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November 10, 2006

1  
2 **REMICADE®**  
3 **(infliximab)**  
4 **for IV Injection**  
5

6 **WARNINGS**  
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8 **RISK OF INFECTIONS**  
9

10 **Patients treated with REMICADE are at increased risk for infections, including**  
11 **progression to serious infections leading to hospitalization or death (see WARNINGS and**  
12 **ADVERSE REACTIONS). These infections have included bacterial sepsis, tuberculosis,**  
13 **invasive fungal and other opportunistic infections. Patients should be educated about the**  
14 **symptoms of infection, closely monitored for signs and symptoms of infection during and**  
15 **after treatment with REMICADE, and should have access to appropriate medical care.**  
16 **Patients who develop an infection should be evaluated for appropriate antimicrobial**  
17 **therapy and for serious infections REMICADE should be discontinued.**

18  
19 **Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been**  
20 **observed in patients receiving REMICADE. Patients should be evaluated for tuberculosis**  
21 **risk factors and be tested for latent tuberculosis infection<sup>1,2</sup> prior to initiating REMICADE**  
22 **and during therapy. Treatment of latent tuberculosis infection should be initiated prior to**  
23 **therapy with REMICADE. Treatment of latent tuberculosis in patients with a reactive**  
24 **tuberculin test reduces the risk of tuberculosis reactivation in patients receiving**  
25 **REMICADE. Some patients who tested negative for latent tuberculosis prior to receiving**  
26 **REMICADE have developed active tuberculosis. Physicians should monitor patients**  
27 **receiving REMICADE for signs and symptoms of active tuberculosis, including patients**  
28 **who tested negative for latent tuberculosis infection.**

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31 **HEPATOSPLENIC T-CELL LYMPHOMAS**  
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33 **Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in**  
34 **adolescent and young adult patients with Crohn's disease treated with REMICADE. This**  
35 **rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All**  
36 **of these hepatosplenic T-cell lymphomas with REMICADE have occurred in patients on**  
37 **concomitant treatment with azathioprine or 6-mercaptopurine.**  
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41 **DESCRIPTION**

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43 REMICADE is a chimeric IgG1 $\kappa$  monoclonal antibody with an approximate molecular weight of  
44 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab  
45 binds specifically to human tumor necrosis factor alpha (TNF $\alpha$ ) with an association constant of  
46  $10^{10} \text{ M}^{-1}$ . Infliximab is produced by a recombinant cell line cultured by continuous perfusion and  
47 is purified by a series of steps that includes measures to inactivate and remove viruses.

48  
49 REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion.  
50 Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is  
51 approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg  
52 polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium  
53 phosphate, dihydrate. No preservatives are present.

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55 **CLINICAL PHARMACOLOGY**

56  
57 **General**

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59 Infliximab neutralizes the biological activity of TNF $\alpha$  by binding with high affinity to the  
60 soluble and transmembrane forms of TNF $\alpha$  and inhibits binding of TNF $\alpha$  with its receptors.<sup>3,4</sup>  
61 Infliximab does not neutralize TNF $\beta$  (lymphotoxin  $\alpha$ ), a related cytokine that utilizes the same  
62 receptors as TNF $\alpha$ . Biological activities attributed to TNF $\alpha$  include: induction of pro-  
63 inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration  
64 by increasing endothelial layer permeability and expression of adhesion molecules by endothelial  
65 cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of  
66 acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by  
67 synoviocytes and/or chondrocytes. Cells expressing transmembrane TNF $\alpha$  bound by infliximab  
68 can be lysed *in vitro*<sup>4</sup> or *in vivo*.<sup>5</sup> Infliximab inhibits the functional activity of TNF $\alpha$  in a wide  
69 variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T  
70 lymphocytes and epithelial cells. The relationship of these biological response markers to the  
71 mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNF $\alpha$   
72 antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis  
73 and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease  
74 in transgenic mice that develop polyarthritis as a result of constitutive expression of human  
75 TNF $\alpha$ , and when administered after disease onset, allows eroded joints to heal.

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77 **Pharmacodynamics**

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

98

99 **Pharmacokinetics**

100

101 In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship  
102 between the dose administered and the maximum serum concentration. The volume of  
103 distribution at steady state was independent of dose and indicated that infliximab was distributed  
104 primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg  
105 to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in  
106 plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

107

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

118

119 Infliximab peak and trough concentrations were similar in pediatric (aged 6 to 17 years old) and  
120 adult patients with Crohn's disease following the administration of the recommended regimen  
121 (see DOSAGE AND ADMINISTRATION, Crohn's Disease or Fistulizing Crohn's Disease).

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## CLINICAL STUDIES

### Rheumatoid Arthritis

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

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

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

Data on use of REMICADE without concurrent MTX are limited (see ADVERSE REACTIONS, Immunogenicity).<sup>6,7</sup>

#### *Clinical response*

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

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

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

Response	Study RA I				Study RA II			
	REMICADE + MTX							
	3 mg/kg		10 mg/kg		3 mg/kg		6 mg/kg	
Placebo + MTX (n=88)	q 8 wks (n=86)	q 4 wks (n=86)	q 8 wks (n=87)	q 4 wks (n=81)	Placebo + MTX (n=274)	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	
Week 54	17%	42% <sup>a</sup>	48% <sup>a</sup>	59% <sup>a</sup>	59% <sup>a</sup>	54%	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	
Week 54	9%	21% <sup>c</sup>	34% <sup>a</sup>	40% <sup>a</sup>	38% <sup>a</sup>	32%	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	
Week 54	2%	11% <sup>c</sup>	18% <sup>a</sup>	26% <sup>a</sup>	19% <sup>a</sup>	21%	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%	17% <sup>a</sup>	

<sup>#</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 ≤ 0.0001

<sup>b</sup> p < 0.01

<sup>c</sup> p < 0.05

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**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)

164

165 *Radiographic response*

166

167 Structural damage in both hands and feet was assessed radiographically at week 54 by the  
 168 change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of  
 169 structural damage that measures the number and size of joint erosions and the degree of joint  
 170 space narrowing in hands/wrists and feet.<sup>8</sup>

171

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

175

176 In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of  
 177 structural damage was observed at weeks 30 and 54 (Table 3) in the REMICADE + MTX groups  
 178 compared to MTX alone. Patients treated with REMICADE + MTX demonstrated less  
 179 progression of structural damage compared to MTX alone, whether baseline acute phase  
 180 reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute phase  
 181 reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units  
 182 compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of  
 183 progression; patients with normal baseline acute phase reactants treated with MTX alone  
 184 demonstrated a mean progression in vdH-S score of 1.8 units compared to REMICADE + MTX

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185 who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had  
 186 no progression (vdH-S score  $\leq 0$  unit) of structural damage compared to 45% patients receiving  
 187 MTX alone. In a subset of patients who began the study without erosions, REMICADE + MTX  
 188 maintained an erosion free state at 1 year in a greater proportion of patients than MTX alone,  
 189 79% (77/98) vs. 58% (23/40), respectively ( $p < 0.01$ ). Fewer patients in the REMICADE + MTX  
 190 groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).  
 191

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

	Study RA I			Study RA II		
	Placebo + MTX (n=64)	REMICADE + MTX		Placebo + MTX (n=282)	REMICADE + MTX	
		3 mg/kg q 8 wks (n=71)	10 mg/kg q 8 wks (n=77)		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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193 *Physical function response*

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

197

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

206

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

211

212 **Active Crohn's Disease**

213

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

220

221 In the single-dose trial<sup>9</sup> of 108 patients, 16% (4/25) of placebo patients achieved a clinical  
222 response (decrease in CDAI  $\geq 70$  points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg  
223 REMICADE ( $p < 0.001$ , two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo  
224 patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission  
225 (CDAI  $< 150$ ) at week 4.

226

227 In a multidose trial (ACCENT I [Study Crohn's I])<sup>10</sup>, 545 patients received 5 mg/kg at week 0  
228 and were then randomized to one of three treatment groups; the placebo maintenance group  
229 received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group  
230 received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance  
231 group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in  
232 response at week 2 were randomized and analyzed separately from those not in response at week  
233 2. Corticosteroid taper was permitted after week 6.

234

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

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

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

	Single 5 mg/kg Dose <sup>a</sup>	Three Dose Induction <sup>b</sup> REMICADE Maintenance q 8	
	<u>Placebo Maintenance</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

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

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

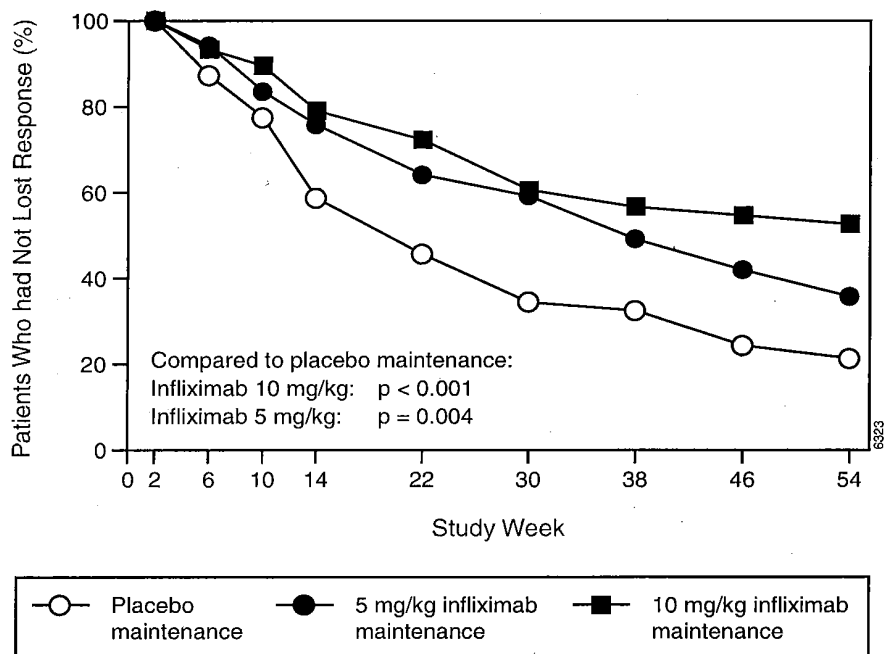
<sup>c</sup> p-values represent pairwise comparisons to placebo

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

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

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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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283 In the first trial,<sup>11</sup> 94 patients received three doses of either placebo or REMICADE at weeks 0,  
284 2 and 6. Fistula response ( $\geq 50\%$  reduction in number of enterocutaneous fistulas draining upon  
285 gentle compression on at least two consecutive visits without an increase in medication or  
286 surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE  
287 group ( $p=0.002$ ) and 56% (18/32) of patients in the 10 mg/kg REMICADE group ( $p=0.021$ ) vs.  
288 26% (8/31) of patients in the placebo arm. The median time to onset of response and median  
289 duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure  
290 of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of  
291 placebo-treated patients ( $p<0.001$ ).

292

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

301

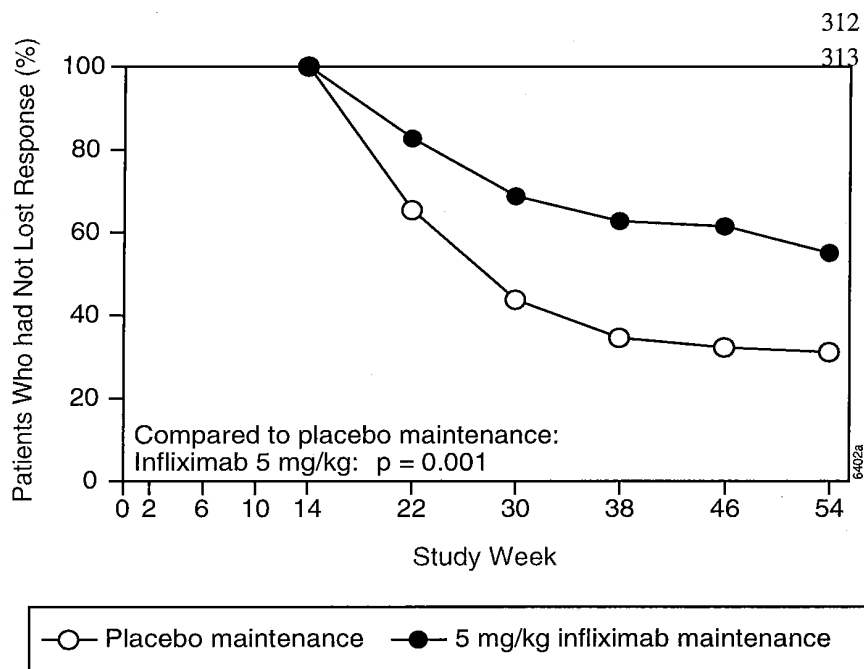
302 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and  
303 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of  
304 the patients had received previous immunosuppressive and antibiotic therapy.

305

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

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

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

324  
325 Patients who had not achieved a response by week 14 were unlikely to respond to additional  
326 doses of REMICADE.

327  
328 Similar proportions of patients in either group developed new fistulas (17% overall) and similar  
329 numbers developed abscesses (15% overall).

### 330 331 **Active Crohn's Disease in Pediatric Patients**

332  
333 The safety and efficacy of REMICADE were assessed in a randomized, open-label study (Study  
334 Peds Crohn's) in 112 pediatric patients 6 to 17 years old with moderately to severely active  
335 Crohn's disease and an inadequate response to conventional therapies. The median age was 13  
336 years and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0  
337 to 100). All patients were required to be on a stable dose of 6-mercaptopurine, azathioprine, or  
338 methotrexate; 35% were also receiving corticosteroids at baseline.

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340 All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. At Week  
341 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given  
342 either every 8 weeks or every 12 weeks.

343

344 At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in  
345 the PCDAI score of  $\geq 15$  points and total PCDAI score of  $\leq 30$  points), and 59% were in clinical  
346 remission (defined as PCDAI score of  $\leq 10$  points).

347

348 The proportion of pediatric patients achieving clinical response at Week 10 compared favorably  
349 with the proportion of adults achieving a clinical response in Study Crohn's I. The study  
350 definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas  
351 the CDAI score was used in the adult Study Crohn's I.

352

353 At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the  
354 every 8 week treatment group than in the every 12 week treatment group (73% vs. 47% at Week  
355 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in  
356 clinical remission was also greater in the every 8 week treatment group than in the every  
357 12 week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), (Table 5).

358

359 For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of  
360 patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every  
361 8-week maintenance group and 33% for the every 12 week maintenance group. At Week 54, the  
362 proportion of patients able to discontinue corticosteroids while in remission was 46% for the  
363 every 8 week maintenance group and 17% for the every 12 week maintenance group.

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**Table 5**  
**RESPONSE AND REMISSION IN STUDY PEDS CROHN'S**

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	5 mg/kg REMICADE	
	Every 8 Week Treatment Group	Every 12 Week Treatment Group
Patients randomized	52	51
Clinical Response <sup>1</sup>		
Week 30	73%**	47%
Week 54	64%**	33%
Clinical Remission <sup>2</sup>		
Week 30	60%*	35%
Week 54	56%**	24%

<sup>1</sup>Defined as a decrease from baseline in the PCDAI score of  $\geq 15$  points and total score of  $\leq 30$  points.

<sup>2</sup>Defined as a PCDAI score of  $\leq 10$  points.

\* p-value < 0.05

\*\*p-value < 0.01

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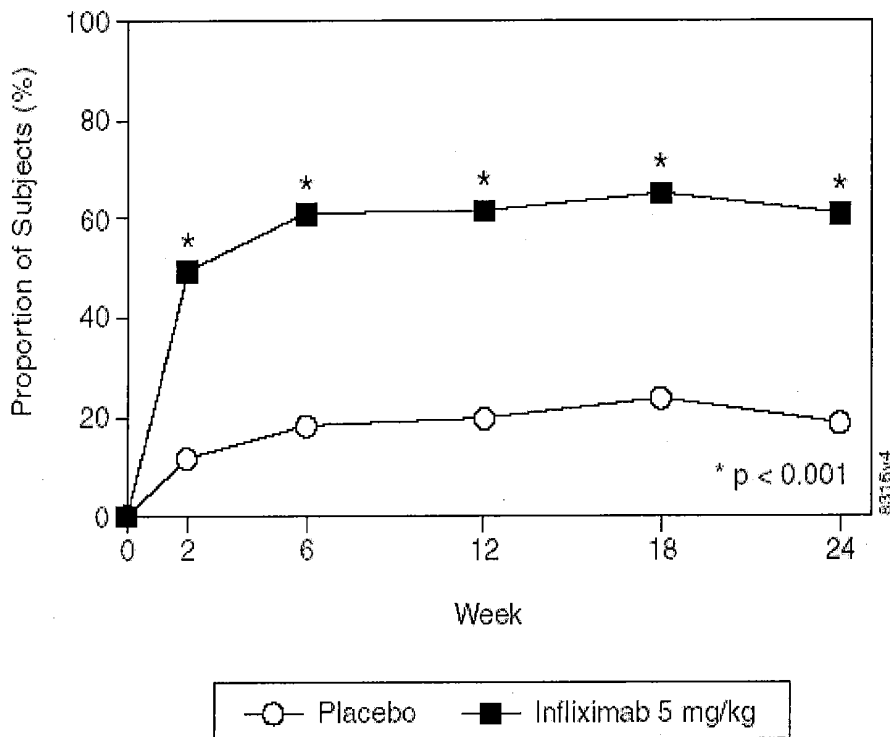
390 **Ankylosing Spondylitis**

391

392 The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-  
393 blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were  
394 between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New  
395 York criteria for Ankylosing Spondylitis.<sup>12</sup> Patients were to have had active disease as  
396 evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4  
397 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients  
398 with complete ankylosis of the spine were excluded from study participation, and the use of  
399 Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were  
400 prohibited. Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks  
401 0, 2, 6, 12 and 18.

402

403 At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by  
404 the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20),  
405 was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo  
406 group (p<0.001). Improvement was observed at week 2 and maintained through week 24  
407 (Figure 3 and Table 6).



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

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At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE, compared to 9% and 4%, respectively, for patients receiving placebo ( $p < 0.001$ , REMICADE vs. placebo). A low level of disease activity (defined as a value  $< 20$  [on a scale of 0-100 mm] in each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated patients vs. 1% in placebo-treated patients ( $p < 0.001$ ).

**Table 6**  
**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

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

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

**Psoriatic Arthritis**

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435 Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-  
436 controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID  
437 therapy ( $\geq 5$  swollen joints and  $\geq 5$  tender joints) with one or more of the following subtypes:  
438 arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis  
439 (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients  
440 also had plaque psoriasis with a qualifying target lesion  $\geq 2$  cm in diameter. Forty-six percent of  
441 patients continued on stable doses of methotrexate ( $\leq 25$  mg/week). During the 24-week double-  
442 blind phase, patients received either 5 mg/kg REMICADE or placebo at weeks 0, 2, 6, 14, and 22  
443 (100 patients in each group). At week 16, placebo patients with  $< 10\%$  improvement from  
444 baseline in both swollen and tender joint counts were switched to REMICADE induction (early  
445 escape). At week 24, all placebo-treated patients crossed over to REMICADE induction.  
446 Dosing continued for all patients through week 46.

447

#### 448 *Clinical response*

449

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

459

460 Compared to placebo, treatment with REMICADE resulted in improvements in the components  
461 of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 7). The clinical  
462 response was maintained through week 54. Similar ACR responses were observed in an earlier  
463 randomized, placebo-controlled study of 104 psoriatic arthritis patients, and the responses were  
464 maintained through 98 weeks in an open label extension phase.

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**Table 7**  
**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**

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

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

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

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

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

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

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

467

468

469 Improvement in Psoriasis Area and Severity Index (PASI) in psoriatic arthritis patients with  
470 baseline body surface area (BSA)  $\geq$  3% (n=87 placebo, n=83 REMICADE) was achieved at  
471 week 14, regardless of concomitant methotrexate use, with 64% of REMICADE-treated patients  
472 achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients;  
473 improvement was observed in some patients as early as week 2. At 6 months, the PASI 75 and  
474 PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving  
475 REMICADE compared to 1% and 0%, respectively, of patients receiving placebo. The PASI  
476 response was generally maintained through week 54. See also CLINICAL STUDIES: Plaque  
477 Psoriasis section below.

478

479 *Radiographic response*

480

481 Structural damage in both hands and feet was assessed radiographically by the change from  
482 baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints.

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483 The total modified vdH-S score is a composite score of structural damage that measures the  
484 number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and  
485 feet. At Week 24, REMICADE-treated patients had less radiographic progression than placebo-  
486 treated patients (mean change of -0.70 vs. 0.82,  $p < 0.001$ ). REMICADE-treated patients also had  
487 less progression in their erosion scores (-0.56 vs. 0.51) and JSN scores (-0.14 vs. 0.31). The  
488 patients in the REMICADE group demonstrated continued inhibition of structural damage at  
489 week 54. Most patients showed little or no change in the vdH-S score during this 12-month  
490 study (median change of 0 in both patients who initially received REMICADE or placebo).  
491 More patients in the placebo group (12%) had readily apparent radiographic progression  
492 compared with the REMICADE group (3%).

493

#### 494 *Physical function*

495

496 Physical function status was assessed using the HAQ Disability Index (HAQ-DI) and the SF-36  
497 Health Survey. REMICADE-treated patients demonstrated significant improvement in physical  
498 function as assessed by HAQ-DI (median percent improvement in HAQ-DI score from baseline  
499 to week 14 and 24 of 43% for REMICADE-treated patients vs. 0% for placebo-treated patients).

500

501 During the placebo-controlled portion of the trial (24 weeks), 54% of REMICADE-treated  
502 patients achieved a clinically meaningful improvement in HAQ-DI ( $\geq 0.3$  unit decrease)  
503 compared to 22% of placebo-treated patients. REMICADE-treated patients also demonstrated  
504 greater improvement in the SF-36 physical and mental component summary scores than placebo-  
505 treated patients. The responses were maintained for up to 2 years in an open label extension  
506 study.

507

#### 508 **Plaque Psoriasis**

509

510 The safety and efficacy of REMICADE were assessed in three randomized, double-blind,  
511 placebo-controlled studies in patients 18 years of age and older with chronic, stable plaque  
512 psoriasis involving  $\geq 10\%$  BSA, a minimum PASI score of 12, and who were candidates for  
513 systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis  
514 were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during  
515 the study, with the exception of low-potency topical corticosteroids on the face and groin after  
516 week 10 of study initiation.

517

518 Study I (EXPRESS) evaluated 378 patients who received placebo or REMICADE at a dose of 5  
519 mg/kg at weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks.  
520 At week 24, the placebo group crossed over to REMICADE induction therapy (5 mg/kg),  
521 followed by maintenance therapy every 8 weeks. Patients originally randomized to REMICADE  
522 continued to receive REMICADE 5 mg/kg every 8 weeks through week 46. Across all treatment  
523 groups, the median baseline PASI score was 21 and the baseline Static Physician Global  
524 Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe  
525 (2%). In addition, 75% of patients had a BSA  $>20\%$ . Seventy-one percent of patients  
526 previously received systemic therapy and 82% received phototherapy.

527

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528 Study II (EXPRESS II) evaluated 835 patients who received placebo or REMICADE at doses of  
529 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At week 14, within each  
530 REMICADE dose group, patients were randomized to either scheduled (every 8 weeks) or as  
531 needed (PRN) maintenance treatment through week 46. At week 16, the placebo group crossed  
532 over to REMICADE induction therapy (5 mg/kg), followed by maintenance therapy every 8  
533 weeks. Across all treatment groups, the median baseline PASI score was 18 and 63% of patients  
534 had a BSA >20%. Fifty-five percent of patients previously received systemic therapy and 64%  
535 received a phototherapy.

536  
537 Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus  
538 ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients  
539 were randomized to receive either placebo or REMICADE at doses of 3 mg/kg or 5 mg/kg at  
540 weeks 0, 2, and 6. At week 26, patients with a sPGA score of moderate or worse (greater than or  
541 equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across  
542 all treatment groups, the median baseline PASI score was 19 and the baseline sPGA score ranged  
543 from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients  
544 had a BSA >20%. Of the enrolled patients 114 (46%) received the week 26 additional dose.

545  
546 In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a  
547 reduction in score of at least 75% from baseline at week 10 by the PASI (PASI 75). In Study I  
548 and Study III, another evaluated outcome included the proportion of patients who achieved a  
549 score of "cleared" or "minimal" by the sPGA. The sPGA is a 6 category scale ranging from  
550 "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis  
551 severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared"  
552 or "minimal", consisted of none or minimal elevation in plaque, up to faint red coloration in  
553 erythema, and none or minimal fine scale over < 5% of the plaque.

554  
555 Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent"  
556 by the relative Physician's Global Assessment (rPGA). The rPGA is a 6 category scale ranging  
557 from "6 = worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were  
558 graded with consideration to the percent of body involvement as well as overall induration,  
559 scaling, and erythema. Treatment success, defined as "clear" or "excellent", consisted of some  
560 residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some  
561 erythema may be present). The results of these studies are presented in Table 8.

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**TABLE 8**  
**Psoriasis Studies I, II, and III, Week 10 Percentage of Patients Who Achieved PASI 75 and Percentage Who Achieved Treatment “Success” with Physician’s Global Assessment**

	Placebo	REMICADE	
		3 mg/kg	5 mg/kg
Psoriasis Study I - patients randomized <sup>a</sup>	77	---	301
PASI 75	2 (3%)	---	242 (80%)*
sPGA	3 (4%)	---	242 (80%)*
Psoriasis Study II - patients randomized <sup>a</sup>	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*
Psoriasis Study III - patients randomized <sup>b</sup>	51	99	99
PASI 75	3 (6%)	71 (72%)*	87 (88%)*
sPGA	5 (10%)	71 (72%)*	89 (90%)*

\* p<0.001 compared with placebo

a Patients with missing data at week 10 were considered as nonresponders.

b Patients with missing data at week 10 were imputed by last observation.

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In Study I, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 85% of patients on 5 mg/kg REMICADE achieved a PASI 75 at week 10 compared with 4% of patients on placebo.

In Study II, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg REMICADE achieved a PASI 75 at week 10 respectively compared with 1% on placebo. In Study II, among patients with more extensive psoriasis who had failed or were intolerant to phototherapy, 70% and 78% of patients on 3 mg/kg and 5 mg/kg REMICADE achieved a PASI 75 at week 10 respectively, compared with 2% on placebo.

Maintenance of response was studied in a subset of 292 and 297 REMICADE treated patients in the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at week 10 and investigational site, patients in the active treatment groups were re-randomized to either a scheduled or as needed maintenance (PRN) therapy, beginning on week 14.

The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through week 50 as compared to patients who received the as needed or PRN doses and the best response was maintained with the 5 mg/kg every 8 week dose. These results are shown in Figure 4. At week 46, when REMICADE serum concentrations were at trough level, in the every 8 week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in

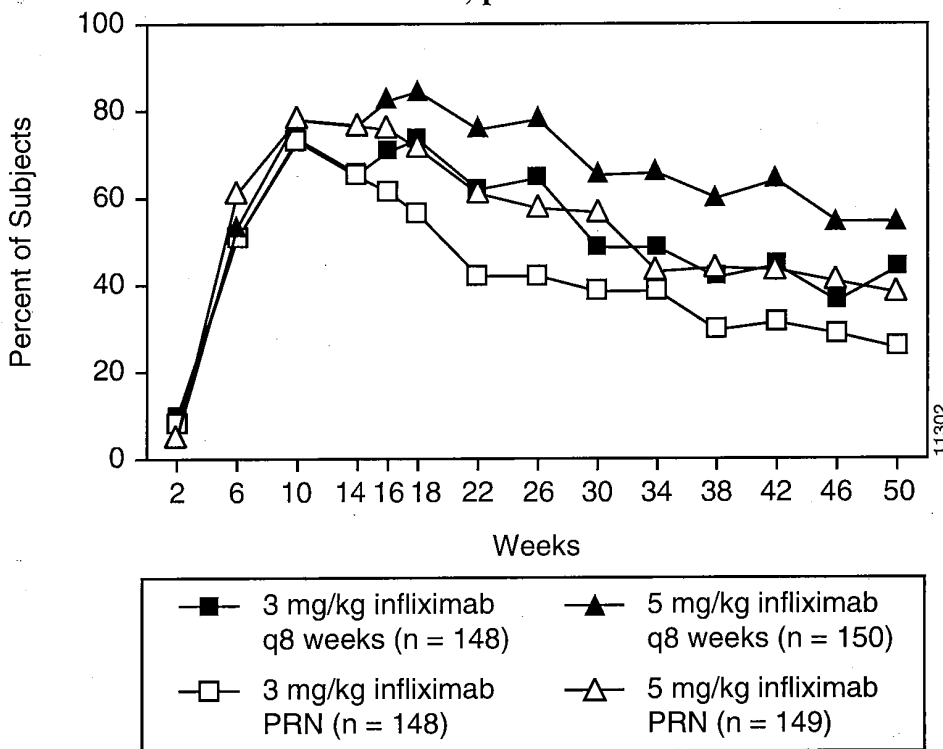
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589 the 3mg/kg every 8 week dose group compared to the 5mg/kg group was associated with a lower  
 590 percentage of patients with detectable trough serum infliximab levels. This may be related in  
 591 part to higher antibody rates (see ADVERSE REACTIONS: Immunogenicity). In addition, in a  
 592 subset of patients who had achieved a response at week 10, maintenance of response appears to  
 593 be greater in patients who received REMICADE every 8 weeks at the 5 mg/kg dose. Regardless  
 594 of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a  
 595 subpopulation of patients in each group over time. The results of Study I through Week 50 in the  
 596 5mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

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**Figure 4**  
**Proportion of patients achieving  $\geq 75\%$  improvement in PASI from baseline through Week 50; patients randomized at Week 14**



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Efficacy and safety of REMICADE treatment beyond 50 weeks have not been evaluated in patients with plaque psoriasis.

**Ulcerative Colitis**

609 The safety and efficacy of REMICADE were assessed in two randomized, double-blind,  
 610 placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative  
 611 colitis (UC) (Mayo score<sup>13</sup> 6 to 12 [of possible range 0-12], Endoscopy subscore  $\geq 2$ ) with an  
 612 inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant  
 613 treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory

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614 agents was permitted. Corticosteroid taper was permitted after week 8. Patients were  
615 randomized at week 0 to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE  
616 at weeks 0, 2, 6, and every 8 weeks thereafter through week 46 in Study UC I, and at weeks 0, 2,  
617 6, and every 8 weeks thereafter through week 22 in Study UC II. In Study UC II, patients were  
618 allowed to continue blinded therapy to week 46 at the investigator's discretion.

619

620 Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-  
621 mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or  
622 were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients  
623 in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-  
624 MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More  
625 patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%,  
626 respectively). Clinical response was defined as a decrease from baseline in the Mayo score by  $\geq$   
627 30% and  $\geq$  3 points, accompanied by a decrease in the rectal bleeding subscore of  $\geq$  1 or a rectal  
628 bleeding subscore of 0 or 1.

629

630 *Clinical Response, Clinical Remission, and Mucosal Healing*

631

632 In both Study UC I and Study UC II, greater percentages of patients in both REMICADE groups  
633 achieved clinical response, clinical remission and mucosal healing than in the placebo group.  
634 Each of these effects was maintained through the end of each trial (week 54 in Study UC I, and  
635 week 30 in Study UC II). In addition, a greater proportion of patients in REMICADE groups  
636 demonstrated sustained response and sustained remission than in the placebo groups (Table 9).

637

638 Of patients on corticosteroids at baseline, greater proportions of patients in the REMICADE  
639 treatment groups were in clinical remission and able to discontinue corticosteroids at week 30  
640 compared with the patients in the placebo treatment groups (22% in REMICADE treatment  
641 groups vs. 10% in placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in  
642 placebo group in Study UC II). In Study UC I, this effect was maintained through week 54 (21%  
643 in REMICADE treatment groups vs. 9% in placebo group). The REMICADE-associated  
644 response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

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**Table 9**  
**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
<b>Clinical Response<sup>1, 4</sup></b>						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
Week 54	20%	45%*	44%*	NA	NA	NA
<b>Sustained Response<sup>4</sup></b>						
(Clinical response at both Week 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
(Clinical response at Weeks 8, 30, and 54)	14%	39%*	37%*	NA	NA	NA
<b>Clinical Remission<sup>2, 4</sup></b>						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%**	37%*	11%	26%**	36%*
Week 54	17%	35%**	34%**	NA	NA	NA
<b>Sustained Remission<sup>4</sup></b>						
(Clinical remission at both Week 8 and 30)	8%	23%**	26%*	2%	15%*	23%*

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(Clinical remission at Weeks 8, 30 and 54)	7%	20%**	20%**	NA	NA	NA
<hr/>						
Mucosal Healing <sup>3,4</sup>						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%**	57%*
Week 54	18%	45%*	47%*	NA	NA	NA

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

<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.)

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

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

<sup>4</sup> Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

The improvement with REMICADE was consistent across all Mayo subscores through week 54 (Study UC I shown in Table 10; Study UC II through week 30 was similar).

**Table 10**  
**Proportion of patients in Study UC I with Mayo subscores indicating inactive or mild disease through week 54**

	Study UC I		
	Placebo (n=121)	5 mg/kg (n=121)	10 mg/kg (n=122)
Stool frequency			
Baseline	17%	17%	10%
Week 8	35%	60%	58%
Week 30	35%	51%	53%
Week 54	31%	52%	51%
Rectal bleeding			
Baseline	54%	40%	48%
Week 8	74%	86%	80%
Week 30	65%	74%	71%
Week 54	62%	69%	67%
Physician's global assessment			
Baseline	4%	6%	3%

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Week 8	44%	74%	64%
Week 30	36%	57%	55%
Week 54	26%	53%	53%
Endoscopy findings			
Baseline	0%	0%	0%
Week 8	34%	62%	59%
Week 30	26%	51%	52%
Week 54	21%	50%	51%

664

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666

## INDICATIONS AND USAGE

667

668

### Rheumatoid Arthritis

669

670

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

671

672

673

674

### Crohn's Disease

675

676

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy (see Boxed WARNINGS, WARNINGS, and PRECAUTIONS-Pediatric Use).

677

678

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681

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

682

683

684

### Ankylosing Spondylitis

685

686

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

687

688

689

### Psoriatic Arthritis

690

691

REMICADE is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

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### Plaque Psoriasis

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697 REMICADE is indicated for the treatment of adult patients with chronic severe (i.e., extensive  
698 and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other  
699 systemic therapies are medically less appropriate. REMICADE should only be administered to  
700 patients who will be closely monitored and have regular follow-up visits with a physician (See  
701 Boxed WARNINGS, WARNINGS, and PRECAUTIONS).

702

### 703 **Ulcerative Colitis**

704

705 REMICADE is indicated for reducing signs and symptoms, inducing and maintaining clinical  
706 remission and mucosal healing, and eliminating corticosteroid use in patients with moderately to  
707 severely active ulcerative colitis who have had an inadequate response to conventional therapy.

708

### 709 **CONTRAINDICATIONS**

710

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

717

718 REMICADE should not be re-administered to patients who have experienced a severe  
719 hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered  
720 to patients with known hypersensitivity to inactive components of the product or to any murine  
721 proteins.

722

### 723 **WARNINGS**

724

#### 725 **RISK OF INFECTIONS**

726 (See Boxed WARNINGS)

727

728 **Serious infections, including sepsis and pneumonia, have been reported in patients**  
729 **receiving TNF-blocking agents. Some of these infections have been fatal. Although some of**  
730 **the serious infections in patients treated with REMICADE have occurred in patients on**  
731 **concomitant immunosuppressive therapy which in addition to their underlying disease,**  
732 **could further predispose them to infections, some patients who were hospitalized or had a**  
733 **fatal outcome from infection were treated with REMICADE alone.**

734

735 **REMICADE should not be given to patients with a clinically important, active infection.**  
736 **Caution should be exercised when considering the use of REMICADE in patients with a**  
737 **chronic infection or a history of recurrent infection. Patients should be monitored for signs**  
738 **and symptoms of infection while on or after treatment with REMICADE. New infections**  
739 **should be closely monitored. If a patient develops a serious infection, REMICADE therapy**  
740 **should be discontinued (see ADVERSE REACTIONS: Infections).**

741

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742 **Cases of tuberculosis, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystosis, other**  
743 **bacterial, mycobacterial and fungal infections have been observed in patients receiving**  
744 **REMICADE. Patients should be evaluated for tuberculosis risk factors and be tested for**  
745 **latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated**  
746 **prior to therapy with REMICADE. When tuberculin skin testing is performed for latent**  
747 **tuberculosis infection an induration size of 5 mm or greater should be considered positive,**  
748 **even if vaccinated previously with Bacille Calmette-Guerin (BCG).**

749  
750 **Patients receiving REMICADE should be monitored closely for signs and symptoms of**  
751 **active tuberculosis, particularly since tests for latent tuberculosis infection may be falsely**  
752 **negative. The possibility of undetected latent tuberculosis should be considered, especially**  
753 **in patients who have immigrated from or traveled to countries with a high prevalence of**  
754 **tuberculosis or had close contact with a person with active tuberculosis. All patients**  
755 **treated with REMICADE should have a thorough history taken prior to initiating therapy.**  
756 **Some patients who have previously received treatment for latent or active tuberculosis**  
757 **have developed active tuberculosis while being treated with REMICADE. Anti-**  
758 **tuberculosis therapy should be considered prior to initiation of REMICADE in patients**  
759 **with a past history of latent or active tuberculosis in whom an adequate course of**  
760 **treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating REMICADE**  
761 **should also be considered in patients who have several or highly significant risk factors for**  
762 **tuberculosis infection<sup>14</sup> and have a negative test for latent tuberculosis. The decision to**  
763 **initiate anti-tuberculosis therapy in these patients should only be made following**  
764 **consultation with a physician with expertise in the treatment of tuberculosis and taking**  
765 **into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis**  
766 **therapy.**

767  
768 **For patients who have resided in regions where histoplasmosis or coccidioidomycosis is**  
769 **endemic, the benefits and risks of REMICADE treatment should be carefully considered**  
770 **before initiation of REMICADE therapy.**

771  
772 **Serious infections were seen in clinical studies with concurrent use of anakinra and another**  
773 **TNF $\alpha$ -blocking agent, etanercept, with no added clinical benefit compared to etanercept alone.**  
774 **Because of the nature of the adverse events seen with combination of etanercept and anakinra**  
775 **therapy, similar toxicities may also result from the combination of anakinra and other TNF $\alpha$ -**  
776 **blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended.**

777

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778 **HEPATOSPLENIC T-CELL LYMPHOMAS**  
779 **(See Boxed WARNINGS)**

780

781 **Rare postmarketing cases of hepatosplenic T-cell lymphomas have been reported in**  
782 **adolescent and young adult patients with Crohn's disease treated with REMICADE. All of**  
783 **these reports have occurred in patients on concomitant treatment with azathioprine or 6-**  
784 **mercaptopurine. The clinical course of this disease is very aggressive with a fatal outcome**  
785 **in most patients within 2 years of diagnosis.<sup>15</sup> The causal relationship of hepatosplenic T-**  
786 **cell lymphoma to REMICADE therapy remains unclear.**

787

788 **Hepatitis B Virus Reactivation**

789

790 Use of TNF blockers, including REMICADE has been associated with reactivation of  
791 hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances,  
792 HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The  
793 majority of these reports have occurred in patients concomitantly receiving other medications  
794 that suppress the immune system, which may also contribute to HBV reactivation. Patients at  
795 risk for HBV infection should be evaluated for prior evidence of HBV infection before  
796 initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF  
797 blockers, including REMICADE, for patients identified as carriers of HBV. Adequate data  
798 are not available on the safety or efficacy of treating patients who are carriers of HBV with  
799 anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation.  
800 Patients who are carriers of HBV and require treatment with TNF blockers should be closely  
801 monitored for clinical and laboratory signs of active HBV infection throughout therapy and  
802 for several months following termination of therapy. In patients who develop HBV  
803 reactivation, TNF blockers should be stopped and antiviral therapy with appropriate  
804 supportive treatment should be initiated. The safety of resuming TNF blocker therapy after  
805 HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution  
806 when considering resumption of TNF blocker therapy in this situation and monitor patients  
807 closely.

808

809 **Hepatotoxicity**

810

811 Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have  
812 been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune  
813 hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between  
814 two weeks to more than a year after initiation of REMICADE; elevations in hepatic  
815 aminotransferase levels were not noted prior to discovery of the liver injury in many of these  
816 cases. Some of these cases were fatal or necessitated liver transplantation. Patients with  
817 symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If  
818 jaundice and/or marked liver enzyme elevations (e.g.,  $\geq 5$  times the upper limit of normal)  
819 develops, REMICADE should be discontinued, and a thorough investigation of the abnormality  
820 should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been  
821 observed in patients receiving REMICADE without progression to severe hepatic injury (see  
822 ADVERSE REACTIONS, Hepatotoxicity).

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823

### 824 **Patients with Heart Failure**

825

826 REMICADE has been associated with adverse outcomes in patients with heart failure, and  
827 should be used in patients with heart failure only after consideration of other treatment options.  
828 The results of a randomized study evaluating the use of REMICADE in patients with heart  
829 failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10  
830 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and  
831 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without  
832 identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-  
833 marketing reports of new onset heart failure, including heart failure in patients without known  
834 pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a  
835 decision is made to administer REMICADE to patients with heart failure, they should be closely  
836 monitored during therapy, and REMICADE should be discontinued if new or worsening  
837 symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE  
838 REACTIONS, Patients with Heart Failure).

839

### 840 **Hematologic Events**

841

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

850

### 851 **Hypersensitivity**

852

853 REMICADE has been associated with hypersensitivity reactions that vary in their time of onset  
854 and required hospitalization in some cases. Most hypersensitivity reactions, which include  
855 urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE  
856 infusion.

857

858 However, in some cases, serum sickness-like reactions have been observed in patients after  
859 initial REMICADE therapy (i.e., as early as after the second dose), and when REMICADE  
860 therapy was reinstated following an extended period without REMICADE treatment.  
861 Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias,  
862 polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with  
863 marked increase in antibodies to infliximab, loss of detectable serum concentrations of  
864 infliximab, and possible loss of drug efficacy.

865

866 REMICADE should be discontinued for severe hypersensitivity reactions (see also  
867 CONTRAINDICATIONS). Medications for the treatment of hypersensitivity reactions (e.g.,

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868 acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for  
869 immediate use in the event of a reaction (see ADVERSE REACTIONS: Infusion-related  
870 Reactions).

871

## 872 **Neurologic Events**

873

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

881

## 882 **Malignancies**

883

884 In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE,  
885 more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been  
886 observed in patients receiving those TNF-blockers compared with control patients. During the  
887 controlled portions of REMICADE trials in patients with moderately to severely active  
888 rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis,  
889 and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and  
890 NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of  
891 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years  
892 among control patients), with median duration of follow-up 0.5 years for REMICADE-treated  
893 patients and 0.4 years for control patients. Of these, the most common malignancies were breast,  
894 colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was  
895 similar to that expected in the general population whereas the rate in control patients was lower  
896 than expected.

897

898 In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of  
899 lymphoma have been observed among patients receiving a TNF blocker compared with control  
900 patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients  
901 developed lymphomas among 5707 patients treated with REMICADE (median duration of  
902 follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4  
903 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per  
904 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the  
905 general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's  
906 disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5  
907 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is  
908 approximately 4-fold higher than expected in the general population. Patients with Crohn's  
909 disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease  
910 and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several  
911 fold) than the general population for the development of lymphoma, even in the absence of TNF-  
912 blocking therapy.

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913

914 In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic  
915 obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and  
916 neck origin, were reported in REMICADE-treated patients compared with control patients. All  
917 patients had a history of heavy smoking (see ADVERSE REACTIONS, Malignancies).  
918 Prescribers should exercise caution when considering the use of REMICADE in patients with  
919 moderate to severe COPD.

920

921 Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly  
922 those patients who have had prior prolonged phototherapy treatment. In the maintenance portion  
923 of clinical trials for REMICADE, NMSCs were more common in patients with previous  
924 phototherapy (see ADVERSE REACTIONS: Adverse Reactions in Psoriasis Studies).

925

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

932

## 933 **PRECAUTIONS**

934

### 935 **Autoimmunity**

936

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

941

### 942 **Vaccinations**

943

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

947

948 It is recommended that all pediatric Crohn's disease patients be brought up to date with all  
949 vaccinations prior to initiating REMICADE therapy. The interval between vaccination and  
950 initiation of REMICADE therapy should be in accordance with current vaccination guidelines.

951

### 952 **Information for Patients**

953

954 **Patients developing signs and symptoms of infection should seek medical evaluation**  
955 **immediately.**

956

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957 Patients or their caregivers should be provided the REMICADE Medication Guide and provided  
958 an opportunity to read it and ask questions prior to each treatment infusion session. Because  
959 caution should be exercised in administering REMICADE to patients with clinically important  
960 active infections, it is important that the patient's overall health be assessed at each treatment  
961 visit and any questions resulting from the patient's or caregiver's reading of the Medication  
962 Guide be discussed.

963

#### 964 **Drug Interactions**

965

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

972

973 Specific drug interaction studies, including interactions with MTX, have not been conducted.  
974 The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one  
975 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides  
976 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.  
977 Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids,  
978 6-MP/AZA and aminosaliculates. In psoriatic arthritis clinical trials, concomitant medications  
979 included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory  
980 agents, folic acid and corticosteroids.

981

982 Patients with Crohn's disease who received immunosuppressants tended to experience fewer  
983 infusion reactions compared to patients on no immunosuppressants (see ADVERSE  
984 REACTIONS, Immunogenicity and Infusion-related Reactions). Serum infliximab  
985 concentrations appeared to be unaffected by baseline use of medications for the treatment of  
986 Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and  
987 aminosaliculates.

988

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

990

991 A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF $\alpha$  to evaluate  
992 tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNF $\alpha$  in mice.  
993 Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly  
994 for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the  
995 human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause  
996 tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the  
997 *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.  
998 Chromosomal aberrations were not observed in an assay performed using human lymphocytes.  
999 The significance of these findings for human risk is unknown. It is not known whether infliximab  
1000 can impair fertility in humans. No impairment of fertility was observed in a fertility and general

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1001 reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic  
1002 toxicity study.

1003

1004 **Pregnancy Category B**

1005

1006 Since infliximab does not cross-react with TNF $\alpha$  in species other than humans and chimpanzees,  
1007 animal reproduction studies have not been conducted with REMICADE. No evidence of  
1008 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity  
1009 study conducted in mice using an analogous antibody that selectively inhibits the functional  
1010 activity of mouse TNF $\alpha$ . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the  
1011 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to  
1012 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not  
1013 known whether REMICADE can cause fetal harm when administered to a pregnant woman or  
1014 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if  
1015 clearly needed.

1016

1017 **Nursing Mothers**

1018

1019 It is not known whether REMICADE is excreted in human milk or absorbed systemically after  
1020 ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because  
1021 of the potential for adverse reactions in nursing infants from REMICADE, women should not  
1022 breast-feed their infants while taking REMICADE. A decision should be made whether to  
1023 discontinue nursing or to discontinue the drug, taking into account the importance of the drug to  
1024 the mother.

1025

1026 **Pediatric Use**

1027

1028 REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical  
1029 remission in pediatric patients with moderately to severely active Crohn's disease who have had  
1030 an inadequate response to conventional therapy (see Boxed WARNINGS, WARNINGS,  
1031 INDICATIONS AND USAGE, PRECAUTIONS-Vaccinations, DOSAGE AND  
1032 ADMINISTRATION, CLINICAL STUDIES-Active Crohn's Disease in Pediatric Patients and  
1033 ADVERSE REACTIONS – Adverse Reactions in Pediatric Crohn's Disease).

1034

1035 REMICADE has not been studied in children with Crohn's disease < 6 years of age. The longer  
1036 term (greater than one year) safety and effectiveness of REMICADE in pediatric Crohn's disease  
1037 patients have not been established in clinical trials.

1038

1039 Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and  
1040 pediatric patients with ulcerative colitis and plaque psoriasis have not been established.

1041

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1042 **Geriatric Use**

1043

1044 In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed  
1045 in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque  
1046 psoriasis, aged 65 or older who received REMICADE, compared to younger patients although  
1047 the incidence of serious adverse events in patients aged 65 or older was higher in both  
1048 REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative  
1049 colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of  
1050 patients aged 65 and over to determine whether they respond differently from patients aged 18 to  
1051 65. Because there is a higher incidence of infections in the elderly population in general, caution  
1052 should be used in treating the elderly (see ADVERSE REACTIONS, Infections).

1053

1054 **ADVERSE REACTIONS**

1055

1056 The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients  
1057 with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis,  
1058 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17  
1059 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374  
1060 exposed beyond one year. (For information on adverse reactions in pediatric patients see  
1061 ADVERSE REACTIONS – Adverse Reactions in Pediatric Crohn's Disease.) One of the most  
1062 common reasons for discontinuation of treatment was infusion-related reactions (e.g. dyspnea,  
1063 flushing, headache and rash). Adverse events have been reported in a higher proportion of  
1064 rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no  
1065 differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10  
1066 mg/kg dose in patients with Crohn's disease.

1067

1068 **Infusion-related Reactions**

1069 *Infusion reactions*

1070

1071 An infusion reaction was defined in clinical trials as any adverse event occurring during an  
1072 infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated  
1073 patients in all clinical studies experienced an infusion reaction compared to approximately 10%  
1074 of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by  
1075 nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary  
1076 reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were  
1077 accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and  
1078 cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included  
1079 anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients  
1080 discontinued REMICADE because of infusion reactions, and all patients recovered with  
1081 treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial  
1082 infusion were not associated with a higher incidence of reactions. The infusion reaction rates  
1083 remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates  
1084 were variable over time and somewhat higher following the final infusion than after the initial  
1085 infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion

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1086 reactions (i.e. an adverse event occurring within 1 to 2 hours) was 7% in the 3 mg/kg group, 4%  
1087 in the 5 mg/kg group, and 1% in the placebo group.

1088

1089 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to  
1090 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant  
1091 immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and  
1092 infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug  
1093 Interactions).

1094

1095 In post-marketing experience, cases of anaphylactic-like reactions, including  
1096 laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with  
1097 REMICADE administration.

1098

1099 *Delayed Reactions/Reactions following readministration*

1100 *Plaque Psoriasis*

1101 In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible  
1102 delayed hypersensitivity reaction, generally reported as serum sickness or a combination of  
1103 arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within two  
1104 weeks after repeat infusion.

1105

1106 *Crohn's disease*

1107 In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following  
1108 a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events  
1109 manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and  
1110 symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also  
1111 experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.  
1112 Patients experiencing these adverse events had not experienced infusion-related adverse events  
1113 associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of  
1114 patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients  
1115 who received lyophilized formulation. The clinical data are not adequate to determine if  
1116 occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms  
1117 improved substantially or resolved with treatment in all cases. There are insufficient data on the  
1118 incidence of these events after drug-free intervals of 1 to 2 years. These events have been  
1119 observed only infrequently in clinical studies and post-marketing surveillance with retreatment  
1120 intervals up to 1 year.

1121

## 1122 **Infections**

1123

1124 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated  
1125 patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of  
1126 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections  
1127 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among  
1128 REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin  
1129 ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were  
1130 reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was

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1131 fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was  
1132 reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis,  
1133 including disseminated tuberculosis, also have been reported post-marketing. Most of these cases  
1134 of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE  
1135 and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). In  
1136 the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE  
1137 every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients  
1138 receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4%  
1139 developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter  
1140 (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg  
1141 or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX,  
1142 serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3  
1143 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients  
1144 with fistulizing Crohn's disease developed a new fistula-related abscess.

1145  
1146 In REMICADE clinical studies in patients with ulcerative colitis, infections treated with  
1147 antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of  
1148 follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of  
1149 infections, including serious infections, reported in patients with ulcerative colitis were similar to  
1150 those reported in other clinical studies.

1151  
1152 In post-marketing experience in the various indications, infections have been observed with  
1153 various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have  
1154 been noted in all organ systems and have been reported in patients receiving REMICADE alone  
1155 or in combination with immunosuppressive agents.

1156  
1157 The onset of serious infections may be preceded by constitutional symptoms such as fever, chills,  
1158 weight loss, and fatigue. The majority of serious infections, however, may also be preceded by  
1159 signs or symptoms localized to the site of the infection.

1160

#### 1161 **Autoantibodies/Lupus-like Syndrome**

1162

1163 Approximately half of REMICADE-treated patients in clinical trials who were antinuclear  
1164 antibody (ANA) negative at baseline developed a positive ANA during the trial compared with  
1165 approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected  
1166 in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated  
1167 patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

1168

#### 1169 **Malignancies**

1170

1171 In controlled trials, more REMICADE-treated patients developed malignancies than placebo-  
1172 treated patients. (See WARNINGS, Malignancies.)

1173

1174 In a randomized controlled clinical trial exploring the use of REMICADE in patients with  
1175 moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were

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1176 treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's  
1177 disease. Nine of these REMICADE-treated patients developed a malignancy, including 1  
1178 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of  
1179 follow-up 0.8 years; 95% CI 3.51 - 14.56). There was one reported malignancy among 77 control  
1180 patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up  
1181 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head  
1182 and neck.

1183

1184 Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been  
1185 reported in patients receiving REMICADE during post-approval use.

1186

### 1187 **Patients with Heart Failure**

1188

1189 In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class  
1190 III/IV; left ventricular ejection fraction  $\leq 35\%$ ), 150 patients were randomized to receive  
1191 treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks.  
1192 Higher incidences of mortality and hospitalization due to worsening heart failure were observed  
1193 in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg  
1194 REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the  
1195 placebo groups. There were trends towards increased dyspnea, hypotension, angina, and  
1196 dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo.  
1197 REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See  
1198 CONTRAINDICATIONS and WARNINGS, Patients with Heart Failure.)

1199

### 1200 **Immunogenicity**

1201

1202 Treatment with REMICADE can be associated with the development of antibodies to infliximab.  
1203 The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed  
1204 by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE  
1205 treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease  
1206 patients receiving REMICADE after drug free intervals  $>16$  weeks. In a study of psoriatic  
1207 arthritis, where 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab  
1208 occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients  
1209 who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy  
1210 and to experience an infusion reaction (see ADVERSE REACTIONS: Infusion-related  
1211 Reactions) than were patients who were antibody negative. Antibody development was lower  
1212 among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies  
1213 such as 6-MP/AZA or MTX.

1214

1215 In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were  
1216 observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of  
1217 patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also  
1218 included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients  
1219 treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg  
1220 induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and

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1221 II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for one year  
1222 and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion  
1223 reaction rates (<1%) were similar to those observed in other study populations. The clinical  
1224 significance of apparent increased immunogenicity on efficacy and infusion reactions in  
1225 psoriasis patients as compared to patients with other diseases treated with REMICADE over the  
1226 long term is not known.

1227  
1228 The data reflect the percentage of patients whose test results were positive for antibodies to  
1229 infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the  
1230 assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced  
1231 by several factors including sample handling, timing of sample collection, concomitant  
1232 medication, and underlying disease. For these reasons, comparison of the incidence of antibodies  
1233 to infliximab with the incidence of antibodies to other products may be misleading.

1234

1235 **Hepatotoxicity**

1236

1237 Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported  
1238 rarely in patients receiving REMICADE (see WARNINGS, Hepatotoxicity). Reactivation of  
1239 hepatitis B virus has occurred in patients receiving TNF-blocking agents, including  
1240 REMICADE, who are chronic carriers of this virus (see WARNINGS, Hepatitis B Virus  
1241 Reactivation).

1242

1243 In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing  
1244 spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were  
1245 observed (ALT more common than AST) in a greater proportion of patients receiving  
1246 REMICADE than in controls (Table 11), both when REMICADE was given as monotherapy and  
1247 when it was used in combination with other immunosuppressive agents. In general, patients who  
1248 developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or  
1249 resolved with either continuation or discontinuation of REMICADE, or modification of  
1250 concomitant medications.

1251

**Table 11**  
**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%	17%	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%
Plaque psoriasis <sup>6</sup>	24%	49%	<1%	8%	0%	3%

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1252 <sup>1</sup>Placebo patients received methotrexate while REMICADE patients received both REMICADE and  
1253 methotrexate. Median follow-up was 58 weeks.

1254 <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  
1255 study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo  
1256 maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT  
1257 analysis. Median follow-up was 54 weeks.

1258 <sup>3</sup>Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and  
1259 31 weeks for REMICADE.

1260 <sup>4</sup>Median follow-up was 24 weeks.

1261 <sup>5</sup>Median follow-up was 24 weeks for REMICADE group and 18 weeks for placebo group.

1262 <sup>6</sup>ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and  
1263 16 weeks for placebo.

1264  
1265

### 1266 **Adverse Reactions in Pediatric Crohn's Disease**

1267

1268 There were some differences in the adverse reactions observed in the pediatric patients receiving  
1269 REMICADE compared to those observed in adults with Crohn's disease. These differences are  
1270 discussed in the following paragraphs.

1271

1272 The following adverse events were reported more commonly in 103 randomized pediatric  
1273 Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult  
1274 Crohn's disease patients receiving a similar treatment regimen: anemia (11%), blood in stool  
1275 (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture  
1276 (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

1277

1278 Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in  
1279 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more  
1280 frequently for patients who received every 8 week as opposed to every 12 week infusions (74%  
1281 and 38%, respectively), while serious infections were reported for 3 patients in the every 8 week  
1282 and 4 patients in the every 12 week maintenance treatment group. The most commonly reported  
1283 infections were upper respiratory tract infection and pharyngitis, and the most commonly  
1284 reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8  
1285 week and 1 in the every 12 week maintenance treatment groups). Herpes zoster was reported for  
1286 2 patients in the every 8 week maintenance treatment group.

1287

1288 In Study Peds Crohn's, 18% of randomized patients experienced one or more infusion reactions,  
1289 with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's,  
1290 there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

1291

1292 Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn's.

1293

1294 Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric  
1295 patients in Crohn's disease clinical trials; 4% had ALT elevations  $\geq 3 \times$  ULN, and 1% had  
1296 elevations  $\geq 5 \times$  ULN. (Median follow-up was 53 weeks.)

1297

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1298 The most common serious adverse events reported in the post-marketing experience in children  
1299 were infections (some fatal) including opportunistic infections and tuberculosis, infusion  
1300 reactions, and hypersensitivity reactions.

1301

1302 Serious adverse events in the post-marketing experience with REMICADE in the pediatric  
1303 population have also included malignancies, including hepatosplenic T-cell lymphomas (see  
1304 Boxed WARNINGS and WARNINGS), transient hepatic enzyme abnormalities, lupus-like  
1305 syndromes, and the development of autoantibodies.

1306

### 1307 **Adverse Reactions in Psoriasis Studies**

1308

1309 During the placebo-controlled portion across the three clinical trials up to week 16, the  
1310 proportion of patients who experienced at least 1 SAE (defined as resulting in death, life  
1311 threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7%  
1312 in the 3 mg/kg REMICADE group, 3.2% in the placebo group, and 3.9% in the 5 mg/kg  
1313 REMICADE group.

1314

1315 Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every  
1316 8 weeks through one year of maintenance treatment experienced at least 1 SAE in Study I. In  
1317 Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks,  
1318 respectively, through one year of maintenance treatment experienced at least 1 SAE.

1319

1320 One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg  
1321 REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients  
1322 receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment  
1323 experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving  
1324 REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least  
1325 1 serious infection. The most common serious infection (requiring hospitalization) were  
1326 abscesses (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg  
1327 REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after  
1328 starting REMICADE.

1329

1330 In placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received  
1331 REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients  
1332 who received placebo.

1333

1334 In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination  
1335 of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of  
1336 these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints,  
1337 and immobility.

1338

### 1339 **Other Adverse Reactions**

1340

1341 Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with  
1342 rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing  
1343 spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions.

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1344 (For information on other adverse reactions in pediatric patients, see ADVERSE REACTIONS –  
1345 Adverse Reactions in Pediatric Crohn's Disease). Adverse events reported in  $\geq 5\%$  of all patients  
1346 with rheumatoid arthritis receiving 4 or more infusions are in Table 12. The types and  
1347 frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid  
1348 arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients  
1349 except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's  
1350 disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-  
1351 up for patients who never received REMICADE to provide meaningful comparisons.

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 1353  
 1354  
 1355

**Table 12**  
**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%

1356  
 1357  
 1358  
 1359  
 1360

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

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1361

1362 The most common serious adverse events observed in clinical trials were infections (see  
1363 ADVERSE REACTIONS, Infections). Other serious, medically relevant adverse events  $\geq 0.2\%$   
1364 or clinically significant adverse events by body system were as follows:

1365

1366 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela

1367 *Blood:* pancytopenia

1368 *Cardiovascular:* circulatory failure, hypotension, syncope

1369 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,  
1370 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia

1371 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness

1372 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia

1373 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis

1374 *Metabolic and Nutritional:* dehydration

1375 *Musculoskeletal:* intervertebral disk herniation, tendon disorder

1376 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction

1377 *Platelet, Bleeding and Clotting:* thrombocytopenia

1378 *Neoplasms:* basal cell, breast, lymphoma

1379 *Psychiatric:* confusion, suicide attempt

1380 *Red Blood Cell:* anemia, hemolytic anemia

1381 *Reproductive:* menstrual irregularity

1382 *Resistance Mechanism:* cellulitis, sepsis, serum sickness

1383 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including  
1384 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency

1385 *Skin and Appendages:* increased sweating, ulceration

1386 *Urinary:* renal calculus, renal failure

1387 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis

1388 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

1389

### 1390 **Post-marketing Adverse Events**

1391

1392 The following adverse events have been reported during post-approval use of REMICADE:  
1393 neutropenia (see WARNINGS, Hematologic Events), interstitial pneumonitis/fibrosis, idiopathic  
1394 thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic  
1395 and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal  
1396 necrolysis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional  
1397 neurologic events have also been observed, see WARNINGS, Neurologic Events) and acute liver  
1398 failure, jaundice, hepatitis, and cholestasis (see WARNINGS, Hepatotoxicity). Because these  
1399 events are reported voluntarily from a population of uncertain size, it is not always possible to  
1400 reliably estimate their frequency or establish a causal relationship to REMICADE exposure.

1401

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1402 **OVERDOSAGE**

1403

1404 Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of  
1405 overdosage, it is recommended that the patient be monitored for any signs or symptoms of  
1406 adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

1407

1408 **DOSAGE AND ADMINISTRATION**

1409

1410 **Rheumatoid Arthritis**

1411

1412 The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed  
1413 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks  
1414 thereafter. REMICADE should be given in combination with methotrexate. For patients who  
1415 have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or  
1416 treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at  
1417 higher doses (see ADVERSE REACTIONS, Infections).

1418

1419 **Crohn's Disease or Fistulizing Crohn's Disease**

1420

1421 The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at  
1422 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the  
1423 treatment of adults with moderately to severely active Crohn's disease or fistulizing Crohn's  
1424 disease. For adult patients who respond and then lose their response, consideration may be given  
1425 to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond  
1426 with continued dosing and consideration should be given to discontinue REMICADE in these  
1427 patients.

1428

1429 The recommended dose of REMICADE for children with moderately to severely active Crohn's  
1430 disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a  
1431 maintenance regimen of 5 mg/kg every 8 weeks.

1432

1433 **Ankylosing Spondylitis**

1434

1435 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed  
1436 with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks  
1437 thereafter.

1438

1439 **Psoriatic Arthritis**

1440

1441 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed  
1442 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks  
1443 thereafter. REMICADE can be used with or without methotrexate.

1444

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1445 **Plaque Psoriasis**

1446

1447 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion, followed  
1448 by additional doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

1449

1450 **Ulcerative Colitis**

1451

1452 The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6  
1453 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment  
1454 of moderately to severely active ulcerative colitis.

1455

1456 **Administration Instructions Regarding Infusion Reactions**

1457

1458 Adverse effects during administration of REMICADE have included flu-like symptoms,  
1459 headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin  
1460 rashes. Anaphylaxis might occur at any time during REMICADE infusion. Approximately 20%  
1461 of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared  
1462 with 10% of placebo-treated patients (see ADVERSE REACTIONS, Infusion-related Reactions).  
1463 Prior to infusion with REMICADE, premedication may be administered at the physician's  
1464 discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen  
1465 and/or corticosteroids.

1466

1467 During infusion, mild to moderate infusion reactions may improve following slowing or  
1468 suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion  
1469 rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids.  
1470 For patients that do not tolerate the infusion following these interventions, REMICADE should  
1471 be discontinued.

1472

1473 During or following infusion, patients that have severe infusion-related hypersensitivity reactions  
1474 should be discontinued from further REMICADE treatment. The management of severe infusion  
1475 reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel  
1476 and medication should be available to treat anaphylaxis if it occurs.

1477

1478 **Preparation and Administration Instructions**

1479 **Use aseptic technique.**

1480

1481 REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after  
1482 reconstitution should be used immediately, not re-entered or stored. The diluent to be used for  
1483 reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted  
1484 product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The  
1485 infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE  
1486 infusion should begin within 3 hours of preparation.

1487

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- 1488 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial  
1489 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE  
1490 solution required.  
1491
- 1492 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a  
1493 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and  
1494 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center  
1495 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass  
1496 wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution  
1497 by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous  
1498 agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.  
1499 Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to  
1500 light yellow and opalescent, and the solution may develop a few translucent particles as  
1501 infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign  
1502 particles are present.  
1503
- 1504 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with  
1505 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride  
1506 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium  
1507 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted  
1508 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.  
1509
- 1510 4. The infusion solution must be administered over a period of not less than 2 hours and must  
1511 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore  
1512 size of 1.2  $\mu\text{m}$  or less). Any unused portion of the infusion solution should not be stored for  
1513 reuse.  
1514
- 1515 5. No physical biochemical compatibility studies have been conducted to evaluate the co-  
1516 administration of REMICADE with other agents. REMICADE should not be infused  
1517 concomitantly in the same intravenous line with other agents.  
1518
- 1519 6. Parenteral drug products should be inspected visually for particulate matter and  
1520 discoloration prior to administration, whenever solution and container permit. If visibly  
1521 opaque particles, discoloration or other foreign particulates are observed, the solution  
1522 should not be used.  
1523

#### 1524 **Storage**

1525  
1526 Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do  
1527 not use beyond the expiration date. This product contains no preservative.  
1528  
1529

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1530 **HOW SUPPLIED**

1531

1532 REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-  
1533 use vials in the following strength:

1534

1535 NDC 57894-030-01            100 mg infliximab in a 20 mL vial

1536

1537

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1602 **Rx Only**

1603 **MEDICATION GUIDE**  
1604 **REMICADE® (Rem-eh-kaid)**  
1605 **(infliximab)**  
1606

1607 Read the Medication Guide that comes with REMICADE before you receive the first treatment,  
1608 and before each time you get a treatment of REMICADE. This Medication Guide does not take  
1609 the place of talking with your doctor about your medical condition or treatment.

1610

1611 **What is the most important information I should know about REMICADE?**

1612

1613 REMICADE is a medicine that affects your immune system. It can cause serious side effects  
1614 including:

1615

1616 Serious Infections

1617 • Patients treated with REMICADE and other medicines that block TNF have an increased  
1618 risk for infections. Some patients have had serious infections while receiving  
1619 REMICADE. In some cases, the infections got worse (progressed) and became serious  
1620 enough that patients needed to be in the hospital for treatment. These serious infections  
1621 include TB (tuberculosis), and infections caused by viruses, fungi or bacteria that have  
1622 spread throughout the body. Some patients have died from these infections.

1623 • Tell your doctor right away if you have any of the following symptoms, which may be  
1624 early signs of a serious infection, while taking or after taking REMICADE:

1625

1626 • a fever

1627 • feel very tired

1628 • have a cough

1629 • have flu-like symptoms

1630 • warm, red, or painful skin

1631 These may be early signs of a serious infection.

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Cancer

• Some children and young adults with Crohn's disease who have received REMICADE have developed a rare type of cancer called Hepatosplenic T-cell Lymphoma. This type of cancer often results in death. These patients were also receiving drugs known as azathioprine or 6-mercaptopurine.

• Tell your doctor if you have ever had any type of cancer.

See also, "What are the possible side effects of REMICADE?" below.

**What is REMICADE?**

REMICADE is a prescription medicine that is approved for patients with:

• Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis, along with the medicine methotrexate

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- 1646 • Crohn's Disease - children over the age of 6 and adults with Crohn's disease who have not
- 1647 responded well enough to other medicines
- 1648 • Ankylosing Spondylitis
- 1649 • Psoriatic Arthritis
- 1650 • Plaque Psoriasis - adult patients with plaque psoriasis that is chronic (doesn't go away)
- 1651 severe, extensive, and/or disabling.
- 1652 • Ulcerative Colitis - adults with moderately to severely active ulcerative colitis who have
- 1653 not responded well enough to other medicines.
- 1654

1655 REMICADE blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-

1656 alpha). TNF-alpha is made by your body's immune system. People with certain diseases have

1657 too much TNF-alpha that can cause the immune system to attack normal healthy parts of the

1658 body. REMICADE can block the damage caused by too much TNF-alpha.

1659

#### 1660 **Who should not receive REMICADE?**

1661

1662 You should not receive REMICADE if you have:

- 1663 • heart failure, unless your doctor has examined you and decided that you are able to take
- 1664 REMICADE. Talk to your doctor about your heart failure.
- 1665 • had an allergic reaction to REMICADE, or any of the other ingredients in REMICADE.
- 1666 See the end of this Medication Guide for a complete list of ingredients in REMICADE.
- 1667

#### 1668 **What should I tell my doctor before starting treatment with REMICADE?**

1669

1670 Your doctor will assess your health before each treatment.

1671

1672 Tell your doctor about all of your medical conditions, including if you:

- 1673 • have any kind of infection even if it is very minor (such as an open cut or sore).
- 1674 REMICADE affects the body's immune system and makes you less able to fight
- 1675 infections.
- 1676 • have an infection that won't go away or a history of infection that keeps coming back.
- 1677 • have had TB (tuberculosis), or if you have recently been near anyone who might have TB.
- 1678 If you have been near someone with TB and have the TB germ in your body, even if you
- 1679 don't have symptoms of an infection, you can get a serious TB infection while taking
- 1680 REMICADE. Sometimes these serious TB infections can cause death.
- 1681 • were born in, lived in or traveled to countries where there is more risk for getting TB.
- 1682 Ask your doctor if you are not sure.
- 1683 • live or have lived in certain parts of the country where there is more risk for certain kinds
- 1684 of fungal infections (histoplasmosis or coccidioidomycosis). These infections may
- 1685 develop or become more severe if you take REMICADE. If you don't know if you have
- 1686 lived in an area where histoplasmosis or coccidioidomycosis is common, ask your doctor.
- 1687 • have or had hepatitis B. If you are a chronic carrier of the virus that causes hepatitis B,
- 1688 taking REMICADE could cause the hepatitis B virus to become an active infection again.
- 1689 • have other liver problems including liver failure.

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- 1690 • have heart failure or other heart conditions. If you have heart failure, it may get worse
- 1691 while you take REMICADE.
- 1692 • have or have had any type of cancer.
- 1693 • have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine
- 1694 to make your skin sensitive to light) for psoriasis. You may have a higher chance of
- 1695 getting skin cancer while receiving REMICADE.
- 1696 • have COPD (Chronic Obstructive Pulmonary Disease), a specific type of lung disease.
- 1697 Patients with COPD may have an increased risk of getting cancer while taking
- 1698 REMICADE.
- 1699 • have or have had a condition that affects your nervous system such as
- 1700 • multiple sclerosis, or Guillain-Barré syndrome, or
- 1701 • if you experience any numbness or tingling, or
- 1702 • if you have had a seizure.
- 1703 • have recently received or are scheduled to receive a vaccine. **Adults and children**
- 1704 **should not receive a live vaccine while taking REMICADE.** Children with Crohn's
- 1705 disease should have all of their vaccines brought up to date before starting treatment with
- 1706 REMICADE.
- 1707 • are pregnant or planning to become pregnant. It is not known if REMICADE harms your
- 1708 unborn baby. REMICADE should be given to a pregnant woman only if clearly needed.
- 1709 Talk to your doctor about stopping REMICADE if you are pregnant or planning to
- 1710 become pregnant.
- 1711 • are breast-feeding or planning to breast-feed. It is not known whether REMICADE
- 1712 passes into your breast milk. Talk to your doctor about the best way to feed your baby
- 1713 while taking REMICADE. You should not breast-feed while taking REMICADE.
- 1714

#### 1715 **How should I receive REMICADE?**

- 1716
- 1717 • You will be given REMICADE through a needle placed in a vein (IV or intravenous
- 1718 infusion) in your arm.
- 1719 • Your doctor may decide to give you medicine before starting the REMICADE infusion to
- 1720 prevent or lessen side effects.
- 1721 • Only a healthcare professional should prepare the medicine and administer it to you.
- 1722 • REMICADE will be given to you over a period of about 2 hours.
- 1723 • If you have side effects from REMICADE, the infusion may need to be adjusted or
- 1724 stopped. In addition, your healthcare professional may decide to treat your symptoms.
- 1725 • A healthcare professional will monitor you during the REMICADE infusion and for a
- 1726 period of time afterward for side effects. Your doctor may do certain tests while you are
- 1727 taking REMICADE to monitor you for side effects and to see how well you respond to
- 1728 the treatment.
- 1729 • Your doctor will determine the right dose of REMICADE for you and how often you
- 1730 should receive it. Make sure to discuss with your doctor when you will receive infusions
- 1731 and to come in for all your infusions and follow-up appointments.
- 1732

#### 1733 **What should I avoid while receiving REMICADE?**

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Do not take REMICADE and the medication KINERET (Anakinra) together.

**Tell your doctor about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of your medicines and show them to your doctor and pharmacist when you get a new medicine.

### **What are the possible side effects of REMICADE?**

Serious and sometimes fatal side effects have been reported in patients taking REMICADE (see also **“What is the most important information I should know about REMICADE?”**). These include:

#### Serious Infections

- Some patients have had serious infections while receiving REMICADE. These serious infections include tuberculosis (TB) and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some patients die from these infections. If you get an infection while receiving treatment with REMICADE your doctor will treat your infection and may need to stop your REMICADE treatment.
- Tell your doctor right away if you have any of the following signs of an infection while taking or after taking REMICADE:
  - a fever
  - feel very tired
  - have a cough
  - have flu-like symptoms
  - warm, red, or painful skin
- Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with REMICADE and during treatment with REMICADE.
- Even if your TB test is negative your doctor should carefully monitor you for TB infections while you are taking REMICADE. Patients who had a **negative** TB skin test before receiving REMICADE have developed active TB.
- If you are a chronic carrier of the hepatitis B virus, the virus can become active while you are being treated with REMICADE. In some cases patients have died as a result of hepatitis B virus being reactivated. Your doctor may do a blood test before you start treatment with REMICADE and occasionally while you are being treated. Tell your doctor if you have any of the following symptoms:
  - feel unwell
  - poor appetite
  - tiredness (fatigue)
  - fever, skin rash and/or joint pain

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1778 Cancer

- 1779 • In clinical studies, more cancers were seen in patients who took REMICADE and other  
1780 medicines that block TNF than patients who did not receive these treatments.
- 1781 • Some children and young adults with Crohn's disease who have received REMICADE  
1782 have developed a rare type of cancer called Hepatosplenic T-cell Lymphoma. This type  
1783 of cancer often results in death. These patients were also receiving drugs known as  
1784 azathioprine or 6-mercaptopurine.
- 1785 • People who have been treated for rheumatoid arthritis, Crohn's disease, ankylosing  
1786 spondylitis, psoriatic arthritis and plaque psoriasis for a long time may be more likely to  
1787 develop lymphoma. This is especially true for people with very active disease.
- 1788 • Patients with COPD (a specific type of lung disease) may have an increased risk for  
1789 getting cancer while being treated with REMICADE.
- 1790 • If you take REMICADE, your chances of getting lymphoma or other cancers may  
1791 increase.

1792

1793 Heart Failure

1794 If you have a heart problem called congestive heart failure, your doctor should check you closely  
1795 while you are taking REMICADE. Your congestive heart failure may get worse while you are  
1796 taking REMICADE. Be sure to tell your doctor of any new or worse symptoms including:

- 1797 • Shortness of breath  
1798 • Swelling of ankles or feet  
1799 • Sudden weight gain

1800 Treatment with REMICADE may need to be stopped if you get new or worse congestive heart  
1801 failure.

1802

1803 Liver Injury

1804 In rare cases, some patients taking REMICADE have developed serious liver problems. Tell  
1805 your doctor if you have

- 1806 • Jaundice (skin and eyes turning yellow)  
1807 • Dark brown-colored urine  
1808 • Pain on the right side of your stomach area (right-sided abdominal pain)  
1809 • Fever  
1810 • Extreme tiredness (severe fatigue)

1811

1812 Blood Problems

1813 In some patients taking REMICADE, the body may not make enough of the blood cells that help  
1814 fight infections or help stop bleeding. Tell your doctor if you

- 1815 • Have a fever that does not go away  
1816 • Bruise or bleed very easily  
1817 • Look very pale

1818

1819 Nervous System Disorders

1820 In rare cases, patients taking REMICADE have developed problems with their nervous system.  
1821 Tell your doctor if you have

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- 1822 • Changes in your vision
- 1823 • Weakness in your arms and/or legs
- 1824 • Numbness or tingling in any part of your body
- 1825 • Seizures

1826

1827 Allergic Reactions

1828 Some patients have had allergic reactions to REMICADE. Some of these reactions were severe.  
1829 These reactions can happen while you are getting your REMICADE treatment or shortly  
1830 afterwards. Your doctor may need to stop or pause your treatment with REMICADE and may  
1831 give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:

- 1832 • Hives (red, raised, itchy patches of skin)
- 1833 • Difficulty breathing
- 1834 • Chest pain
- 1835 • High or low blood pressure
- 1836 • Fever
- 1837 • Chills

1838 Some patients treated with REMICADE have had delayed allergic reactions. The delayed  
1839 reactions occurred 3 to 12 days after receiving treatment with REMICADE. Tell your doctor  
1840 right away if you have any of these signs of delayed allergic reaction to REMICADE:

- 1841 • Fever
- 1842 • Rash
- 1843 • Headache
- 1844 • Sore throat
- 1845 • Muscle or joint pain
- 1846 • Swelling of the face and hands
- 1847 • Difficulty swallowing

1848

1849 Lupus-like Syndrome

1850 Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any  
1851 of the following symptoms your doctor may decide to stop your treatment with REMICADE.

- 1852 • Chest discomfort or pain that does not go away
- 1853 • Shortness of breath
- 1854 • Joint pain
- 1855 • Rash on the cheeks or arms that gets worse in sun

1856

1857 **The most common side effects of REMICADE are**

1858

- 1859 • Respiratory infections, such as sinus infections and sore throat)
- 1860 • Headache
- 1861 • Rash
- 1862 • Coughing
- 1863 • Stomach pain

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1864 Children who took REMICADE in studies for Crohn's disease, showed some differences in side  
1865 effects compared with adults who took REMICADE for Crohn's disease. The side effects that  
1866 happened more in children were: anemia (low red blood cells), blood in stool, leukopenia (low  
1867 white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils,  
1868 the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions  
1869 of the breathing tract.

1870 Tell your doctor about any side effect that bothers you or does not go away.

1871 These are not all of the side effects with REMICADE. Ask your doctor or pharmacist for more  
1872 information.

1873

1874 **General information about REMICADE**

1875

1876 Medicines are sometimes prescribed for purposes that are not mentioned in Medication Guides or  
1877 patient information sheets. Do not use REMICADE for a condition for which it was not  
1878 prescribed.

1879

1880 This information sheet summarizes the most important information about REMICADE. You can  
1881 ask your doctor or pharmacist for information about REMICADE that is written for health  
1882 professionals.

1883

1884 For more information go to [www.remicade.com](http://www.remicade.com) or call 1-800-457-6399.

1885

1886 **What are the ingredients in REMICADE?**

1887

1888 The active ingredient is Infliximab.

1889 The inactive ingredients in REMICADE include: sucrose, polysorbate 80, monobasic sodium  
1890 phosphate monohydrate, and dibasic sodium phosphate dihydrate. No Preservatives are present.

1891

1892 Product developed and manufactured by:

1893 Centocor, Inc.

1894 200 Great Valley Parkway

1895 Malvern, PA 19355

1896

1897 Revised November 2006

1898

1899 This Medication Guide has been approved by the U.S. Food and Drug Administration.