1014 **Use aseptic technique.**

1015

1016 REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after  
1017 reconstitution should be used immediately, not re-entered or stored. The diluent to be used for  
1018 reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted  
1019 product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The  
1020 infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE  
1021 infusion should begin within 3 hours of preparation.

1022

1023 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial  
1024 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE  
1025 solution required.

1026

1027 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a  
1028 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and  
1029 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center  
1030 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass  
1031 wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution  
1032 by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous  
1033 agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.  
1034 Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to  
1035 light yellow and opalescent, and the solution may develop a few translucent particles as  
1036 infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign  
1037 particles are present.

1038

1039 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with  
1040 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride  
1041 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium  
1042 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted  
1043 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.

1044

1045 4. The infusion solution must be administered over a period of not less than 2 hours and must  
1046 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore  
1047 size of 1.2 µm or less). Any unused portion of the infusion solution should not be stored for  
1048 reuse.

1049

1050 5. No physical biochemical compatibility studies have been conducted to evaluate the co-  
1051 administration of REMICADE with other agents. REMICADE should not be infused  
1052 concomitantly in the same intravenous line with other agents.

1053

1054 6. Parenteral drug products should be inspected visually for particulate matter and  
1055 discoloration prior to administration, whenever solution and container permit. If visibly  
1056 opaque particles, discoloration or other foreign particulates are observed, the solution  
1057 should not be used.

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1058

1059 **Storage**

1060

1061 Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do  
1062 not use beyond the expiration date. This product contains no preservative.

1063

1064 **HOW SUPPLIED**

1065

1066 REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-  
1067 use vials in the following strength:

1068

1069 NDC 57894-030-01            100 mg infliximab in a 20 mL vial

1070

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1123 **Rx Only**

1124 **REMICADE® (infliximab)**  
1125 **Patient Information Sheet**  
1126

1127 You should read this information sheet before you start using REMICADE® (pronounced rem-  
1128 eh-kaid) and before each time you are scheduled to receive REMICADE. This information sheet  
1129 does not take the place of talking with your doctor. You and your doctor should talk about your  
1130 health and how you are feeling before you start taking REMICADE, while you are taking it and  
1131 at regular checkups. If you do not understand any of the information in this sheet, you should ask  
1132 your doctor to explain what it means.

1133

1134 **What is REMICADE?**

1135 REMICADE is a medicine that is used to treat adults with moderately to severely active  
1136 rheumatoid arthritis, Crohn’s disease and ulcerative colitis. In Crohn’s disease and ulcerative  
1137 colitis, REMICADE is for people who have not responded well enough to other medicines.  
1138 REMICADE is also used to treat active ankylosing spondylitis and psoriatic arthritis.

1139

1140 **How does REMICADE work?**

1141 The medicine REMICADE is a type of protein that recognizes, attaches to and blocks the action  
1142 of a substance in your body called tumor necrosis factor. Tumor necrosis factor (TNF) is made  
1143 by certain blood cells in your body. REMICADE will not cure rheumatoid arthritis, Crohn’s  
1144 disease, ulcerative colitis, ankylosing spondylitis or psoriatic arthritis, but blocking TNF with  
1145 REMICADE may reduce the inflammation caused by TNF in your body. You should also know  
1146 that REMICADE may help you feel better but can also cause serious side effects and can reduce  
1147 your body’s ability to fight infections (see below).

1148

1149 **What should I know about the immune system, and taking REMICADE for Rheumatoid**  
1150 **Arthritis, Crohn’s Disease, Ulcerative Colitis, Ankylosing Spondylitis or Psoriatic**  
1151 **Arthritis?**

1152 The immune system protects the body by responding to “invaders” like bacteria, viruses and  
1153 other foreign matter that enter your body by producing antibodies and putting them into action to  
1154 fight off the “invaders.” In diseases like rheumatoid arthritis, Crohn’s disease, ulcerative colitis,  
1155 ankylosing spondylitis and psoriatic arthritis, TNF can cause your immune system to attack  
1156 healthy tissues in your body and cause inflammation and damage. If these diseases are untreated,  
1157 it can cause permanent damage to the body’s bones, cartilage and tissue.

1158

1159 While taking REMICADE can block the TNF that causes inflammation, it can also lower your  
1160 body’s ability to fight infections. So, taking REMICADE can make you more prone to getting  
1161 infections or it can make an infection that you already have worse. You should call your doctor  
1162 right away if you think you have an infection.

1163

1164 **What important information should I know about treatment with REMICADE?**

1165 REMICADE, like other medicines that affect your immune system, is a strong medicine that can  
1166 cause serious side effects. Possible serious side effects include:

1167

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1168 Serious Infections:

- 1169 • Some patients have had serious infections while receiving REMICADE. Some of the patients  
1170 have died from these infections. Serious infections include TB (tuberculosis), and infections  
1171 caused by viruses, fungi or bacteria that have spread throughout the body. If you develop a  
1172 fever, feel very tired, have a cough, or have flu-like symptoms, these could be signs that you  
1173 may be getting an infection. If you have any of these symptoms while you are taking or after  
1174 you have taken REMICADE, you should tell your doctor right away.

1175  
1176 Heart Failure:

- 1177 • If you have been told that you have a heart problem called congestive heart failure and you  
1178 are currently being treated with REMICADE, you will need to be closely monitored by your  
1179 doctor. If you develop new or worse symptoms that are related to your heart condition, such  
1180 as shortness of breath or swelling of your ankles or feet, you must contact your doctor  
1181 immediately.

1182  
1183 Blood Problems:

- 1184 • In some patients the body may fail to produce enough of the blood cells that help your body  
1185 fight infections or help you stop bleeding. Some of the patients have died from this failure to  
1186 produce blood cells. If you develop a fever that doesn't go away, bruise or bleed very easily  
1187 or look very pale, call your doctor right away. Your doctor may decide to stop your  
1188 treatment.

1189  
1190 Allergic Reactions:

- 1191 • Some patients have had severe allergic reactions to REMICADE. These reactions can happen  
1192 while you are getting your REMICADE infusion or shortly afterwards. The symptoms of an  
1193 allergic reaction may include hives (red, raised, itchy patches of skin), difficulty breathing,  
1194 chest pain and high or low blood pressure. Your doctor may decide to stop REMICADE  
1195 treatment and give you medicines to treat the allergic reaction.
- 1196 • Some patients who have been taking REMICADE for Crohn's disease have had allergic  
1197 reactions 3 to 12 days after receiving their REMICADE treatment. The symptoms of this  
1198 type of delayed reaction may include fever, rash, headache and muscle or joint pain. Call  
1199 your doctor right away if you develop any of these symptoms or any other unusual symptoms  
1200 such as difficulty swallowing.

1201  
1202 Nervous System Disorders:

- 1203 • There have been rare cases where people taking REMICADE or other TNF blockers have  
1204 developed disorders that affected their nervous system. Signs that you could be having a  
1205 problem include: changes in your vision, weakness in your arms and/or legs, and numbness  
1206 or tingling in any part of your body.

1207  
1208 Cancer:

- 1209 • Reports of a type of blood cancer called lymphoma in patients on REMICADE or other TNF  
1210 blockers are rare but occur more often than expected for people in general. People who have  
1211 been treated for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis or psoriatic  
1212 arthritis for a long time, particularly those with highly active disease may be more prone to

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1213 develop lymphoma. Cancers, other than lymphoma, have also been reported. If you take  
1214 REMICADE or other TNF blockers, your risk for developing lymphoma or other cancers  
1215 may increase. You should also tell your doctor if you have had or develop lymphoma or  
1216 other cancers while you are taking REMICADE.

1217

1218 Liver Injury:

- 1219 • There have been rare cases where people taking REMICADE have developed serious liver  
1220 problems, some fatal. Signs that you could be having a problem include: jaundice (skin and  
1221 eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever, and  
1222 severe fatigue (tiredness). You should contact your doctor immediately if you develop any  
1223 of these symptoms.

1224

1225 **Other Important Information**

1226

1227 Some patients have developed symptoms that can resemble a disease called lupus. Lupus-like  
1228 symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint  
1229 pain, or a rash on the cheeks or arms that gets worse in the sun. If you develop any of these  
1230 symptoms your doctor may decide to stop your treatment with REMICADE.

1231

1232 **What are the more common side effects of REMICADE?**

1233 The more common side effects with REMICADE are respiratory infections (that may include  
1234 sinus infections and sore throat), coughing and stomach pain.

1235

1236 **Who should not take REMICADE?**

1237 YOU SHOULD NOT take REMICADE if you have:

- 1238 • Heart failure, unless your doctor has talked to you and decided that you are able to take  
1239 REMICADE.  
1240 • Had an allergic reaction to REMICADE or any other product that was made with murine  
1241 (mouse) proteins.

1242

1243 **What health concerns should I talk to my doctor about?**

1244 Before receiving your first treatment with REMICADE you should tell your doctor if you:

- 1245 • Have or think you may have any kind of infection. The infection could be in only one place  
1246 in your body (such as an open cut or sore), or an infection that affects your whole body (such  
1247 as the flu). Having an infection could put you at risk for serious side effects from  
1248 REMICADE.  
1249 • Have an infection that won't go away or a history of infection that keeps coming back.  
1250 • Have had TB (tuberculosis), or if you have recently been with anyone who might have TB.  
1251 Your doctor will examine you for TB and perform a skin test. If your doctor feels that you  
1252 are at risk for TB, he or she may start treating you for TB before you begin REMICADE  
1253 therapy.  
1254 • Have lived in or visited an area of the country where an infection called histoplasmosis or  
1255 coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common. If  
1256 you don't know if the area you live in is one where histoplasmosis or coccidioidomycosis is  
1257 common, ask your doctor.

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- 1258 • Have or have previously had heart failure or other heart conditions.
- 1259 • Have or have had a condition that affects your nervous system, like multiple sclerosis, or
- 1260 Guillain-Barré syndrome, or if you experience any numbness, or tingling, or have had a
- 1261 seizure.
- 1262 • Are pregnant or nursing.
- 1263 • Have recently received or are scheduled to receive a vaccine.
- 1264

1265 **Can I take REMICADE while I am on other medicines?**

1266 Tell your doctor if you are taking any other medicines including over the counter medicines,  
1267 supplements or herbal products before you are treated with REMICADE. If you start taking or  
1268 plan to start taking any new medicine while you are taking REMICADE, tell your doctor.

1269

1270 REMICADE and KINERET should not be taken together.

1271

1272 **How will REMICADE be given to me?**

1273 REMICADE will be given to you by a healthcare professional. REMICADE will be given to you  
1274 by an IV. This means that the medicine will be given to you through a needle placed in a vein in  
1275 your arm. It will take about 2 hours to give you the full dose of medicine. During that time and for  
1276 a period after you receive REMICADE, you will be monitored by a healthcare professional. Your  
1277 doctor may ask you to take other medicines along with REMICADE.

1278

1279 Only a health care professional should prepare the medicine and administer it to you.

1280

1281 **How often will I receive REMICADE?**

1282 Rheumatoid Arthritis

1283 If you are receiving REMICADE for rheumatoid arthritis you will receive your first dose  
1284 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose  
1285 every 8 weeks. Your doctor will monitor your response to REMICADE and may change your  
1286 dose or treat you more frequently (as often as every 4 weeks).

1287

1288 Crohn's Disease or Fistulizing Crohn's Disease

1289 If you are receiving REMICADE for active Crohn's disease or fistulizing Crohn's disease, you  
1290 will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You  
1291 will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE  
1292 and may change your dose.

1293

1294 Ulcerative Colitis

1295 If you are receiving REMICADE for ulcerative colitis, you will receive your first dose followed  
1296 by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8  
1297 weeks and your doctor will monitor your response to REMICADE.

1298

1299 Ankylosing Spondylitis

1300 If you are receiving REMICADE for ankylosing spondylitis you will receive your first dose  
1301 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose  
1302 every 6 weeks.

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1303

1304 Psoriatic Arthritis

1305 If you are receiving REMICADE for psoriatic arthritis you will receive your first dose followed  
1306 by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8  
1307 weeks.

1308

1309 **What if I still have questions?**

1310 If you have any questions, or problems, always talk first with your doctor. You can also visit the  
1311 REMICADE internet site at [www.remicade.com](http://www.remicade.com).

1312

1313 Product developed and manufactured by:

1314 Centocor, Inc.

1315 200 Great Valley Parkway

1316 Malvern, PA 19355

1317

1318 Revised September 2005

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