

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

5 **WARNINGS**

6
7 **SERIOUS INFECTIONS**
8

9 **Patients treated with REMICADE are at increased risk for developing serious infections**
10 **that may lead to hospitalization or death (see [WARNINGS](#) and [ADVERSE REACTIONS](#)).**
11 **Most patients who developed these infections were taking concomitant**
12 **immunosuppressants such as methotrexate or corticosteroids.**
13

14 **REMICADE should be discontinued if a patient develops a serious infection or sepsis.**
15

16 **Reported infections include:**

- 17 • **Active tuberculosis, including reactivation of latent tuberculosis. Patients with**
18 **tuberculosis have frequently presented with disseminated or extrapulmonary**
19 **disease. Patients should be tested for latent tuberculosis before REMICADE use**
20 **and during therapy.^{1,2} Treatment for latent infection should be initiated prior to**
21 **REMICADE use.**
- 22 • **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis,**
23 **aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or**
24 **other invasive fungal infections may present with disseminated, rather than**
25 **localized, disease. Antigen and antibody testing for histoplasmosis may be negative**
26 **in some patients with active infection. Empiric anti-fungal therapy should be**
27 **considered in patients at risk for invasive fungal infections who develop severe**
28 **systemic illness.**
- 29 • **Bacterial, viral and other infections due to opportunistic pathogens.**
30

31 **The risks and benefits of treatment with REMICADE should be carefully considered prior**
32 **to initiating therapy in patients with chronic or recurrent infection.**
33

34 **Patients should be closely monitored for the development of signs and symptoms of**
35 **infection during and after treatment with REMICADE, including the possible development**
36 **of tuberculosis in patients who tested negative for latent tuberculosis infection prior to**
37 **initiating therapy.**
38

39 **MALIGNANCY**
40

41 **Lymphoma and other malignancies, some fatal, have been reported in children and**
42 **adolescent patients treated with TNF blockers, including REMICADE. [See [WARNINGS,](#)**
43 **[Malignancy](#)]**
44

45 **Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma,**
46 **have been reported in patients treated with TNF blockers including REMICADE. These**
47 **cases have had a very aggressive disease course and have been fatal. All reported**
48 **REMICADE cases have occurred in patients with Crohn's disease or ulcerative colitis and**
49 **the majority were in adolescent and young adult males. All of these patients had received**
50 **treatment with azathioprine or 6-mercaptopurine concomitantly with REMICADE at or**
51 **prior to diagnosis.**
52

53 DESCRIPTION

54
55
56 REMICADE is a chimeric IgG1 κ monoclonal antibody with an approximate molecular weight of
57 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab
58 binds specifically to human tumor necrosis factor alpha (TNF α) with an association constant of
59 10^{10} M^{-1} . Infliximab is produced by a recombinant cell line cultured by continuous perfusion and
60 is purified by a series of steps that includes measures to inactivate and remove viruses.

61
62 REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion.
63 Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is
64 approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg
65 polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium
66 phosphate, dihydrate. No preservatives are present.

67 CLINICAL PHARMACOLOGY

68 General

69
70
71
72 Infliximab neutralizes the biological activity of TNF α by binding with high affinity to the
73 soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors.^{3,4}
74 Infliximab does not neutralize TNF β (lymphotoxin α), a related cytokine that utilizes the same
75 receptors as TNF α . Biological activities attributed to TNF α include: induction of pro-
76 inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration
77 by increasing endothelial layer permeability and expression of adhesion molecules by endothelial
78 cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of
79 acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by
80 synoviocytes and/or chondrocytes. Cells expressing transmembrane TNF α bound by infliximab
81 can be lysed *in vitro*⁴ or *in vivo*.⁵ Infliximab inhibits the functional activity of TNF α in a wide
82 variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T
83 lymphocytes and epithelial cells. The relationship of these biological response markers to the
84 mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNF α
85 antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis
86 and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease
87 in transgenic mice that develop polyarthritis as a result of constitutive expression of human
88 TNF α , and when administered after disease onset, allows eroded joints to heal.
89

90 Pharmacodynamics

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

111 Pharmacokinetics

112
113
114 In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship
115 between the dose administered and the maximum serum concentration. The volume of
116 distribution at steady state was independent of dose and indicated that infliximab was distributed
117 primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg
118 to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in
119 plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

120
121 Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in
122 predictable concentration-time profiles following each treatment. No systemic accumulation of
123 infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-
124 week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8
125 weeks after a maintenance dose of 3 to 10 mg/kg of REMICADE, median infliximab serum
126 concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations
127 were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab.
128 No major differences in clearance or volume of distribution were observed in patient subgroups
129 defined by age, weight, or gender. It is not known if there are differences in clearance or volume
130 of distribution in patients with marked impairment of hepatic or renal function.

131
132 Infliximab peak and trough concentrations were similar in pediatric (aged 6 to 17 years old) and
133 adult patients with Crohn's disease following the administration of the recommended regimen
134 (see [DOSAGE AND ADMINISTRATION, Crohn's Disease or Fistulizing Crohn's Disease](#)).

135

136 Population pharmacokinetic analysis showed that in children with juvenile rheumatoid arthritis
137 (JRA) with a body weight of up to 35 kg receiving 6 mg/kg REMICADE and children with JRA
138 with body weight greater than 35 kg up to adult body weight receiving 3mg/kg REMICADE, the
139 steady state area under the concentration curve (AUC_{ss}) was similar to that observed in adults
140 receiving 3 mg/kg of REMICADE.

141

142 **CLINICAL STUDIES**

143 **Rheumatoid Arthritis**

144

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

149

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

156

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

163

164 Data on use of REMICADE without concurrent MTX are limited (see [ADVERSE REACTIONS,](#)
165 [Immunogenicity](#)).^{6,7}

166

167 *Clinical response*

168

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

176

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

Table 1
ACR RESPONSE (PERCENT OF PATIENTS)

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

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.

^ap ≥ 0.001

^bp < 0.01

^cp < 0.05

182

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^a</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 ^b	6.7	6.1	6.8	3.3
Physician's Global Assessment ^b	6.5	5.2	6.2	2.1
Patient's Global Assessment ^b	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI) ^c	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

^aAll doses/schedules of REMICADE + MTX

^bVisual Analog Scale (0=best, 10=worst)

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

183

184 *Radiographic response*

185

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

190

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

194

195 In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of
196 structural damage was observed at weeks 30 and 54 (Table 3) in the REMICADE + MTX groups
197 compared to MTX alone. Patients treated with REMICADE + MTX demonstrated less
198 progression of structural damage compared to MTX alone, whether baseline acute phase
199 reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute phase
200 reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units
201 compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of
202 progression; patients with normal baseline acute phase reactants treated with MTX alone
203 demonstrated a mean progression in vdH-S score of 1.8 units compared to REMICADE + MTX

204 who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had
 205 no progression (vdH-S score ≤ 0 unit) of structural damage compared to 45% patients receiving
 206 MTX alone. In a subset of patients who began the study without erosions, REMICADE + MTX
 207 maintained an erosion free state at 1 year in a greater proportion of patients than MTX alone,
 208 79% (77/98) vs. 58% (23/40), respectively ($p < 0.01$). Fewer patients in the REMICADE + MTX
 209 groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).
 210

Table 3
RADIOGRAPHIC CHANGE FROM BASELINE TO WEEK 54

	Study RA I			Study RA II		
	REMICADE + MTX			REMICADE + MTX		
	Placebo + MTX (n=64)	3 mg/kg q 8 wks (n=71)	10 mg/kg q 8 wks (n=77)	Placebo + MTX (n=282)	3 mg/kg q 8 wks (n=359)	6 mg/kg q 8 wks (n=363)
<i>Total Score</i>						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3 ^a	0.2 ^a	3.7	0.4 ^a	0.5 ^a
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 ^a	0.2 ^a	3.0	0.3 ^a	0.1 ^a
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 ^a	0.0 ^a	0.6	0.1 ^a	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

^a P < 0.001 for each outcome against placebo.

212 *Physical function response*

213
214 Physical function and disability were assessed using the Health Assessment Questionnaire
215 (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

216
217 In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater
218 improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged
219 over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental
220 component summary score. The median (interquartile range) improvement from baseline to
221 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
222 REMICADE + MTX ($p < 0.001$). Both HAQ-DI and SF-36 effects were maintained through week
223 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in
224 the trial through 102 weeks.

225
226 In Study RA II, both REMICADE treatment groups showed greater improvement in HAQ-DI
227 from baseline averaged over time through week 54 compared to MTX alone; 0.7 for
228 REMICADE + MTX vs. 0.6 for MTX alone ($p \leq 0.001$). No worsening in the SF-36 mental
229 component summary score was observed.

230
231 **Active Crohn's Disease**

232
233 The safety and efficacy of single and multiple doses of REMICADE were assessed in two
234 randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to
235 severely active Crohn's disease [Crohn's Disease Activity Index (CDAI) ≥ 220 and ≤ 400] with
236 an inadequate response to prior conventional therapies. Concomitant stable doses of
237 aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of
238 patients continued to receive at least one of these medications.

239
240 In the single-dose trial⁹ of 108 patients, 16% (4/25) of placebo patients achieved a clinical
241 response (decrease in CDAI ≥ 70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg
242 REMICADE ($p < 0.001$, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo
243 patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission
244 (CDAI < 150) at week 4.

245
246 In a multidose trial (ACCENT I [Study Crohn's I])¹⁰, 545 patients received 5 mg/kg at week 0
247 and were then randomized to one of three treatment groups; the placebo maintenance group
248 received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group
249 received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance
250 group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in
251 response at week 2 were randomized and analyzed separately from those not in response at week
252 2. Corticosteroid taper was permitted after week 6.

253
254 At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly
255 greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved
256 clinical remission compared to patients in the placebo maintenance group (Table 4).

257
258 Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg
259 REMICADE maintenance groups were in clinical remission and were able to discontinue
260 corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).
261

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

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

262

263 ^a REMICADE at week 0264 ^b REMICADE 5 mg/kg administered at weeks 0, 2 and 6265 ^c p-values represent pairwise comparisons to placebo266 ^d Of those receiving corticosteroids at baseline

267

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

274

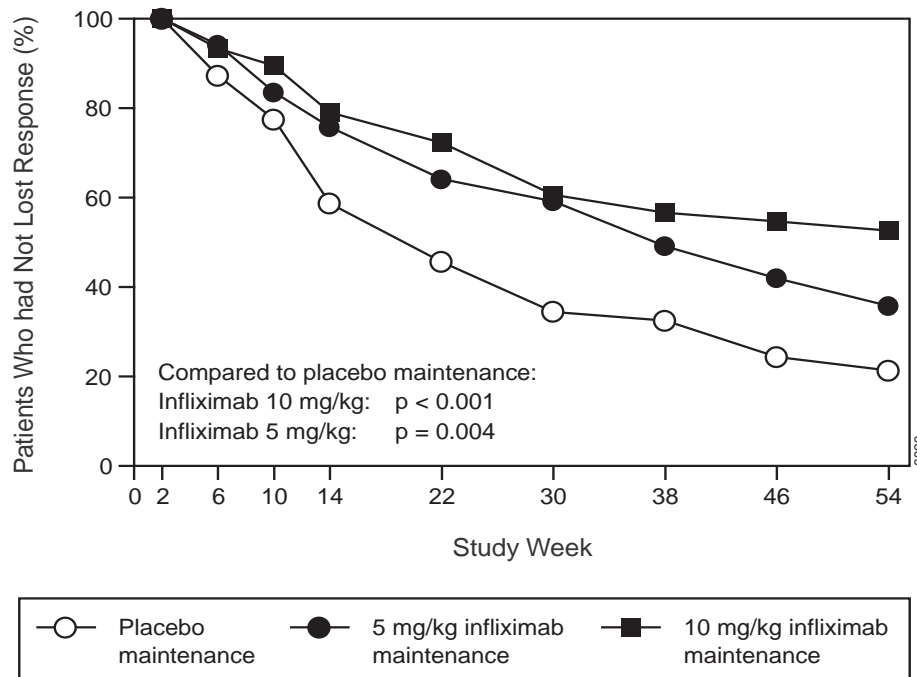


Figure 1
Kaplan-Meier estimate of the proportion of patients
who had not lost response through week 54

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.

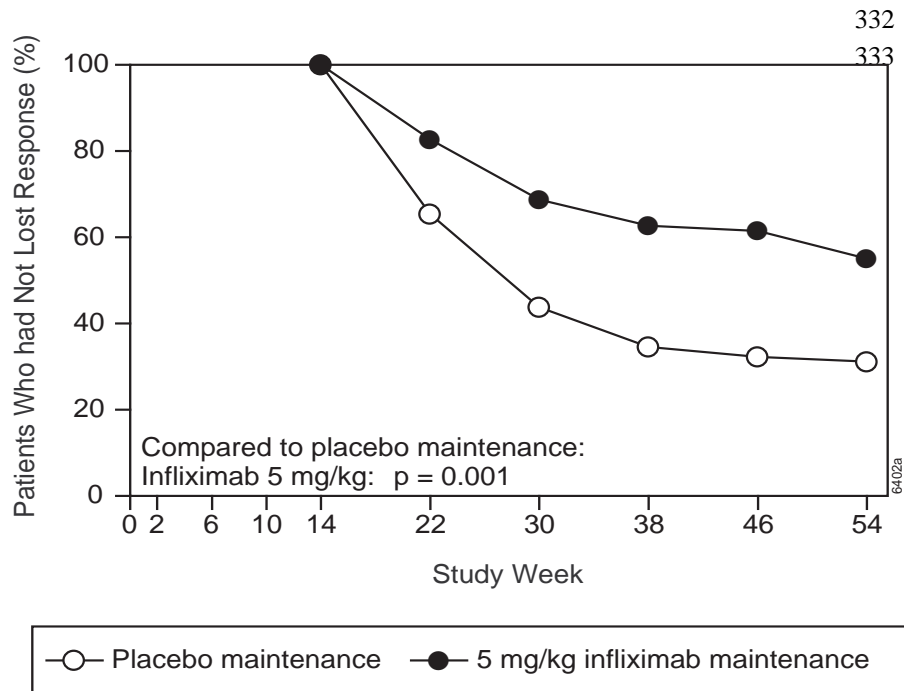
302 In the first trial,¹¹ 94 patients received three doses of either placebo or REMICADE at weeks 0,
303 2 and 6. Fistula response ($\geq 50\%$ reduction in number of enterocutaneous fistulas draining upon
304 gentle compression on at least two consecutive visits without an increase in medication or
305 surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE
306 group ($p=0.002$) and 56% (18/32) of patients in the 10 mg/kg REMICADE group ($p=0.021$) vs.
307 26% (8/31) of patients in the placebo arm. The median time to onset of response and median
308 duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure
309 of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of
310 placebo-treated patients ($p<0.001$).

311
312 In the second trial (ACCENT II [Study Crohn's II]), patients who were enrolled had to have at
313 least one draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg
314 REMICADE at weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE
315 maintenance at week 14. Patients received maintenance doses at week 14 and then every eight
316 weeks through week 46. Patients who were in fistula response (fistula response was defined the
317 same as in the first trial) at both weeks 10 and 14 were randomized separately from those not in
318 response. The primary endpoint was time from randomization to loss of response among those
319 patients who were in fistula response.

320
321 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and
322 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of
323 the patients had received previous immunosuppressive and antibiotic therapy.

324
325 At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to
326 REMICADE maintenance had a longer time to loss of fistula response compared to the placebo
327 maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no
328 draining fistulas compared with 22% (20/90) of placebo-treated patients ($p=0.02$). Compared to
329 placebo maintenance, patients on REMICADE maintenance had a trend toward fewer
330 hospitalizations.

331



334
335
336
337
338
339

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

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

344

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

347

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

350

351 Active Crohn's Disease in Pediatric Patients

352

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

359

360 All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. At Week
361 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given
362 either every 8 weeks or every 12 weeks.

363
364 At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in
365 the PCDAI score of ≥ 15 points and total PCDAI score of ≤ 30 points), and 59% were in clinical
366 remission (defined as PCDAI score of ≤ 10 points).

367
368 The proportion of pediatric patients achieving clinical response at Week 10 compared favorably
369 with the proportion of adults achieving a clinical response in Study Crohn's I. The study
370 definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas
371 the CDAI score was used in the adult Study Crohn's I.

372
373 At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the
374 every 8 week treatment group than in the every 12 week treatment group (73% vs. 47% at Week
375 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in
376 clinical remission was also greater in the every 8 week treatment group than in the every
377 12 week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), ([Table 5](#)).

378
379 For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of
380 patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every
381 8 week maintenance group and 33% for the every 12 week maintenance group. At Week 54, the
382 proportion of patients able to discontinue corticosteroids while in remission was 46% for the
383 every 8 week maintenance group and 17% for the every 12 week maintenance group.

384

Table 5
RESPONSE AND REMISSION IN STUDY PEDS CROHN'S

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

¹Defined as a decrease from baseline in the PCDAI score of ≥ 15 points and total score of ≤ 30 points.

²Defined as a PCDAI score of ≤ 10 points.

* p-value < 0.05

**p-value < 0.01

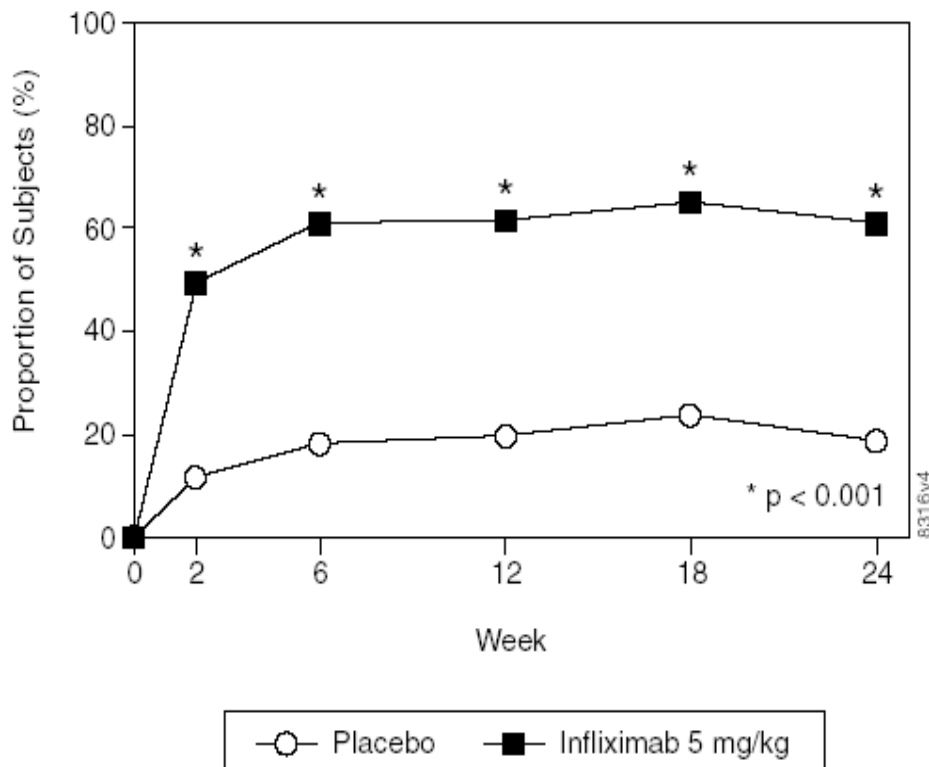
411 **Ankylosing Spondylitis**

412

413 The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-
 414 blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were
 415 between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New
 416 York criteria for Ankylosing Spondylitis.¹² Patients were to have had active disease as
 417 evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4
 418 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients
 419 with complete ankylosis of the spine were excluded from study participation, and the use of
 420 Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were
 421 prohibited. Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks
 422 0, 2, 6, 12 and 18.

423

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



429

430

431

432

Figure 3
Proportion of patients achieving ASAS 20 response

433
 434 At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs
 435 and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and
 436 ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE,
 437 compared to 9% and 4%, respectively, for patients receiving placebo ($p < 0.001$, REMICADE vs.
 438 placebo). A low level of disease activity (defined as a value < 20 [on a scale of 0-100 mm] in
 439 each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated
 440 patients vs. 1% in placebo-treated patients ($p < 0.001$).

441
 442 **Table 6**
 443 **Components of Ankylosing Spondylitis Disease Activity**
 444

	<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 ^a	6.6	6.0	6.8	3.8	<0.001
Spinal pain ^a	7.3	6.5	7.6	4.0	<0.001
BASFI ^b	5.8	5.6	5.7	3.6	<0.001
Inflammation ^c	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP ^d (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test ^e	4.0	5.0	4.3	4.4	0.75
Chest expansion ^e	3.6	3.7	3.3	3.9	0.04
Tragus to wall ^e	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion ^e	10.6	11.0	11.4	12.9	0.03

^a measured on a VAS with 0="none" and 10="severe"

^b Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions

^c Inflammation, average of last 2 questions on the 6 question BASDAI

^d CRP normal range 0-1.0 mg/dL

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

445
 446 The median improvement from baseline in the general health-related quality of life questionnaire
 447 SF-36 physical component summary score at week 24 was 10.2 for the REMICADE group vs.
 448 0.8 for the placebo group ($p < 0.001$). There was no change in the SF-36 mental component
 449 summary score in either the REMICADE group or the placebo group.

450
 451 Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled
 452 study of 70 patients with ankylosing spondylitis.
 453

454 Psoriatic Arthritis

455

456 Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-
457 controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID
458 therapy (≥ 5 swollen joints and ≥ 5 tender joints) with one or more of the following subtypes:
459 arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis
460 (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients
461 also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Forty-six percent of
462 patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-week double-
463 blind phase, patients received either 5 mg/kg REMICADE or placebo at weeks 0, 2, 6, 14, and 22
464 (100 patients in each group). At week 16, placebo patients with $< 10\%$ improvement from
465 baseline in both swollen and tender joint counts were switched to REMICADE induction (early
466 escape). At week 24, all placebo-treated patients crossed over to REMICADE induction.
467 Dosing continued for all patients through week 46.

468

469 Clinical response

470

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

480

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

486

487

488

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

<u>Patients Randomized</u>	Placebo (n=100)		REMICADE 5mg/kg ^a (n=100)	
	Baseline	Week 24	Baseline	Week 24
Parameter (medians)				
No of Tender Joints ^b	24	20	20	6
No. of Swollen Joints ^c	12	9	12	3
Pain ^d	6.4	5.6	5.9	2.6
Physician's Global Assessment ^d	6.0	4.5	5.6	1.5
Patient's Global Assessment ^d	6.1	5.0	5.9	2.5
Disability Index (HAQ- DI) ^e	1.1	1.1	1.1	0.5
CRP (mg/dL) ^f	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

^a 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

^bScale 0-68

^cScale 0-66

^dVisual Analog Scale (0=best, 10=worst)

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

^fNormal range 0-0.6 mg/dL

489

490

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

500

501 *Radiographic response*

502

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

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

515

516 *Physical function*

517

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

522

523 During the placebo-controlled portion of the trial (24 weeks), 54% of REMICADE-treated
524 patients achieved a clinically meaningful improvement in HAQ-DI (≥ 0.3 unit decrease)
525 compared to 22% of placebo-treated patients. REMICADE-treated patients also demonstrated
526 greater improvement in the SF-36 physical and mental component summary scores than placebo-
527 treated patients. The responses were maintained for up to 2 years in an open label extension
528 study.

529

530 **Plaque Psoriasis**

531

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

539

540 Study I (EXPRESS) evaluated 378 patients who received placebo or REMICADE at a dose of 5
541 mg/kg at weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks.
542 At week 24, the placebo group crossed over to REMICADE induction therapy (5 mg/kg),
543 followed by maintenance therapy every 8 weeks. Patients originally randomized to REMICADE
544 continued to receive REMICADE 5 mg/kg every 8 weeks through week 46. Across all treatment
545 groups, the median baseline PASI score was 21 and the baseline Static Physician Global
546 Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe
547 (2%). In addition, 75% of patients had a BSA $>20\%$. Seventy-one percent of patients
548 previously received systemic therapy and 82% received phototherapy.

549

550 Study II (EXPRESS II) evaluated 835 patients who received placebo or REMICADE at doses of
551 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At week 14, within each
552 REMICADE dose group, patients were randomized to either scheduled (every 8 weeks) or as
553 needed (PRN) maintenance treatment through week 46. At week 16, the placebo group crossed
554 over to REMICADE induction therapy (5 mg/kg), followed by maintenance therapy every 8
555 weeks. Across all treatment groups, the median baseline PASI score was 18 and 63% of patients
556 had a BSA >20%. Fifty-five percent of patients previously received systemic therapy and 64%
557 received a phototherapy.

558
559 Study III (SPIRIT) evaluated 249 patients who had previously received either psoralen plus
560 ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients
561 were randomized to receive either placebo or REMICADE at doses of 3 mg/kg or 5 mg/kg at
562 weeks 0, 2, and 6. At week 26, patients with a sPGA score of moderate or worse (greater than or
563 equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across
564 all treatment groups, the median baseline PASI score was 19 and the baseline sPGA score ranged
565 from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients
566 had a BSA >20%. Of the enrolled patients 114 (46%) received the week 26 additional dose.

567
568 In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a
569 reduction in score of at least 75% from baseline at week 10 by the PASI (PASI 75). In Study I
570 and Study III, another evaluated outcome included the proportion of patients who achieved a
571 score of "cleared" or "minimal" by the sPGA. The sPGA is a 6 category scale ranging from
572 "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis
573 severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared"
574 or "minimal", consisted of none or minimal elevation in plaque, up to faint red coloration in
575 erythema, and none or minimal fine scale over < 5% of the plaque.

576
577 Study II also evaluated the proportion of patients who achieved a score of "clear" or "excellent"
578 by the relative Physician's Global Assessment (rPGA). The rPGA is a 6 category scale ranging
579 from "6 = worse" to "1 = clear" that was assessed relative to baseline. Overall lesions were
580 graded with consideration to the percent of body involvement as well as overall induration,
581 scaling, and erythema. Treatment success, defined as "clear" or "excellent", consisted of some
582 residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some
583 erythema may be present). The results of these studies are presented in [Table 8](#).

584

585 **TABLE 8**
 586 **Psoriasis Studies I, II, and III, Week 10 Percentage of Patients Who Achieved PASI 75 and**
 587 **Percentage Who Achieved Treatment “Success” with Physician’s Global Assessment**
 588

	Placebo	REMICADE	
		3 mg/kg	5 mg/kg
Psoriasis Study I - patients randomized ^a	77	---	301
PASI 75	2 (3%)	---	242 (80%)*
sPGA	3 (4%)	---	242 (80%)*
Psoriasis Study II - patients randomized ^a	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*
Psoriasis Study III - patients randomized ^b	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.

589 In Study I, in the subgroup of patients with more extensive psoriasis who had previously
 590 received phototherapy, 85% of patients on 5 mg/kg REMICADE achieved a PASI 75 at week 10
 591 compared with 4% of patients on placebo.
 592

593 In Study II, in the subgroup of patients with more extensive psoriasis who had previously
 594 received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg REMICADE achieved
 595 a PASI 75 at week 10 respectively compared with 1% on placebo. In Study II, among patients
 596 with more extensive psoriasis who had failed or were intolerant to phototherapy, 70% and 78%
 597 of patients on 3 mg/kg and 5 mg/kg REMICADE achieved a PASI 75 at week 10 respectively,
 598 compared with 2% on placebo.
 599

600 Maintenance of response was studied in a subset of 292 and 297 REMICADE treated patients in
 601 the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at week
 602 10 and investigational site, patients in the active treatment groups were re-randomized to either a
 603 scheduled or as needed maintenance (PRN) therapy, beginning on week 14.
 604

605 The groups that received a maintenance dose every 8 weeks appear to have a greater percentage
 606 of patients maintaining a PASI 75 through week 50 as compared to patients who received the as
 607 needed or PRN doses and the best response was maintained with the 5 mg/kg every 8 week dose.
 608 These results are shown in [Figure 4](#). At week 46, when REMICADE serum concentrations were
 609 at trough level, in the every 8 week dose group, 54% of patients in the 5 mg/kg group compared
 610 to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in
 611

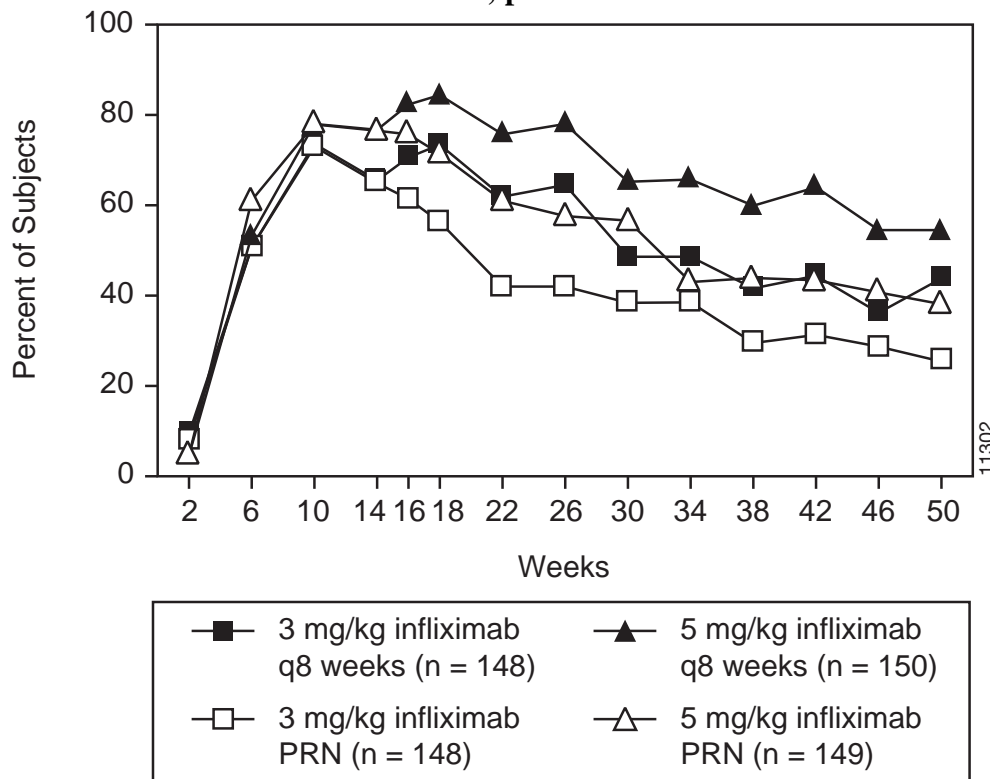
612 the 3mg/kg every 8 week dose group compared to the 5mg/kg group was associated with a lower
 613 percentage of patients with detectable trough serum infliximab levels. This may be related in
 614 part to higher antibody rates (see [ADVERSE REACTIONS: Immunogenicity](#)). In addition, in a
 615 subset of patients who had achieved a response at week 10, maintenance of response appears to
 616 be greater in patients who received REMICADE every 8 weeks at the 5 mg/kg dose. Regardless
 617 of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a
 618 subpopulation of patients in each group over time. The results of Study I through Week 50 in the
 619 5mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

620

621

Figure 4

622 **Proportion of patients achieving $\geq 75\%$ improvement in PASI from baseline through Week**
 623 **50; patients randomized at Week 14**



624

625

626

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

629

630 Ulcerative Colitis

631

632 The safety and efficacy of REMICADE were assessed in two randomized, double-blind,
 633 placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative
 634 colitis (UC) (Mayo score¹³ 6 to 12 [of possible range 0-12], Endoscopy subscore ≥ 2) with an
 635 inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant
 636 treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory

637 agents was permitted. Corticosteroid taper was permitted after week 8. Patients were
638 randomized at week 0 to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE
639 at weeks 0, 2, 6, and every 8 weeks thereafter through week 46 in Study UC I, and at weeks 0, 2,
640 6, and every 8 weeks thereafter through week 22 in Study UC II. In Study UC II, patients were
641 allowed to continue blinded therapy to week 46 at the investigator's discretion.

642

643 Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-
644 mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or
645 were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients
646 in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-
647 MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More
648 patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%,
649 respectively). Clinical response was defined as a decrease from baseline in the Mayo score by \geq
650 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal
651 bleeding subscore of 0 or 1.

652

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

654

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

660

661 Of patients on corticosteroids at baseline, greater proportions of patients in the REMICADE
662 treatment groups were in clinical remission and able to discontinue corticosteroids at week 30
663 compared with the patients in the placebo treatment groups (22% in REMICADE treatment
664 groups vs. 10% in placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in
665 placebo group in Study UC II). In Study UC I, this effect was maintained through week 54 (21%
666 in REMICADE treatment groups vs. 9% in placebo group). The REMICADE-associated
667 response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.
668

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
Clinical Response^{1, 4}						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
Week 54	20%	45%*	44%*	NA	NA	NA
Sustained Response⁴						
(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
Clinical Remission^{2, 4}						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%**	37%*	11%	26%**	36%*
Week 54	17%	35%**	34%**	NA	NA	NA
Sustained Remission⁴						
(Clinical remission at both Week 8 and 30)	8%	23%**	26%*	2%	15%*	23%*

(Clinical remission at Weeks 8, 30 and 54)	7%	20% **	20% **	NA	NA	NA
--	----	--------	--------	----	----	----

Mucosal Healing^{3,4}

Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%**	57%*
Week 54	18%	45%*	47%*	NA	NA	NA

670

671 * P < 0.001, ** P < 0.01

672 ¹ Defined as a decrease from baseline in the Mayo score by $\geq 30\%$ and ≥ 3 points, accompanied by a decrease in the
673 rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four
674 subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings.)675 ² Defined as a Mayo score ≤ 2 points, no individual subscore >1 .676 ³ Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.677 ⁴ Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions
678 due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the
679 time of the event onward.

680

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

683

684

Table 10

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

685

686

687

	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%

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%

688

689

690 **INDICATIONS AND USAGE**

691

692 **Rheumatoid Arthritis**

693

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

697

698 **Crohn's Disease**

699

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

704

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

707

708 **Ankylosing Spondylitis**

709

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

712

713 **Psoriatic Arthritis**

714

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

718

719 **Plaque Psoriasis**

720

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

726

727 **Ulcerative Colitis**

728

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

732

733 **CONTRAINDICATIONS**

734

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

741

742 REMICADE should not be re-administered to patients who have experienced a severe
743 hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered
744 to patients with known hypersensitivity to inactive components of the product or to any murine
745 proteins.

746

747 **WARNINGS**

748

749 **SERIOUS INFECTIONS**

750 (See *Boxed WARNINGS*)

751

752 **Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal,**
753 **viral, or other opportunistic pathogens have been reported in patients receiving TNF-**
754 **blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis,**
755 **aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most**
756 **commonly reported. Patients have frequently presented with disseminated rather than**
757 **localized disease, and are often taking concomitant immunosuppressants such as**
758 **methotrexate or corticosteroids with REMICADE.**

759

760 **Treatment with REMICADE should not be initiated in patients with an active infection,**
761 **including clinically important localized infections. The risks and benefits of treatment**
762 **should be considered prior to initiating therapy in patients:**

- 763
- with chronic or recurrent infection;

- 764 • who have been exposed to tuberculosis;
- 765 • who have resided or traveled in areas of endemic tuberculosis or endemic mycoses,
- 766 such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- 767 • with underlying conditions that may predispose them to infection.

768

769 **Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in**
770 **patients receiving REMICADE, including patients who have previously received treatment**
771 **for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors**
772 **and tested for latent infection prior to initiating REMICADE and periodically during**
773 **therapy.**

774

775 **Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has**
776 **been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5**
777 **mm or greater with tuberculin skin testing should be considered a positive test result when**
778 **assessing if treatment for latent tuberculosis is needed prior to initiating REMICADE, even**
779 **for patients previously vaccinated with Bacille Calmette-Guerin (BCG).**

780

781 **Anti-tuberculosis therapy should also be considered prior to initiation of REMICADE in**
782 **patients with a past history of latent or active tuberculosis in whom an adequate course of**
783 **treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis**
784 **but having risk factors for tuberculosis infection.¹⁴ Consultation with a physician with**
785 **expertise in the treatment of tuberculosis is recommended to aid in the decision whether**
786 **initiating anti-tuberculosis therapy is appropriate for an individual patient.**

787

788 **Tuberculosis should be strongly considered in patients who develop a new infection during**
789 **REMICADE treatment, especially in patients who have previously or recently traveled to**
790 **countries with a high prevalence of tuberculosis, or who have had close contact with a**
791 **person with active tuberculosis.**

792

793 **Patients should be closely monitored for the development of signs and symptoms of**
794 **infection during and after treatment with REMICADE, including the development of**
795 **tuberculosis in patients who tested negative for latent tuberculosis infection prior to**
796 **initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while**
797 **on therapy with REMICADE.**

798

799 **REMICADE should be discontinued if a patient develops a serious infection or sepsis. A**
800 **patient who develops a new infection during treatment with REMICADE should be closely**
801 **monitored, undergo a prompt and complete diagnostic workup appropriate for an**
802 **immunocompromised patient, and appropriate antimicrobial therapy should be initiated.**

803

804 **For patients who reside or travel in regions where mycoses are endemic, invasive fungal**
805 **infection should be suspected if they develop a serious systemic illness. Appropriate**
806 **empiric antifungal therapy should be considered while a diagnostic workup is being**
807 **performed. Antigen and antibody testing for histoplasmosis may be negative in some**

808 **patients with active infection. When feasible, the decision to administer empiric antifungal**
809 **therapy in these patients should be made in consultation with a physician with expertise in**
810 **the diagnosis and treatment of invasive fungal infections and should take into account both**
811 **the risk for severe fungal infection and the risks of antifungal therapy.**

812
813 **Serious infections were seen in clinical studies with concurrent use of anakinra and another**
814 **TNF α -blocking agent, etanercept, with no added clinical benefit compared to etanercept**
815 **alone. Because of the nature of the adverse events seen with combination of etanercept and**
816 **anakinra therapy, similar toxicities may also result from the combination of anakinra and**
817 **other TNF α -blocking agents. Therefore, the combination of REMICADE and anakinra is**
818 **not recommended.**

819 **MALIGNANCY (See [Boxed WARNINGS](#))**

820
821
822 **Malignancies, some fatal, have been reported among children, adolescents and young**
823 **adults who received treatment with TNF-blocking agents (initiation of therapy \leq 18 years**
824 **of age), including REMICADE. Approximately half of these cases were lymphomas,**
825 **including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety**
826 **of malignancies, including rare malignancies that are usually associated with**
827 **immunosuppression and malignancies that are not usually observed in children and**
828 **adolescents. The malignancies occurred after a median of 30 months (range 1 to 84**
829 **months) after the first dose of TNF blocker therapy. Most of the patients were receiving**
830 **concomitant immunosuppressants. These cases were reported post-marketing and are**
831 **derived from a variety of sources, including registries and spontaneous postmarketing**
832 **reports.**

833
834 **Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell**
835 **lymphoma, have been reported in patients treated with TNF blockers including**
836 **REMICADE. These cases have had a very aggressive disease course and have been fatal.¹⁵**
837 **All reported REMICADE cases have occurred in patients with Crohn's disease or**
838 **ulcerative colitis and the majority were in adolescent and young adult males. All of these**
839 **patients had received treatment with the immunosuppressants azathioprine or 6-**
840 **mercaptopurine concomitantly with REMICADE at or prior to diagnosis. It is uncertain**
841 **whether the occurrence of HSTCL is related to REMICADE or REMICADE in**
842 **combination with these other immunosuppressants.**

843 844 **Hepatitis B Virus Reactivation**

845
846 **Use of TNF blockers, including REMICADE has been associated with reactivation of hepatitis B**
847 **virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV**
848 **reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of**
849 **these reports have occurred in patients concomitantly receiving other medications that suppress**
850 **the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV**
851 **infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker**
852 **therapy. Prescribers should exercise caution in prescribing TNF blockers, including REMICADE,**

853 for patients identified as carriers of HBV. Adequate data are not available on the safety or
854 efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with
855 TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require
856 treatment with TNF blockers should be closely monitored for clinical and laboratory signs of
857 active HBV infection throughout therapy and for several months following termination of
858 therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and
859 antiviral therapy with appropriate supportive treatment should be initiated. The safety of
860 resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore,
861 prescribers should exercise caution when considering resumption of TNF blocker therapy in this
862 situation and monitor patients closely.

863

864 **Hepatotoxicity**

865

866 Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have
867 been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune
868 hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between
869 two weeks to more than a year after initiation of REMICADE; elevations in hepatic
870 aminotransferase levels were not noted prior to discovery of the liver injury in many of these
871 cases. Some of these cases were fatal or necessitated liver transplantation. Patients with
872 symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If
873 jaundice and/or marked liver enzyme elevations (e.g., ≥ 5 times the upper limit of normal)
874 develops, REMICADE should be discontinued, and a thorough investigation of the abnormality
875 should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been
876 observed in patients receiving REMICADE without progression to severe hepatic injury (*see*
877 *ADVERSE REACTIONS, Hepatotoxicity*).

878

879 **Patients with Heart Failure**

880

881 REMICADE has been associated with adverse outcomes in patients with heart failure, and
882 should be used in patients with heart failure only after consideration of other treatment options.
883 The results of a randomized study evaluating the use of REMICADE in patients with heart
884 failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10
885 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and
886 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without
887 identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-
888 marketing reports of new onset heart failure, including heart failure in patients without known
889 pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a
890 decision is made to administer REMICADE to patients with heart failure, they should be closely
891 monitored during therapy, and REMICADE should be discontinued if new or worsening
892 symptoms of heart failure appear. (*see CONTRAINDICATIONS and ADVERSE REACTIONS,*
893 *Patients with Heart Failure*).

894

Hematologic Events

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

Hypersensitivity

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

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

REMICADE should be discontinued for severe hypersensitivity reactions (see also [CONTRAINDICATIONS](#)). Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see [ADVERSE REACTIONS: Infusion-related Reactions](#)).

Neurologic Events

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

Malignancies

938
939
940 In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE,
941 more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been
942 observed in patients receiving those TNF-blockers compared with control patients. During the
943 controlled portions of REMICADE trials in patients with moderately to severely active
944 rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis,
945 and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and
946 NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of
947 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years
948 among control patients), with median duration of follow-up 0.5 years for REMICADE-treated
949 patients and 0.4 years for control patients. Of these, the most common malignancies were breast,
950 colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was
951 similar to that expected in the general population whereas the rate in control patients was lower
952 than expected.

953
954 In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of
955 lymphoma have been observed among patients receiving a TNF blocker compared with control
956 patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients
957 developed lymphomas among 5707 patients treated with REMICADE (median duration of
958 follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4
959 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per
960 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the
961 general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's
962 disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5
963 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is
964 approximately 4-fold higher than expected in the general population. Patients with Crohn's
965 disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease
966 and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several
967 fold) than the general population for the development of lymphoma, even in the absence of TNF-
968 blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing
969 TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF
970 blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold)
971 than the general population for the development of leukemia.

972
973 In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic
974 obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and
975 neck origin, were reported in REMICADE-treated patients compared with control patients. All
976 patients had a history of heavy smoking (*see ADVERSE REACTIONS, Malignancies*).
977 Prescribers should exercise caution when considering the use of REMICADE in patients with
978 moderate to severe COPD.

979
980 Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly
981 those patients who have had prior prolonged phototherapy treatment. In the maintenance portion

982 of clinical trials for REMICADE, NMSCs were more common in patients with previous
983 phototherapy (see *ADVERSE REACTIONS: Adverse Reactions in Psoriasis Studies*).

984
985 The potential role of TNF-blocking therapy in the development of malignancies is not known
986 (see *ADVERSE REACTIONS, Malignancies*). Rates in clinical trials for REMICADE cannot be
987 compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a
988 broader patient population. Caution should be exercised in considering REMICADE treatment
989 in patients with a history of malignancy or in continuing treatment in patients who develop
990 malignancy while receiving REMICADE.

991

992 **PRECAUTIONS**

993

994 **Autoimmunity**

995

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

1000

1001 **Vaccinations**

1002

1003 No data are available on the response to vaccination with live vaccines or on the secondary
1004 transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is
1005 recommended that live vaccines not be given concurrently.

1006

1007 It is recommended that all pediatric Crohn's disease patients be brought up to date with all
1008 vaccinations prior to initiating REMICADE therapy. The interval between vaccination and
1009 initiation of REMICADE therapy should be in accordance with current vaccination guidelines.

1010

1011 **Information for Patients**

1012

1013 **Patients developing signs and symptoms of infection should seek medical evaluation**
1014 **immediately.**

1015

1016 Patients or their caregivers should be provided the REMICADE Medication Guide and provided
1017 an opportunity to read it and ask questions prior to each treatment infusion session. Because
1018 caution should be exercised in administering REMICADE to patients with clinically important
1019 active infections, it is important that the patient's overall health be assessed at each treatment
1020 visit and any questions resulting from the patient's or caregiver's reading of the Medication
1021 Guide be discussed.

1022

1023 **Drug Interactions**

1024

1025 Concurrent administration of etanercept (another TNF α -blocking agent) and anakinra (an
1026 interleukin-1 receptor antagonist) has been associated with an increased risk of serious

1027 infections, and increased risk of neutropenia and no additional benefit compared to these
1028 medicinal products alone. Other TNF α -blocking agents (including REMICADE) used in
1029 combination with anakinra may also result in similar toxicities (see [WARNINGS, SERIOUS](#)
1030 [INFECTIONS](#)).

1031
1032 Specific drug interaction studies, including interactions with MTX, have not been conducted.
1033 The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one
1034 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides
1035 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.
1036 Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids,
1037 6-MP/AZA and aminosaliculates. In psoriatic arthritis clinical trials, concomitant medications
1038 included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory
1039 agents, folic acid and corticosteroids.

1040
1041 Patients with Crohn's disease who received immunosuppressants tended to experience fewer
1042 infusion reactions compared to patients on no immunosuppressants (see [ADVERSE](#)
1043 [REACTIONS, Immunogenicity and Infusion-related Reactions](#)). Serum infliximab
1044 concentrations appeared to be unaffected by baseline use of medications for the treatment of
1045 Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and
1046 aminosaliculates.

1047

1048 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

1049

1050 A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF α to evaluate
1051 tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNF α in mice.
1052 Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly
1053 for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the
1054 human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause
1055 tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the
1056 *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.
1057 Chromosomal aberrations were not observed in an assay performed using human lymphocytes.
1058 The significance of these findings for human risk is unknown. It is not known whether infliximab
1059 can impair fertility in humans. No impairment of fertility was observed in a fertility and general
1060 reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic
1061 toxicity study.

1062

1063 **Pregnancy Category B**

1064

1065 Since infliximab does not cross-react with TNF α in species other than humans and chimpanzees,
1066 animal reproduction studies have not been conducted with REMICADE. No evidence of
1067 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity
1068 study conducted in mice using an analogous antibody that selectively inhibits the functional
1069 activity of mouse TNF α . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the
1070 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to
1071 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not
1072 known whether REMICADE can cause fetal harm when administered to a pregnant woman or
1073 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if
1074 clearly needed.

1075

1076 **Nursing Mothers**

1077

1078 It is not known whether REMICADE is excreted in human milk or absorbed systemically after
1079 ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because
1080 of the potential for adverse reactions in nursing infants from REMICADE, women should not
1081 breast-feed their infants while taking REMICADE. A decision should be made whether to
1082 discontinue nursing or to discontinue the drug, taking into account the importance of the drug to
1083 the mother.

1084

1085 **Pediatric Use**

1086

1087 REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical
1088 remission in pediatric patients with moderately to severely active Crohn's disease who have had
1089 an inadequate response to conventional therapy (see [Boxed WARNINGS](#), [WARNINGS](#),
1090 [INDICATIONS AND USAGE](#), [PRECAUTIONS-Vaccinations](#), [DOSAGE AND](#)
1091 [ADMINISTRATION](#), [CLINICAL STUDIES-Active Crohn's Disease in Pediatric Patients](#) and
1092 [ADVERSE REACTIONS – Adverse Reactions in Pediatric Crohn's Disease](#)).

1093

1094 REMICADE has been studied only in combination with conventional immunosuppressive
1095 therapy in children with Crohn's disease. REMICADE has not been studied in children with
1096 Crohn's disease < 6 years of age. The longer term (greater than one year) safety and
1097 effectiveness of REMICADE in pediatric Crohn's disease patients have not been established in
1098 clinical trials.

1099

1100 Safety and effectiveness of REMICADE in pediatric patients with ulcerative colitis and plaque
1101 psoriasis have not been established.

1102

1103 The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis (JRA) were
1104 evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks,
1105 followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients
1106 with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least

1107 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤ 0.2 mg/kg/day of
1108 prednisone or equivalent), NSAIDs, and/or DMARDs was permitted.

1109
1110 Doses of 3 mg/kg REMICADE or placebo were administered intravenously at weeks 0, 2 and 6.
1111 Patients randomized to placebo crossed-over to receive 6 mg/kg REMICADE at weeks 14, 16,
1112 and 20, and then every 8 weeks through week 44. Patients who completed the study continued to
1113 receive open-label treatment with REMICADE for up to 2 years in a companion extension study.

1114
1115 The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key
1116 observations in the study included a high placebo response rate and a higher rate of
1117 immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance
1118 of infliximab was observed than had been observed in adults (see [CLINICAL
1119 PHARMACOLOGY, Pharmacokinetics](#)).

1120
1121 A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated
1122 with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg
1123 REMICADE was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who
1124 received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting,
1125 fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious
1126 infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among
1127 the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious
1128 infusion reaction, one of whom had a possible anaphylactic reaction. Two of the 6 patients who
1129 experienced serious infusion reactions received REMICADE by rapid infusion (duration of less
1130 than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3
1131 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg.

1132
1133 A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX
1134 experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6
1135 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported
1136 infections were upper respiratory tract infection and pharyngitis and the most commonly reported
1137 serious infection was pneumonia. Other notable infections included primary varicella infection in
1138 1 patient and herpes zoster in 1 patient.

1139
1140
1141

1142 **Geriatric Use**

1143
1144 In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed
1145 in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque
1146 psoriasis, aged 65 or older who received REMICADE, compared to younger patients although
1147 the incidence of serious adverse events in patients aged 65 or older was higher in both
1148 REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative
1149 colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of
1150 patients aged 65 and over to determine whether they respond differently from patients aged 18 to
1151 65. Because there is a higher incidence of infections in the elderly population in general, caution
1152 should be used in treating the elderly (see [ADVERSE REACTIONS, Infections](#)).

1153

1154 ADVERSE REACTIONS

1155

1156 The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients
1157 with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis,
1158 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17
1159 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374
1160 exposed beyond one year. (For information on adverse reactions in pediatric patients see
1161 [ADVERSE REACTIONS – Adverse Reactions in Pediatric Crohn's Disease](#).) One of the most
1162 common reasons for discontinuation of treatment was infusion-related reactions (e.g. dyspnea,
1163 flushing, headache and rash). Adverse events have been reported in a higher proportion of
1164 rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no
1165 differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10
1166 mg/kg dose in patients with Crohn's disease.

1167

1168 Infusion-related Reactions*1169 Infusion reactions*

1170

1171 An infusion reaction was defined in clinical trials as any adverse event occurring during an
1172 infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated
1173 patients in all clinical studies experienced an infusion reaction compared to approximately 10%
1174 of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by
1175 nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary
1176 reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were
1177 accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and
1178 cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included
1179 anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients
1180 discontinued REMICADE because of infusion reactions, and all patients recovered with
1181 treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial
1182 infusion were not associated with a higher incidence of reactions. The infusion reaction rates
1183 remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates
1184 were variable over time and somewhat higher following the final infusion than after the initial
1185 infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion
1186 reactions (i.e. an adverse event occurring within 1 to 2 hours) was 7% in the 3 mg/kg group, 4%
1187 in the 5 mg/kg group, and 1% in the placebo group.

1188

1189 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to
1190 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant
1191 immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and
1192 infusion reactions (see [ADVERSE REACTIONS, Immunogenicity](#) and [PRECAUTIONS, Drug Interactions](#)).

1193

1194
1195 In post-marketing experience, cases of anaphylactic-like reactions, including
1196 laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with
1197 REMICADE administration.

1198

1199 *Delayed Reactions/Reactions following readministration*1200 *Plaque Psoriasis*

1201 In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible
1202 delayed hypersensitivity reaction, generally reported as serum sickness or a combination of
1203 arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within two
1204 weeks after repeat infusion.

1205

1206 *Crohn's disease*

1207 In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following
1208 a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events
1209 manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and
1210 symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also
1211 experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.
1212 Patients experiencing these adverse events had not experienced infusion-related adverse events
1213 associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of
1214 patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients
1215 who received lyophilized formulation. The clinical data are not adequate to determine if
1216 occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms
1217 improved substantially or resolved with treatment in all cases. There are insufficient data on the
1218 incidence of these events after drug-free intervals of 1 to 2 years. These events have been
1219 observed only infrequently in clinical studies and post-marketing surveillance with retreatment
1220 intervals up to 1 year.

1221

1222 Infections

1223

1224 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated
1225 patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of
1226 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections
1227 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among
1228 REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin
1229 ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were
1230 reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was
1231 fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was
1232 reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis,
1233 including disseminated tuberculosis, also have been reported post-marketing. Most of these cases
1234 of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE
1235 and may reflect recrudescence of latent disease (see [WARNINGS, RISK OF SERIOUS
1236 INFECTIONS](#)). In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients
1237 receiving REMICADE every 8 weeks with MTX developed serious infections as compared to
1238 3.4% of placebo patients receiving MTX. Of 924 patients receiving REMICADE, 1.7%
1239 developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo
1240 arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients
1241 randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks,
1242 followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg

1243 REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54
1244 weeks Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new
1245 fistula-related abscess.

1246
1247 In REMICADE clinical studies in patients with ulcerative colitis, infections treated with
1248 antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of
1249 follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of
1250 infections, including serious infections, reported in patients with ulcerative colitis were similar to
1251 those reported in other clinical studies.

1252
1253 In post-marketing experience in the various indications, infections have been observed with
1254 various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have
1255 been noted in all organ systems and have been reported in patients receiving REMICADE alone
1256 or in combination with immunosuppressive agents.

1257
1258 The onset of serious infections may be preceded by constitutional symptoms such as fever, chills,
1259 weight loss, and fatigue. The majority of serious infections, however, may also be preceded by
1260 signs or symptoms localized to the site of the infection.

1261

1262 **Autoantibodies/Lupus-like Syndrome**

1263

1264 Approximately half of REMICADE-treated patients in clinical trials who were antinuclear
1265 antibody (ANA) negative at baseline developed a positive ANA during the trial compared with
1266 approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected
1267 in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated
1268 patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

1269

1270 **Malignancies**

1271

1272 In controlled trials, more REMICADE-treated patients developed malignancies than placebo-
1273 treated patients (*see* [WARNINGS, MALIGNANCY](#)).

1274

1275 In a randomized controlled clinical trial exploring the use of REMICADE in patients with
1276 moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were
1277 treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's
1278 disease. Nine of these REMICADE-treated patients developed a malignancy, including 1
1279 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of
1280 follow-up 0.8 years; 95% CI 3.51 - 14.56). There was one reported malignancy among 77 control
1281 patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up
1282 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head
1283 and neck.

1284

1285 Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been
1286 reported in patients receiving REMICADE during post-approval use.

1287

1288 **Patients with Heart Failure**

1289

1290 In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class
1291 III/IV; left ventricular ejection fraction $\leq 35\%$), 150 patients were randomized to receive
1292 treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks.
1293 Higher incidences of mortality and hospitalization due to worsening heart failure were observed
1294 in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg
1295 REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the
1296 placebo groups. There were trends towards increased dyspnea, hypotension, angina, and
1297 dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo.
1298 REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) (see
1299 [CONTRAINDICATIONS](#) and [WARNINGS, Patients with Heart Failure](#)).

1300

1301 **Immunogenicity**

1302

1303 Treatment with REMICADE can be associated with the development of antibodies to infliximab.
1304 The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed
1305 by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE
1306 treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease
1307 patients receiving REMICADE after drug free intervals >16 weeks. In a study of psoriatic
1308 arthritis, where 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab
1309 occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients
1310 who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy
1311 and to experience an infusion reaction (see [ADVERSE REACTIONS: Infusion-related
1312 Reactions](#)) than were patients who were antibody negative. Antibody development was lower
1313 among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies
1314 such as 6-MP/AZA or MTX.

1315

1316 In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were
1317 observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of
1318 patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also
1319 included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients
1320 treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg
1321 induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and
1322 II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for one year
1323 and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion
1324 reaction rates ($<1\%$) were similar to those observed in other study populations. The clinical
1325 significance of apparent increased immunogenicity on efficacy and infusion reactions in
1326 psoriasis patients as compared to patients with other diseases treated with REMICADE over the
1327 long term is not known.

1328

1329 The data reflect the percentage of patients whose test results were positive for antibodies to
1330 infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the
1331 assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced
1332 by several factors including sample handling, timing of sample collection, concomitant
1333 medication, and underlying disease. For these reasons, comparison of the incidence of antibodies
1334 to infliximab with the incidence of antibodies to other products may be misleading.
1335

1336 **Hepatotoxicity**

1337

1338 Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported
1339 rarely in patients receiving REMICADE (see [WARNINGS, Hepatotoxicity](#)). Reactivation of
1340 hepatitis B virus has occurred in patients receiving TNF-blocking agents, including
1341 REMICADE, who are chronic carriers of this virus (see [WARNINGS, Hepatitis B Virus](#)
1342 [Reactivation](#)).
1343

1344 In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing
1345 spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were
1346 observed (ALT more common than AST) in a greater proportion of patients receiving
1347 REMICADE than in controls ([Table 11](#)), both when REMICADE was given as monotherapy and
1348 when it was used in combination with other immunosuppressive agents. In general, patients who
1349 developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or
1350 resolved with either continuation or discontinuation of REMICADE, or modification of
1351 concomitant medications.
1352

1353

Table 11
Proportion of patients with elevated ALT in Clinical Trials

	<u>Proportion of patients with elevated ALT</u>					
	<u>>1 to <3 x ULN</u>		<u>≥3 x ULN</u>		<u>≥5 x ULN</u>	
	Placebo	REMICADE	Placebo	REMICADE	Placebo	REMICADE
Rheumatoid arthritis ¹	24%	34%	3%	4%	<1%	<1%
Crohn's disease ²	34%	39%	4%	5%	0%	2%
Ulcerative colitis ³	12%	17%	1%	2%	<1%	<1%
Ankylosing spondylitis ⁴	15%	51%	0%	10%	0%	4%
Psoriatic arthritis ⁵	16%	50%	0%	7%	0%	2%
Plaque psoriasis ⁶	24%	49%	<1%	8%	0%	3%

1354 ¹Placebo patients received methotrexate while REMICADE patients received both REMICADE and
1355 methotrexate. Median follow-up was 58 weeks.

1356 ²Placebo patients in the 2 Phase III trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at
1357 study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo
1358 maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT
1359 analysis. Median follow-up was 54 weeks.

1360 ³Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and
1361 31 weeks for REMICADE.

1362 ⁴Median follow-up was 24 weeks for placebo group and 102 weeks for REMICADE group.

1363 ⁵Median follow-up was 39 weeks for REMICADE group and 18 weeks for placebo group.

1364 ⁶ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and
1365 16 weeks for placebo.

1366

1367

1368 **Adverse Reactions in Pediatric Crohn's Disease**

1369

1370 There were some differences in the adverse reactions observed in the pediatric patients receiving
1371 REMICADE compared to those observed in adults with Crohn's disease. These differences are
1372 discussed in the following paragraphs.

1373

1374 The following adverse events were reported more commonly in 103 randomized pediatric
1375 Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult
1376 Crohn's disease patients receiving a similar treatment regimen: anemia (11%), blood in stool
1377 (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture
1378 (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

1379

1380 Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in
1381 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more
1382 frequently for patients who received every 8 week as opposed to every 12 week infusions (74%
1383 and 38%, respectively), while serious infections were reported for 3 patients in the every 8 week
1384 and 4 patients in the every 12 week maintenance treatment group. The most commonly reported
1385 infections were upper respiratory tract infection and pharyngitis, and the most commonly

1386 reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8
1387 week and 1 in the every 12 week maintenance treatment groups). Herpes zoster was reported for
1388 2 patients in the every 8 week maintenance treatment group.
1389

1390 In Study Peds Crohn's, 18% of randomized patients experienced one or more infusion reactions,
1391 with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's,
1392 there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.
1393

1394 Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn's.
1395

1396 Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric
1397 patients in Crohn's disease clinical trials; 4% had ALT elevations $\geq 3 \times$ ULN, and 1% had
1398 elevations $\geq 5 \times$ ULN. (Median follow-up was 53 weeks.)
1399

1400

1401 **Adverse Reactions in Psoriasis Studies**

1402

1403 During the placebo-controlled portion across the three clinical trials up to week 16, the
1404 proportion of patients who experienced at least 1 SAE (defined as resulting in death, life
1405 threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7%
1406 in the 3 mg/kg REMICADE group, 3.2% in the placebo group, and 3.9% in the 5 mg/kg
1407 REMICADE group.
1408

1409 Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every
1410 8 weeks through one year of maintenance treatment experienced at least 1 SAE in Study I. In
1411 Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks,
1412 respectively, through one year of maintenance treatment experienced at least 1 SAE.
1413

1414 One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg
1415 REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients
1416 receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment
1417 experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving
1418 REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least
1419 1 serious infection. The most common serious infection (requiring hospitalization) were
1420 abscesses (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg
1421 REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after
1422 starting REMICADE.
1423

1424 In placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received
1425 REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients
1426 who received placebo.
1427

1428 In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination
1429 of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of
1430 these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints,
1431 and immobility.

1432

1433 **Other Adverse Reactions**

1434

1435 Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with
1436 rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing
1437 spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions.
1438 (For information on other adverse reactions in pediatric patients, see [ADVERSE REACTIONS –](#)
1439 [Adverse Reactions in Pediatric Crohn's Disease](#)). Adverse events reported in $\geq 5\%$ of all patients
1440 with rheumatoid arthritis receiving 4 or more infusions are in [Table 12](#). The types and
1441 frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid
1442 arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients
1443 except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's
1444 disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-
1445 up for patients who never received REMICADE to provide meaningful comparisons.

1446
1447
1448
1449

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

1450
1451
1452
1453
1454

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.

1455
1456 The most common serious adverse events observed in clinical trials were infections (see
1457 [ADVERSE REACTIONS, Infections](#)). Other serious, medically relevant adverse events $\geq 0.2\%$
1458 or clinically significant adverse events by body system were as follows:
1459

1460 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
1461 *Blood:* pancytopenia
1462 *Cardiovascular:* circulatory failure, hypotension, syncope
1463 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,
1464 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
1465 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness
1466 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia
1467 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis
1468 *Metabolic and Nutritional:* dehydration
1469 *Musculoskeletal:* intervertebral disk herniation, tendon disorder
1470 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction
1471 *Platelet, Bleeding and Clotting:* thrombocytopenia
1472 *Neoplasms:* basal cell, breast, lymphoma
1473 *Psychiatric:* confusion, suicide attempt
1474 *Red Blood Cell:* anemia, hemolytic anemia
1475 *Reproductive:* menstrual irregularity
1476 *Resistance Mechanism:* cellulitis, sepsis, serum sickness
1477 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including
1478 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
1479 *Skin and Appendages:* increased sweating, ulceration
1480 *Urinary:* renal calculus, renal failure
1481 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis
1482 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy
1483

1484 **Post-marketing Adverse Events**

1485

1486 The following adverse events, some with fatal outcome, have been reported during post-approval
1487 use of REMICADE: neutropenia (see [WARNINGS, Hematologic Events](#)), interstitial lung
1488 disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive
1489 disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura,
1490 pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson
1491 Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-
1492 Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor
1493 neuropathy), new onset and worsening psoriasis (all sub-types including pustular, primarily
1494 palmoplantar), transverse myelitis, and neuropathies (additional neurologic events have also been
1495 observed, see [WARNINGS, Neurologic Events](#)) and acute liver failure, jaundice, hepatitis, and
1496 cholestasis (see [WARNINGS, Hepatotoxicity](#)). Because these events are reported voluntarily
1497 from a population of uncertain size, it is not always possible to reliably estimate their frequency
1498 or establish a causal relationship to REMICADE exposure.
1499

1500 The following serious adverse events have been reported in the post-marketing experience in
1501 children: infections (some fatal) including opportunistic infections and tuberculosis, infusion
1502 reactions, and hypersensitivity reactions.

1503
1504 Serious adverse events in the post-marketing experience with REMICADE in the pediatric
1505 population have also included malignancies, including hepatosplenic T-cell lymphomas (see
1506 [Boxed WARNINGS](#) and [WARNINGS](#)), transient hepatic enzyme abnormalities, lupus-like
1507 syndromes, and the development of autoantibodies.

1508
1509 **OVERDOSAGE**
1510
1511 Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of
1512 overdosage, it is recommended that the patient be monitored for any signs or symptoms of
1513 adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

1514
1515 **DOSAGE AND ADMINISTRATION**

1516
1517 **Rheumatoid Arthritis**

1518
1519 The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed
1520 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
1521 thereafter. REMICADE should be given in combination with methotrexate. For patients who
1522 have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or
1523 treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at
1524 higher doses (see [ADVERSE REACTIONS, Infections](#)).

1525
1526 **Crohn's Disease or Fistulizing Crohn's Disease**

1527
1528 The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at
1529 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the
1530 treatment of adults with moderately to severely active Crohn's disease or fistulizing Crohn's
1531 disease. For adult patients who respond and then lose their response, consideration may be given
1532 to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond
1533 with continued dosing and consideration should be given to discontinue REMICADE in these
1534 patients.

1535
1536 The recommended dose of REMICADE for children with moderately to severely active Crohn's
1537 disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a
1538 maintenance regimen of 5 mg/kg every 8 weeks.

1539
1540 **Ankylosing Spondylitis**

1541
1542 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed
1543 with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks
1544 thereafter.

1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584

Psoriatic Arthritis

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

Plaque Psoriasis

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

Ulcerative Colitis

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

Administration Instructions Regarding Infusion Reactions

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

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

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

1585 Preparation and Administration Instructions**1586 Use aseptic technique.**

1587

1588 REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after
1589 reconstitution should be used immediately, not re-entered or stored. The diluent to be used for
1590 reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted
1591 product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The
1592 infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE
1593 infusion should begin within 3 hours of preparation.

1594

1595 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial
1596 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE
1597 solution required.

1598

1599 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a
1600 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and
1601 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center
1602 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass
1603 wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized
1604 powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the
1605 solution on reconstitution is not unusual. Allow the reconstituted solution to stand for
1606 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution
1607 may develop a few translucent particles as infliximab is a protein. Do not use if opaque
1608 particles, discoloration, or other foreign particles are present.

1609

1610 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with
1611 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride
1612 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium
1613 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted
1614 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.

1615

1616 4. The infusion solution must be administered over a period of not less than 2 hours and must
1617 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore
1618 size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for
1619 reuse.

1620

1621 5. No physical biochemical compatibility studies have been conducted to evaluate the co-
1622 administration of REMICADE with other agents. REMICADE should not be infused
1623 concomitantly in the same intravenous line with other agents.

1624

1625 6. Parenteral drug products should be inspected visually for particulate matter and
1626 discoloration prior to administration, whenever solution and container permit. If visibly
1627 opaque particles, discoloration or other foreign particulates are observed, the solution
1628 should not be used.

1629

1630 **Storage**

1631
1632 Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not use
1633 beyond the expiration date. This product contains no preservative.

1634
1635
1636 **HOW SUPPLIED**

1637
1638 REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-
1639 use vials in the following strength:

1640 NDC 57894-030-01 100 mg infliximab in a 20 mL vial

1641
1642
1643
1644 **REFERENCES**

- 1645
1646 1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin
1647 testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*
1648 2000;161:S221-S247.
- 1649
1650 2. See latest Center for Disease Control guidelines and recommendations for tuberculosis
1651 testing in immunocompromised patients.
- 1652
1653 3. Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human
1654 chimeric anti-TNF antibody. *Molec Immunol* 1993;30:1443-1453.
- 1655
1656 4. Scallon BJ, Moore MA, Trinh H, et al. Chimeric anti-TNF α monoclonal antibody cA2 binds
1657 recombinant transmembrane TNF α and activates immune effector functions. *Cytokine*
1658 1995;7:251-259.
- 1659
1660 5. ten Hove T, van Montfrans C, Peppelenbosch MP, et al. Infliximab treatment induces
1661 apoptosis of lamina propria T lymphocytes in Crohn's disease. *Gut* 2002;50:206-211.
- 1662
1663 6. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous
1664 infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose
1665 weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41(9):1552-1563.
- 1666
1667 7. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric
1668 monoclonal antibody to tumour necrosis factor alpha (cA2) vs. placebo in rheumatoid
1669 arthritis. *Lancet* 1994;344(8930):1105-1110.
- 1670
1671 8. Van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic
1672 assessments of hands and feet in a three-year prospective follow-up of patients with early
1673 rheumatoid arthritis. *Arthritis Rheum* 1992;35(1):26-34.
- 1674

- 1675 9. Targan SR, Hanauer SB, van Deventer SJH, et al. A short-term study of chimeric
1676 monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. *N Engl J Med*
1677 1997;337(15):1029-1035.
1678
- 1679 10. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's
1680 disease: the ACCENT I randomized trial. *Lancet* 2002; 359:1541-1549.
1681
- 1682 11. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients
1683 with Crohn's disease. *N Engl J Med* 1999;340:1398-1405.
1684
- 1685 12. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for
1686 ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis*
1687 *Rheum.* 1984;27(4):361-368.
1688
- 1689 13. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for
1690 mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.*
1691 1987;317(26):1625-1629.
1692
- 1693 14. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumor necrosis factor agents and
1694 tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis*
1695 2003;3:148-155.
1696
- 1697 15. Belhadj K, Reyes F, Farcet JP, et al. Hepatosplenic $\gamma\delta$ T-cell lymphoma is a rare
1698 clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood*
1699 2003;102(13):4261-4269.

1700
1701
1702
1703
1704
1705
1706
1707

©Centocor Ortho Biotech Inc. 2009
Malvern, PA 19355, USA
1-800-457-6399

License #1821
November 2009

1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751

MEDICATION GUIDE
REMICADE® (Rem-eh-kaid)
(infliximab)

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

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

REMICADE may cause serious side effects, including:

1. **Risk of infection**

REMICADE is a medicine that affects your immune system. REMICADE can lower the ability of your immune system to fight infections. Serious infections have happened in patients receiving REMICADE. These infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some patients have died from these infections.

- Your doctor should test you for TB before starting REMICADE.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with REMICADE.

Before starting REMICADE, tell your doctor if you:

- think you have an infection. You should not start taking REMICADE if you have any kind of infection.
- are being treated for an infection
- have signs of an infection, such as a fever, cough, flu-like symptoms
- have any open cuts or sores on your body
- get a lot of infections or have infections that keep coming back
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- Have TB, or have been in close contact with someone with TB
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may develop or become more severe if you take REMICADE. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your doctor.
- have or have had hepatitis B
- use the medicine Kineret (anakinra)

After starting REMICADE, if you have an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your doctor right

1752 away. REMICADE can make you more likely to get infections or make any infection that you
1753 have worse.

1754

1755 **2. Risk of Cancer**

- 1756 • There have been cases of unusual cancers in children and teenage patients using TNF-
1757 blocking agents.
 - 1758 • For children and adults taking TNF-blocker medicines, including REMICADE, the
1759 chances of getting lymphoma or other cancers may increase.
 - 1760 • People who have been treated for rheumatoid arthritis, Crohn's disease, ankylosing
1761 spondylitis, psoriatic arthritis and plaque psoriasis for a long time may be more likely to
1762 develop lymphoma. This is especially true for people with very active disease.
 - 1763 • Some patients with Crohn's disease or ulcerative colitis who have received REMICADE
1764 have developed a rare type of cancer called Hepatosplenic T-cell Lymphoma. Most of
1765 these patients were teenage or young adult males. This type of cancer results in death.
1766 All of these patients had also received drugs known as azathioprine or 6-mercaptopurine
1767 together with REMICADE.
 - 1768 • Patients with COPD (a specific type of lung disease) may have an increased risk for
1769 getting cancer while being treated with REMICADE.
 - 1770 • Tell your doctor if you have ever had any type of cancer. Discuss with your doctor any
1771 need to adjust medicines you may be taking.
- 1772

1773 See the section "[What are the possible side effects of REMICADE?](#)" below for more
1774 information.

1775

1776 **What is REMICADE?**

1777

1778 REMICADE is a prescription medicine that is approved for patients with:

- 1779 • Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis,
1780 along with the medicine methotrexate
 - 1781 • Crohn's Disease - children over the age of 6 and adults with Crohn's disease who have not
1782 responded well enough to other medicines
 - 1783 • Ankylosing Spondylitis
 - 1784 • Psoriatic Arthritis
 - 1785 • Plaque Psoriasis - adult patients with plaque psoriasis that is chronic (doesn't go away)
1786 severe, extensive, and/or disabling.
 - 1787 • Ulcerative Colitis - adults with moderately to severely active ulcerative colitis who have
1788 not responded well enough to other medicines.
- 1789

1790 REMICADE blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-
1791 alpha). TNF-alpha is made by your body's immune system. People with certain diseases have
1792 too much TNF-alpha that can cause the immune system to attack normal healthy parts of the
1793 body. REMICADE can block the damage caused by too much TNF-alpha.

1794

1795 **Who should not receive REMICADE?**

- 1796
- 1797 You should not receive REMICADE if you have:
- 1798 • heart failure, unless your doctor has examined you and decided that you are able to take
 - 1799 REMICADE. Talk to your doctor about your heart failure.
 - 1800 • had an allergic reaction to REMICADE, or any of the other ingredients in REMICADE.
 - 1801 See the end of this [Medication Guide for a complete list of ingredients in REMICADE](#).

1802

1803 **What should I tell my doctor before starting treatment with REMICADE?**

1804

1805 Your doctor will assess your health before each treatment.

1806

1807 Tell your doctor about all of your medical conditions, including if you:

- 1808 • have an infection (see [“What is the most important information I should know about](#)
- 1809 [REMICADE](#))
- 1810 • have other liver problems including liver failure.
- 1811 • have heart failure or other heart conditions. If you have heart failure, it may get worse
- 1812 while you take REMICADE.
- 1813 • have or have had any type of cancer.
- 1814 • have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine
- 1815 to make your skin sensitive to light) for psoriasis. You may have a higher chance of
- 1816 getting skin cancer while receiving REMICADE.
- 1817 • have COPD (Chronic Obstructive Pulmonary Disease), a specific type of lung disease.
- 1818 Patients with COPD may have an increased risk of getting cancer while taking
- 1819 REMICADE.
- 1820 • have or have had a condition that affects your nervous system such as
- 1821 • multiple sclerosis, or Guillain-Barré syndrome, or
- 1822 • if you experience any numbness or tingling, or
- 1823 • if you have had a seizure.
- 1824 • have recently received or are scheduled to receive a vaccine. **Adults and children**
- 1825 **should not receive a live vaccine while taking REMICADE.** Children with Crohn's
- 1826 disease should have all of their vaccines brought up to date before starting treatment with
- 1827 REMICADE.
- 1828 • are pregnant or planning to become pregnant. It is not known if REMICADE harms your
- 1829 unborn baby. REMICADE should be given to a pregnant woman only if clearly needed.
- 1830 Talk to your doctor about stopping REMICADE if you are pregnant or planning to
- 1831 become pregnant.
- 1832 • are breast-feeding or planning to breast-feed. It is not known whether REMICADE
- 1833 passes into your breast milk. Talk to your doctor about the best way to feed your baby
- 1834 while taking REMICADE. You should not breast-feed while taking REMICADE.

1835

1836 **How should I receive REMICADE?**

- 1837
- 1838 • You will be given REMICADE through a needle placed in a vein (IV or intravenous
 - 1839 infusion) in your arm.
 - 1840 • Your doctor may decide to give you medicine before starting the REMICADE infusion to
 - 1841 prevent or lessen side effects.
 - 1842 • Only a healthcare professional should prepare the medicine and administer it to you.
 - 1843 • REMICADE will be given to you over a period of about 2 hours.
 - 1844 • If you have side effects from REMICADE, the infusion may need to be adjusted or
 - 1845 stopped. In addition, your healthcare professional may decide to treat your symptoms.
 - 1846 • A healthcare professional will monitor you during the REMICADE infusion and for a
 - 1847 period of time afterward for side effects. Your doctor may do certain tests while you are
 - 1848 taking REMICADE to monitor you for side effects and to see how well you respond to
 - 1849 the treatment.
 - 1850 • Your doctor will determine the right dose of REMICADE for you and how often you
 - 1851 should receive it. Make sure to discuss with your doctor when you will receive infusions
 - 1852 and to come in for all your infusions and follow-up appointments.
- 1853

1854 **What should I avoid while receiving REMICADE?**

1855

1856 Do not take REMICADE and the medication KINERET (Anakinra) together.

1857

1858 **Tell your doctor about all the medicines you take**, including prescription and non-prescription

1859 medicines, vitamins, and herbal supplements.

1860

1861 Know the medicines you take. Keep a list of your medicines and show them to your doctor and

1862 pharmacist when you get a new medicine.

1863

1864 **What are the possible side effects of REMICADE?**

1865

1866 Remicade can cause serious side effects, including:

1867

1868 See **[“What is the most important information I should know about REMICADE?”](#)**

1869

1870 Serious Infections

- 1871 • Some patients have had serious infections while receiving REMICADE. These serious
- 1872 infections include TB and infections caused by viruses, fungi, or bacteria that have spread
- 1873 throughout the body. Some patients die from these infections. If you get an infection
- 1874 while receiving treatment with REMICADE your doctor will treat your infection and may
- 1875 need to stop your REMICADE treatment.
- 1876 • Tell your doctor right away if you have any of the following signs of an infection while
- 1877 taking or after taking REMICADE:
 - 1878 • a fever
 - 1879 • feel very tired
 - 1880 • have a cough

- 1881 • have flu-like symptoms
 1882 • warm, red, or painful skin
 1883 • Your doctor will examine you for TB and perform a test to see if you have TB. If your
 1884 doctor feels that you are at risk for TB, you may be treated with medicine for TB before
 1885 you begin treatment with REMICADE and during treatment with REMICADE.
 1886 • Even if your TB test is negative your doctor should carefully monitor you for TB
 1887 infections while you are taking REMICADE. Patients who had a **negative** TB skin test
 1888 before receiving REMICADE have developed active TB.
 1889 • If you are a chronic carrier of the hepatitis B virus, the virus can become active while you
 1890 are being treated with REMICADE. In some cases patients have died as a result of
 1891 hepatitis B virus being reactivated. Your doctor may do a blood test before you start
 1892 treatment with REMICADE and occasionally while you are being treated. Tell your
 1893 doctor if you have any of the following symptoms:
 1894 • feel unwell
 1895 • poor appetite
 1896 • tiredness (fatigue)
 1897 • fever, skin rash and/or joint pain

1899 Heart Failure

1900 If you have a heart problem called congestive heart failure, your doctor should check you closely
 1901 while you are taking REMICADE. Your congestive heart failure may get worse while you are
 1902 taking REMICADE. Be sure to tell your doctor of any new or worse symptoms including:

- 1903 • Shortness of breath
- 1904 • Swelling of ankles or feet
- 1905 • Sudden weight gain

1906 Treatment with REMICADE may need to be stopped if you get new or worse congestive heart
 1907 failure.

1909 Liver Injury

1910 In rare cases, some patients taking REMICADE have developed serious liver problems. Tell
 1911 your doctor if you have

- 1912 • Jaundice (skin and eyes turning yellow)
- 1913 • Dark brown-colored urine
- 1914 • Pain on the right side of your stomach area (right-sided abdominal pain)
- 1915 • Fever
- 1916 • Extreme tiredness (severe fatigue)

1918 Blood Problems

1919 In some patients taking REMICADE, the body may not make enough of the blood cells that help
 1920 fight infections or help stop bleeding. Tell your doctor if you

- 1921 • Have a fever that does not go away
- 1922 • Bruise or bleed very easily
- 1923 • Look very pale

1925 Nervous System Disorders

1926 In rare cases, patients taking REMICADE have developed problems with their nervous system.

1927 Tell your doctor if you have

- 1928 • Changes in your vision
- 1929 • Weakness in your arms and/or legs
- 1930 • Numbness or tingling in any part of your body
- 1931 • Seizures

1932

1933 Allergic Reactions

1934 Some patients have had allergic reactions to REMICADE. Some of these reactions were severe.

1935 These reactions can happen while you are getting your REMICADE treatment or shortly
1936 afterwards. Your doctor may need to stop or pause your treatment with REMICADE and may
1937 give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:

- 1938 • Hives (red, raised, itchy patches of skin)
- 1939 • Difficulty breathing
- 1940 • Chest pain
- 1941 • High or low blood pressure
- 1942 • Fever
- 1943 • Chills

1944 Some patients treated with REMICADE have had delayed allergic reactions. The delayed
1945 reactions occurred 3 to 12 days after receiving treatment with REMICADE. Tell your doctor
1946 right away if you have any of these signs of delayed allergic reaction to REMICADE:

- 1947 • Fever
- 1948 • Rash
- 1949 • Headache
- 1950 • Sore throat
- 1951 • Muscle or joint pain
- 1952 • Swelling of the face and hands
- 1953 • Difficulty swallowing

1954

1955 Lupus-like Syndrome

1956 Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any
1957 of the following symptoms your doctor may decide to stop your treatment with REMICADE.

- 1958 • Chest discomfort or pain that does not go away
- 1959 • Shortness of breath
- 1960 • Joint pain
- 1961 • Rash on the cheeks or arms that gets worse in sun

1962

1963 Psoriasis

1964 Some people using REMICADE had new psoriasis or worsening of psoriasis they already had.

1965 Tell your doctor if you develop red scaly patches or raised bumps on the skin that are filled with
1966 pus. Your doctor may decide to stop your treatment with REMICADE.

1967

1968

1969 **The most common side effects of REMICADE are**

1970

- 1971 • Respiratory infections, such as sinus infections and sore throat)
- 1972 • Headache
- 1973 • Rash
- 1974 • Coughing
- 1975 • Stomach pain

1976 Children who took REMICADE in studies for Crohn's disease, showed some differences in side
1977 effects compared with adults who took REMICADE for Crohn's disease. The side effects that
1978 happened more in children were: anemia (low red blood cells), blood in stool, leukopenia (low
1979 white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils,
1980 the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions
1981 of the breathing tract.

1982 Tell your doctor about any side effect that bothers you or does not go away.

1983 These are not all of the side effects with REMICADE. Ask your doctor or pharmacist for more
1984 information.

1985

1986 **General information about REMICADE**

1987

1988 Medicines are sometimes prescribed for purposes that are not mentioned in Medication Guides or
1989 patient information sheets. Do not use REMICADE for a condition for which it was not
1990 prescribed.

1991

1992 This information sheet summarizes the most important information about REMICADE. You can
1993 ask your doctor or pharmacist for information about REMICADE that is written for health
1994 professionals.

1995

1996 Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-
1997 800-FDA-1088.

1998

1999 For more information go to www.remicade.com or call 1-800-457-6399.

2000

2001 **What are the ingredients in REMICADE?**

2002

2003 The active ingredient is Infliximab.

2004 The inactive ingredients in REMICADE include: sucrose, polysorbate 80, monobasic sodium
2005 phosphate monohydrate, and dibasic sodium phosphate dihydrate. No preservatives are present.

2006

2007 Product developed and manufactured by:

2008 Centocor Ortho Biotech Inc.

2009 200 Great Valley Parkway

2010 Malvern, PA 19355

2011

STN: BL 103772/5258

October 29, 2009

2012 Revised November 2009

2013

2014 This Medication Guide has been approved by the U.S. Food and Drug Administration.