

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

6 **WARNINGS**
7

8 **RISK OF INFECTIONS**
9

10 **Patients treated with REMICADE are at increased risk for infections, including**
11 **progression to serious infections leading to hospitalization or death (see WARNINGS and**
12 **ADVERSE REACTIONS). These infections have included bacterial sepsis, tuberculosis,**
13 **invasive fungal and other opportunistic infections. Patients should be educated about the**
14 **symptoms of infection, closely monitored for signs and symptoms of infection during and**
15 **after treatment with REMICADE, and should have access to appropriate medical care.**
16 **Patients who develop an infection should be evaluated for appropriate antimicrobial**
17 **therapy and for serious infections REMICADE should be discontinued.**
18

19 **Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation) has been**
20 **observed in patients receiving REMICADE. Patients should be evaluated for tuberculosis**
21 **risk factors and be tested for latent tuberculosis infection^{1,2} prior to initiating REMICADE**
22 **and during therapy. Treatment of latent tuberculosis infection should be initiated prior to**
23 **therapy with REMICADE. Treatment of latent tuberculosis in patients with a reactive**
24 **tuberculin test reduces the risk of tuberculosis reactivation in patients receiving**
25 **REMICADE. Some patients who tested negative for latent tuberculosis prior to receiving**
26 **REMICADE have developed active tuberculosis. Physicians should monitor patients**
27 **receiving REMICADE for signs and symptoms of active tuberculosis, including patients**
28 **who tested negative for latent tuberculosis infection.**
29

30
31 **HEPATOSPLENIC T-CELL LYMPHOMAS**
32

33 **Rare postmarketing cases of hepatosplenic T-cell lymphoma have been reported in**
34 **adolescent and young adult patients with Crohn's disease treated with REMICADE. This**
35 **rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. All**
36 **of these hepatosplenic T-cell lymphomas with REMICADE have occurred in patients on**
37 **concomitant treatment with azathioprine or 6-mercaptopurine.**
38
39
40

DESCRIPTION

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

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

CLINICAL PHARMACOLOGY**General**

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

77 Pharmacodynamics

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

**98
99 Pharmacokinetics**

100
101 In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship
102 between the dose administered and the maximum serum concentration. The volume of
103 distribution at steady state was independent of dose and indicated that infliximab was distributed
104 primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg
105 to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn's disease, and 3 mg/kg to 5 mg/kg in
106 plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days.

107
108 Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in
109 predictable concentration-time profiles following each treatment. No systemic accumulation of
110 infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-
111 week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8
112 weeks after a maintenance dose of 3 to 10 mg/kg of REMICADE, median infliximab serum
113 concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations
114 were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab.
115 No major differences in clearance or volume of distribution were observed in patient subgroups
116 defined by age, weight, or gender. It is not known if there are differences in clearance or volume
117 of distribution in patients with marked impairment of hepatic or renal function.

118
119 Infliximab peak and trough concentrations were similar in pediatric (aged 6 to 17 years old) and
120 adult patients with Crohn's disease following the administration of the recommended regimen
121 (see DOSAGE AND ADMINISTRATION, Crohn's Disease or Fistulizing Crohn's Disease).

122

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

128

129 **CLINICAL STUDIES**

130 **Rheumatoid Arthritis**

131

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

136

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

143

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

150

151 Data on use of REMICADE without concurrent MTX are limited (see ADVERSE REACTIONS,
152 Immunogenicity).^{6,7}

153

154 *Clinical response*

155

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

163

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

Table 1
ACR RESPONSE (PERCENT OF PATIENTS)

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

^a p ≤ 0.001

^b p < 0.01

^c p < 0.05

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

Parameter (medians)	Placebo + MTX (n=88)		REMICADE + MTX ^a (n=340)	
	Baseline	Week 54	Baseline	Week 54
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain ^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)

170

171 *Radiographic response*

172

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

177

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

181

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

191 who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had
 192 no progression (vdH-S score ≤ 0 unit) of structural damage compared to 45% patients receiving
 193 MTX alone. In a subset of patients who began the study without erosions, REMICADE + MTX
 194 maintained an erosion free state at 1 year in a greater proportion of patients than MTX alone,
 195 79% (77/98) vs. 58% (23/40), respectively ($p < 0.01$). Fewer patients in the REMICADE + MTX
 196 groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).
 197

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.

199 *Physical function response*

200
201 Physical function and disability were assessed using the Health Assessment Questionnaire
202 (HAQ-DI) and the general health-related quality of life questionnaire SF-36.

203
204 In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater
205 improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged
206 over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental
207 component summary score. The median (interquartile range) improvement from baseline to
208 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
209 REMICADE + MTX ($p < 0.001$). Both HAQ-DI and SF-36 effects were maintained through week
210 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in
211 the trial through 102 weeks.

212
213 In Study RA II, both REMICADE treatment groups showed greater improvement in HAQ-DI
214 from baseline averaged over time through week 54 compared to MTX alone; 0.7 for
215 REMICADE + MTX vs. 0.6 for MTX alone ($p \leq 0.001$). No worsening in the SF-36 mental
216 component summary score was observed.

217
218 **Active Crohn's Disease**

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

226
227 In the single-dose trial⁹ of 108 patients, 16% (4/25) of placebo patients achieved a clinical
228 response (decrease in CDAI ≥ 70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg
229 REMICADE ($p < 0.001$, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo
230 patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission
231 (CDAI < 150) at week 4.

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

240
241 At week 2, 57% (311/545) of patients were in clinical response. At week 30, a significantly
242 greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved
243 clinical remission compared to patients in the placebo maintenance group (Table 4).

244
 245 Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg
 246 REMICADE maintenance groups were in clinical remission and were able to discontinue
 247 corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).
 248

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

	Single 5 mg/kg Dose ^a	Three Dose Induction ^b	
	<u>Placebo Maintenance</u>	<u>REMICADE Maintenance q 8</u>	
		<u>5 mg/kg</u>	<u>10 mg/kg</u>
Week 30	25/102	41/104	48/105
Clinical remission	25%	39%	46%
p-value ^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

249
 250 ^aREMICADE at week 0
 251 ^bREMICADE 5 mg/kg administered at weeks 0, 2 and 6
 252 ^cp-values represent pairwise comparisons to placebo
 253 ^dOf those receiving corticosteroids at baseline
 254
 255 Patients in the REMICADE maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to
 256 loss of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54,
 257 significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg REMICADE-
 258 treated groups compared to the placebo group in the disease specific inflammatory bowel disease
 259 questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical
 260 component summary score of the general health-related quality of life questionnaire SF-36.
 261

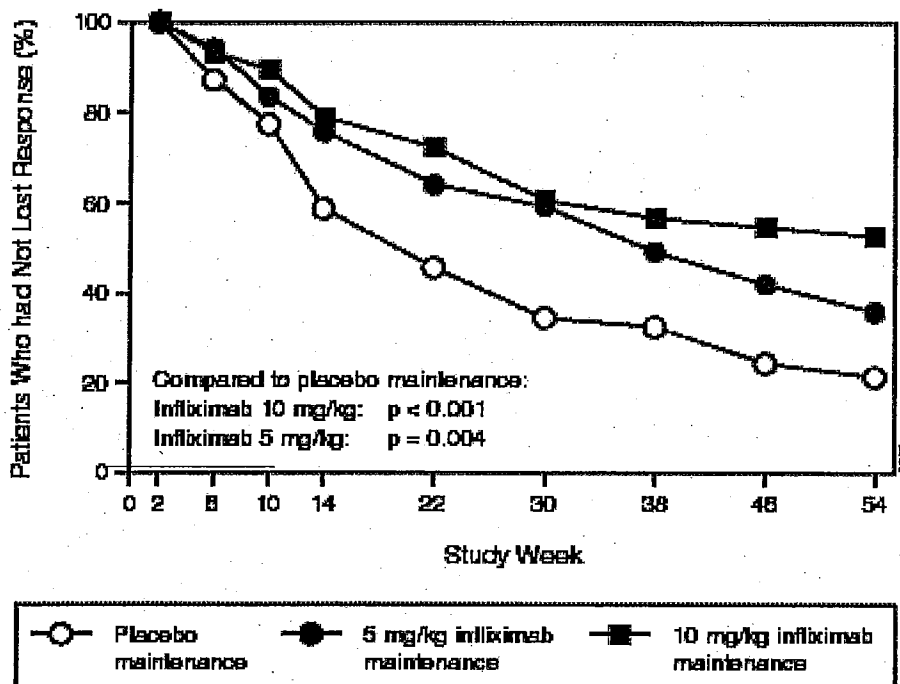


Figure 1
Kaplan-Meier estimate of the proportion of patients
who had not lost response through week 54

262
 263
 264
 265
 266
 267
 268
 269
 270
 271
 272
 273
 274
 275
 276
 277
 278
 279
 280
 281
 282
 283
 284
 285
 286
 287
 288

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.

289 In the first trial,¹¹ 94 patients received three doses of either placebo or REMICADE at weeks 0,
290 2 and 6. Fistula response ($\geq 50\%$ reduction in number of enterocutaneous fistulas draining upon
291 gentle compression on at least two consecutive visits without an increase in medication or
292 surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE
293 group ($p=0.002$) and 56% (18/32) of patients in the 10 mg/kg REMICADE group ($p=0.021$) vs.
294 26% (8/31) of patients in the placebo arm. The median time to onset of response and median
295 duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure
296 of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of
297 placebo-treated patients ($p<0.001$).

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

307
308 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and
309 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of
310 the patients had received previous immunosuppressive and antibiotic therapy.

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

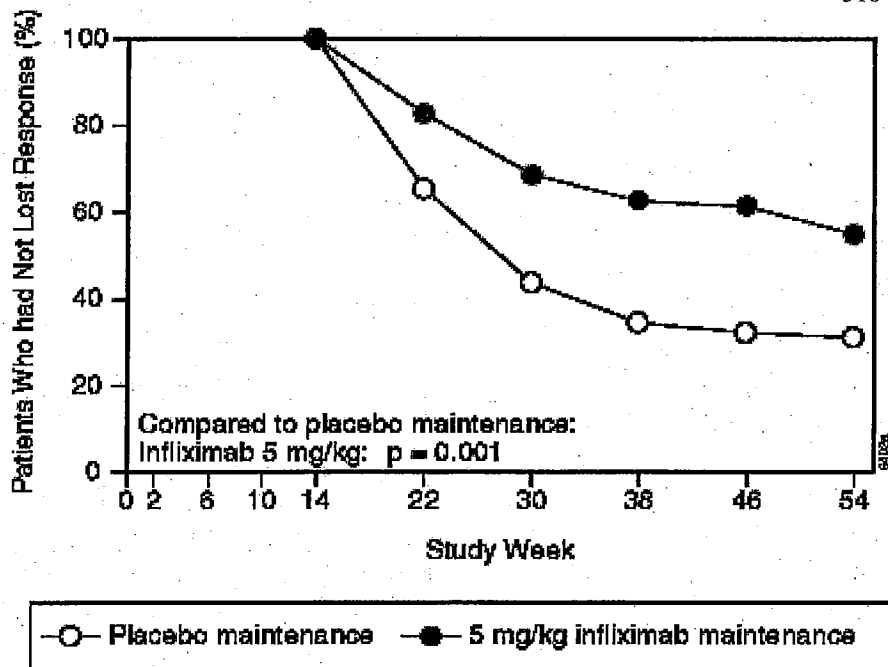


Figure 2
Life table estimates of the proportion of patients
who had not lost fistula response through week 54

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

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

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

Active Crohn’s Disease in Pediatric Patients

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

346 All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. At Week
347 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given
348 either every 8 weeks or every 12 weeks.

349
350 At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in
351 the PCDAI score of ≥ 15 points and total PCDAI score of ≤ 30 points), and 59% were in clinical
352 remission (defined as PCDAI score of ≤ 10 points).

353
354 The proportion of pediatric patients achieving clinical response at Week 10 compared favorably
355 with the proportion of adults achieving a clinical response in Study Crohn's I. The study
356 definition of clinical response in Study Peds Crohn's was based on the PCDAI score, whereas
357 the CDAI score was used in the adult Study Crohn's I.

358
359 At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the
360 every 8 week treatment group than in the every 12 week treatment group (73% vs. 47% at Week
361 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in
362 clinical remission was also greater in the every 8 week treatment group than in the every
363 12 week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), (Table 5).

364
365 For patients in Study Peds Crohn's receiving corticosteroids at baseline, the proportion of
366 patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every
367 8 week maintenance group and 33% for the every 12 week maintenance group. At Week 54, the
368 proportion of patients able to discontinue corticosteroids while in remission was 46% for the
369 every 8 week maintenance group and 17% for the every 12 week maintenance group.

370

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

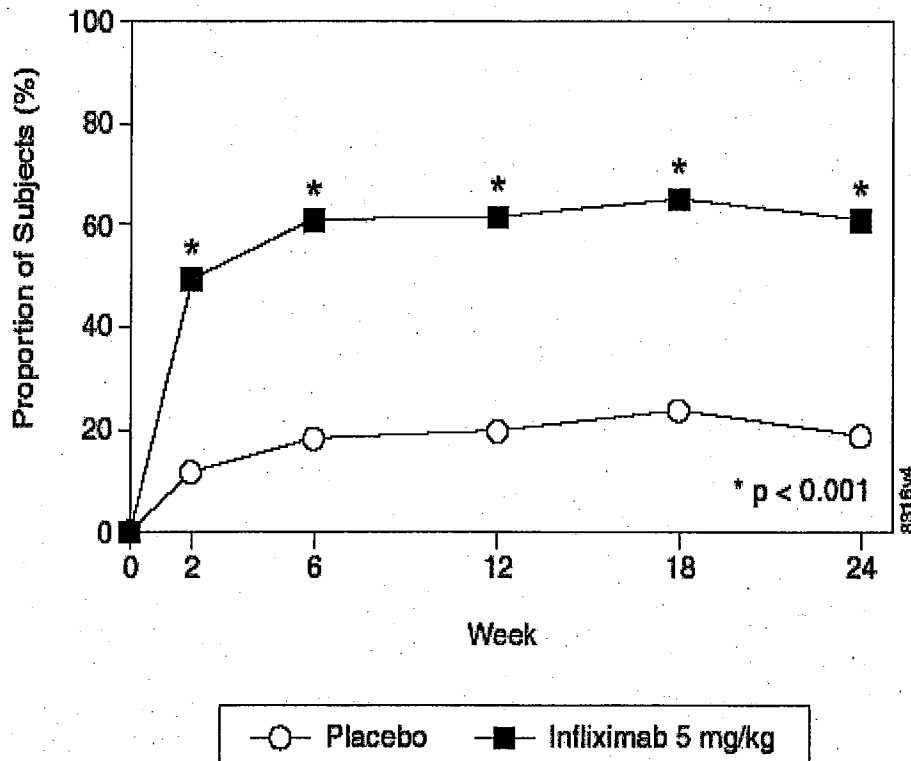
396 **Ankylosing Spondylitis**

397

398 The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-
 399 blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were
 400 between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New
 401 York criteria for Ankylosing Spondylitis.¹² Patients were to have had active disease as
 402 evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4
 403 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients
 404 with complete ankylosis of the spine were excluded from study participation, and the use of
 405 Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were
 406 prohibited. Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks
 407 0, 2, 6, 12 and 18.

408

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



414
 415
 416
 417

Figure 3
 Proportion of patients achieving ASAS 20 response

418
419 At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs
420 and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and
421 ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE,
422 compared to 9% and 4%, respectively, for patients receiving placebo ($p < 0.001$, REMICADE vs.
423 placebo). A low level of disease activity (defined as a value < 20 [on a scale of 0-100 mm] in
424 each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated
425 patients vs. 1% in placebo-treated patients ($p < 0.001$).

426
427 **Table 6**
428 **Components of Ankylosing Spondylitis Disease Activity**
429

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

430
431 The median improvement from baseline in the general health-related quality of life questionnaire
432 SF-36 physical component summary score at week 24 was 10.2 for the REMICADE group vs.
433 0.8 for the placebo group ($p < 0.001$). There was no change in the SF-36 mental component
434 summary score in either the REMICADE group or the placebo group.

435
436 Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled
437 study of 70 patients with ankylosing spondylitis.

438 439 Psoriatic Arthritis

440

441 Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-
442 controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID
443 therapy (≥ 5 swollen joints and ≥ 5 tender joints) with one or more of the following subtypes:
444 arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis
445 (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients
446 also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Forty-six percent of
447 patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-week double-
448 blind phase, patients received either 5 mg/kg REMICADE or placebo at weeks 0, 2, 6, 14, and 22
449 (100 patients in each group). At week 16, placebo patients with $< 10\%$ improvement from
450 baseline in both swollen and tender joint counts were switched to REMICADE induction (early
451 escape). At week 24, all placebo-treated patients crossed over to REMICADE induction.
452 Dosing continued for all patients through week 46.

453

454 *Clinical response*

455

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

465

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

471

472

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

473

474

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

484

485 *Radiographic response*

486

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

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

499

500 *Physical function*

501

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

506

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

513

514 **Plaque Psoriasis**

515

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

523

524 Study I (EXPRESS) evaluated 378 patients who received placebo or REMICADE at a dose of 5
525 mg/kg at weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks.
526 At week 24, the placebo group crossed over to REMICADE induction therapy (5 mg/kg),
527 followed by maintenance therapy every 8 weeks. Patients originally randomized to REMICADE
528 continued to receive REMICADE 5 mg/kg every 8 weeks through week 46. Across all treatment
529 groups, the median baseline PASI score was 21 and the baseline Static Physician Global
530 Assessment (sPGA) score ranged from moderate (52% of patients) to marked (36%) to severe
531 (2%). In addition, 75% of patients had a BSA $>20\%$. Seventy-one percent of patients
532 previously received systemic therapy and 82% received phototherapy.

533

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

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

551
552 In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a
553 reduction in score of at least 75% from baseline at week 10 by the PASI (PASI 75). In Study I
554 and Study III, another evaluated outcome included the proportion of patients who achieved a
555 score of "cleared" or "minimal" by the sPGA. The sPGA is a 6 category scale ranging from
556 "5 = severe" to "0 = cleared" indicating the physician's overall assessment of the psoriasis
557 severity focusing on induration, erythema, and scaling. Treatment success, defined as "cleared"
558 or "minimal", consisted of none or minimal elevation in plaque, up to faint red coloration in
559 erythema, and none or minimal fine scale over < 5% of the plaque.

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

568
569
570
571

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

	Placebo	REMICADE	
		3 mg/kg	5 mg/kg
Psoriasis Study I - patients randomized ^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.

572

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

576

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

583

584 Maintenance of response was studied in a subset of 292 and 297 REMICADE treated patients in
585 the 3 mg/kg and 5 mg/kg groups; respectively, in Study II. Stratified by PASI response at week
586 10 and investigational site, patients in the active treatment groups were re-randomized to either a
587 scheduled or as needed maintenance (PRN) therapy, beginning on week 14.

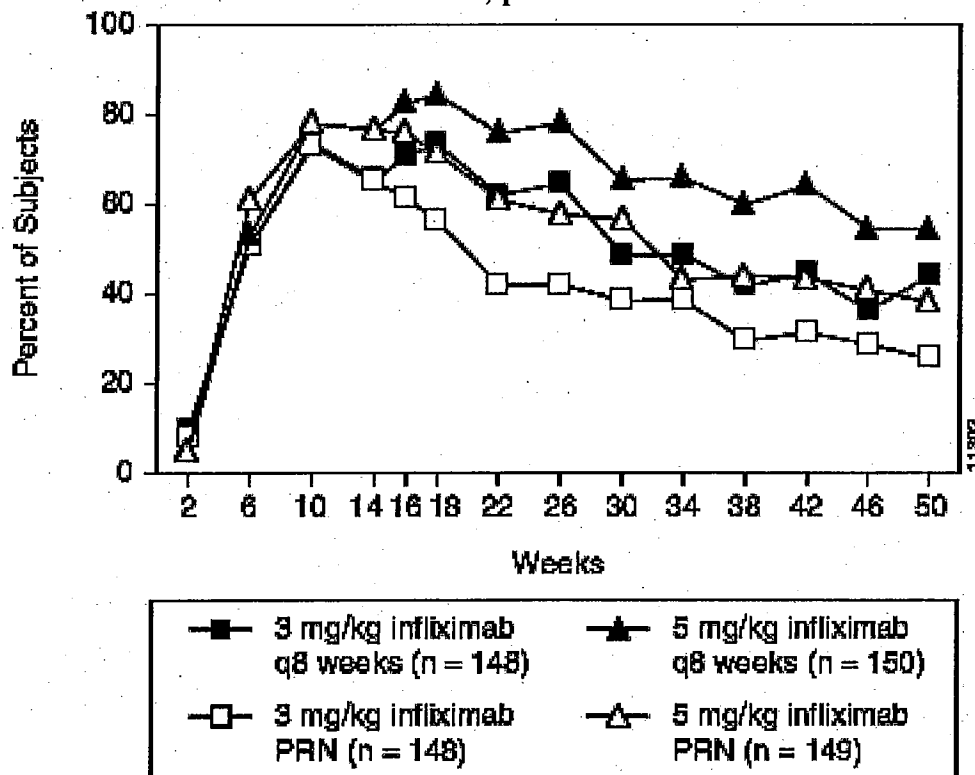
588

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

595 the 3mg/kg every 8 week dose group compared to the 5mg/kg group was associated with a lower
 596 percentage of patients with detectable trough serum infliximab levels. This may be related in
 597 part to higher antibody rates (see ADVERSE REACTIONS: Immunogenicity). In addition, in a
 598 subset of patients who had achieved a response at week 10, maintenance of response appears to
 599 be greater in patients who received REMICADE every 8 weeks at the 5 mg/kg dose. Regardless
 600 of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a
 601 subpopulation of patients in each group over time. The results of Study I through Week 50 in the
 602 5mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

603
604
605
606

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



607
608
609

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

612
613
614

Ulcerative Colitis

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

620 agents was permitted. Corticosteroid taper was permitted after week 8. Patients were
621 randomized at week 0 to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE
622 at weeks 0, 2, 6, and every 8 weeks thereafter through week 46 in Study UC I, and at weeks 0, 2,
623 6, and every 8 weeks thereafter through week 22 in Study UC II. In Study UC II, patients were
624 allowed to continue blinded therapy to week 46 at the investigator's discretion.

625
626 Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-
627 mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or
628 were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients
629 in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-
630 MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More
631 patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%,
632 respectively). Clinical response was defined as a decrease from baseline in the Mayo score by \geq
633 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal
634 bleeding subscore of 0 or 1.

635

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

637

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

643

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

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 Response ⁴						
(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 Remission ⁴						
(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
<hr/>						
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

652

653 * P < 0.001, ** P < 0.01

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

657 ² Defined as a Mayo score ≤ 2 points, no individual subscore > 1 .

658 ³ Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

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

662

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

665

666

Table 10

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

669

	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%

670

671

672 **INDICATIONS AND USAGE**

673

674 **Rheumatoid Arthritis**

675

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

679

680 **Crohn's Disease**

681

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

686

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

689

690 **Ankylosing Spondylitis**

691

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

694

695 **Psoriatic Arthritis**

696

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

700

701 **Plaque Psoriasis**

702

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

708

709 **Ulcerative Colitis**

710

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

714

715 **CONTRAINDICATIONS**

716

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

723

724 REMICADE should not be re-administered to patients who have experienced a severe
725 hypersensitivity reaction to REMICADE. Additionally, REMICADE should not be administered
726 to patients with known hypersensitivity to inactive components of the product or to any murine
727 proteins.

728

729 **WARNINGS**

730

731 **RISK OF INFECTIONS**

732 (See Boxed WARNINGS)

733

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

740

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

747

748 **Cases of tuberculosis, histoplasmosis, coccidioidomycosis, listeriosis, pneumocystosis, other**
749 **bacterial, mycobacterial and fungal infections have been observed in patients receiving**
750 **REMICADE. Patients should be evaluated for tuberculosis risk factors and be tested for**
751 **latent tuberculosis infection. Treatment of latent tuberculosis infections should be initiated**
752 **prior to therapy with REMICADE. When tuberculin skin testing is performed for latent**
753 **tuberculosis infection an induration size of 5 mm or greater should be considered positive,**
754 **even if vaccinated previously with Bacille Calmette-Guerin (BCG).**
755

756 **Patients receiving REMICADE should be monitored closely for signs and symptoms of**
757 **active tuberculosis, particularly since tests for latent tuberculosis infection may be falsely**
758 **negative. The possibility of undetected latent tuberculosis should be considered, especially**
759 **in patients who have immigrated from or traveled to countries with a high prevalence of**
760 **tuberculosis or had close contact with a person with active tuberculosis. All patients**
761 **treated with REMICADE should have a thorough history taken prior to initiating therapy.**
762 **Some patients who have previously received treatment for latent or active tuberculosis**
763 **have developed active tuberculosis while being treated with REMICADE. Anti-**
764 **tuberculosis therapy should be considered prior to initiation of REMICADE in patients**
765 **with a past history of latent or active tuberculosis in whom an adequate course of**
766 **treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating REMICADE**
767 **should also be considered in patients who have several or highly significant risk factors for**
768 **tuberculosis infection¹⁴ and have a negative test for latent tuberculosis. The decision to**
769 **initiate anti-tuberculosis therapy in these patients should only be made following**
770 **consultation with a physician with expertise in the treatment of tuberculosis and taking**
771 **into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis**
772 **therapy.**
773

774 **For patients who have resided in regions where histoplasmosis or coccidioidomycosis is**
775 **endemic, the benefits and risks of REMICADE treatment should be carefully considered**
776 **before initiation of REMICADE therapy.**
777

778 **Serious infections were seen in clinical studies with concurrent use of anakinra and another**
779 **TNF α -blocking agent, etanercept, with no added clinical benefit compared to etanercept**
780 **alone. Because of the nature of the adverse events seen with combination of etanercept and**
781 **anakinra therapy, similar toxicities may also result from the combination of anakinra and**
782 **other TNF α -blocking agents. Therefore, the combination of REMICADE and anakinra is**
783 **not recommended.**
784

785 **HEPATOSPLENIC T-CELL LYMPHOMAS**
786 **(See Boxed WARNINGS)**

787
788 **Rare postmarketing cases of hepatosplenic T-cell lymphomas have been reported in**
789 **adolescent and young adult patients with Crohn's disease treated with REMICADE. All of**
790 **these reports have occurred in patients on concomitant treatment with azathioprine or 6-**
791 **mercaptopurine. The clinical course of this disease is very aggressive with a fatal outcome**
792 **in most patients within 2 years of diagnosis.¹⁵ The causal relationship of hepatosplenic T-**
793 **cell lymphoma to REMICADE therapy remains unclear.**

794
795 **Hepatitis B Virus Reactivation**

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

815
816 **Hepatotoxicity**

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

830

831 Patients with Heart Failure

832

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

846

847 Hematologic Events

848

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

857

858 Hypersensitivity

859

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

864

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

872

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

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

878

879 **Neurologic Events**

880

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

888

889 **Malignancies**

890

891 In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE,
892 more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been
893 observed in patients receiving those TNF-blockers compared with control patients. During the
894 controlled portions of REMICADE trials in patients with moderately to severely active
895 rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis,
896 and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and
897 NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of
898 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years
899 among control patients), with median duration of follow-up 0.5 years for REMICADE-treated
900 patients and 0.4 years for control patients. Of these, the most common malignancies were breast,
901 colorectal, and melanoma. The rate of malignancies among REMICADE-treated patients was
902 similar to that expected in the general population whereas the rate in control patients was lower
903 than expected.

904

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

920
921 In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic
922 obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and
923 neck origin, were reported in REMICADE-treated patients compared with control patients. All
924 patients had a history of heavy smoking (see ADVERSE REACTIONS, Malignancies).
925 Prescribers should exercise caution when considering the use of REMICADE in patients with
926 moderate to severe COPD.

927
928 Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly
929 those patients who have had prior prolonged phototherapy treatment. In the maintenance portion
930 of clinical trials for REMICADE, NMSCs were more common in patients with previous
931 phototherapy (see ADVERSE REACTIONS: Adverse Reactions in Psoriasis Studies).

932
933 The potential role of TNF-blocking therapy in the development of malignancies is not known
934 (see ADVERSE REACTIONS, Malignancies). Rates in clinical trials for REMICADE cannot be
935 compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a
936 broader patient population. Caution should be exercised in considering REMICADE treatment
937 in patients with a history of malignancy or in continuing treatment in patients who develop
938 malignancy while receiving REMICADE.

939

940 **PRECAUTIONS**

941

942 **Autoimmunity**

943

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

948

949 **Vaccinations**

950

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

954

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

958

959 **Information for Patients**

960

961 **Patients developing signs and symptoms of infection should seek medical evaluation**
962 **immediately.**

963

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

970

971 **Drug Interactions**

972

973 Concurrent administration of etanercept (another TNF α -blocking agent) and anakinra (an
974 interleukin-1 receptor antagonist) has been associated with an increased risk of serious
975 infections, and increased risk of neutropenia and no additional benefit compared to these
976 medicinal products alone. Other TNF α -blocking agents (including REMICADE) used in
977 combination with anakinra may also result in similar toxicities (see WARNINGS, RISK OF
978 INFECTIONS).

979

980 Specific drug interaction studies, including interactions with MTX, have not been conducted.
981 The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one
982 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides
983 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.
984 Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids,
985 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications
986 included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory
987 agents, folic acid and corticosteroids.

988

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

995

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

997

998 A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF α to evaluate
999 tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNF α in mice.
1000 Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly
1001 for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the
1002 human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause
1003 tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the
1004 *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.
1005 Chromosomal aberrations were not observed in an assay performed using human lymphocytes.
1006 The significance of these findings for human risk is unknown. It is not known whether infliximab
1007 can impair fertility in humans. No impairment of fertility was observed in a fertility and general

1008 reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic
1009 toxicity study.

1010

1011 **Pregnancy Category B**

1012

1013 Since infliximab does not cross-react with TNF α in species other than humans and chimpanzees,
1014 animal reproduction studies have not been conducted with REMICADE. No evidence of
1015 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity
1016 study conducted in mice using an analogous antibody that selectively inhibits the functional
1017 activity of mouse TNF α . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the
1018 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to
1019 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not
1020 known whether REMICADE can cause fetal harm when administered to a pregnant woman or
1021 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if
1022 clearly needed.

1023

1024 **Nursing Mothers**

1025

1026 It is not known whether REMICADE is excreted in human milk or absorbed systemically after
1027 ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because
1028 of the potential for adverse reactions in nursing infants from REMICADE, women should not
1029 breast-feed their infants while taking REMICADE. A decision should be made whether to
1030 discontinue nursing or to discontinue the drug, taking into account the importance of the drug to
1031 the mother.

1032

1033 **Pediatric Use**

1034

1035 REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical
1036 remission in pediatric patients with moderately to severely active Crohn's disease who have had
1037 an inadequate response to conventional therapy (see Boxed WARNINGS, WARNINGS,
1038 INDICATIONS AND USAGE, PRECAUTIONS-Vaccinations, DOSAGE AND
1039 ADMINISTRATION, CLINICAL STUDIES-Active Crohn's Disease in Pediatric Patients and
1040 ADVERSE REACTIONS – Adverse Reactions in Pediatric Crohn's Disease).

1041

1042 REMICADE has not been studied in children with Crohn's disease < 6 years of age. The longer
1043 term (greater than one year) safety and effectiveness of REMICADE in pediatric Crohn's disease
1044 patients have not been established in clinical trials.

1045

1046 Safety and effectiveness of REMICADE in pediatric patients with ulcerative colitis and plaque
1047 psoriasis have not been established.

1048

1049 The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis (JRA) were
1050 evaluated in a multicenter, randomized, placebo-controlled, double-blind study for 14 weeks,
1051 followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks. Patients
1052 with active JRA between the ages of 4 and 17 years who had been treated with MTX for at least

1053 3 months were enrolled. Concurrent use of folic acid, oral corticosteroids (≤ 0.2 mg/kg/day of
1054 prednisone or equivalent), NSAIDs, and/or DMARDs was permitted.

1055
1056 Doses of 3 mg/kg REMICADE or placebo were administered intravenously at weeks 0, 2 and 6.
1057 Patients randomized to placebo crossed-over to receive 6 mg/kg REMICADE at weeks 14, 16,
1058 and 20, and then every 8 weeks through week 44. Patients who completed the study continued to
1059 receive open-label treatment with REMICADE for up to 2 years in a companion extension study.

1060
1061 The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key
1062 observations in the study included a high placebo response rate and a higher rate of
1063 immunogenicity than what has been observed in adults. Additionally, a higher rate of clearance
1064 of infliximab was observed than had been observed in adults (see CLINICAL
1065 PHARMACOLOGY, Pharmacokinetics).

1066
1067 A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated
1068 with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg
1069 REMICADE was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who
1070 received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting,
1071 fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious
1072 infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among
1073 the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious
1074 infusion reaction, one of whom had a possible anaphylactic reaction. Two of the 6 patients who
1075 experienced serious infusion reactions received REMICADE by rapid infusion (duration of less
1076 than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3
1077 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg.

1078
1079 A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX
1080 experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6
1081 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported
1082 infections were upper respiratory tract infection and pharyngitis and the most commonly reported
1083 serious infection was pneumonia. Other notable infections included primary varicella infection in
1084 1 patient and herpes zoster in 1 patient.

1085
1086
1087

1088 **Geriatric Use**

1089
1090 In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed
1091 in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque
1092 psoriasis, aged 65 or older who received REMICADE, compared to younger patients although
1093 the incidence of serious adverse events in patients aged 65 or older was higher in both
1094 REMICADE and control groups compared to younger patients. In Crohn's disease, ulcerative
1095 colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of
1096 patients aged 65 and over to determine whether they respond differently from patients aged 18 to
1097 65. Because there is a higher incidence of infections in the elderly population in general, caution
1098 should be used in treating the elderly (see ADVERSE REACTIONS, Infections).

1099
1100 **ADVERSE REACTIONS**

1101
1102 The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients
1103 with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis,
1104 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17
1105 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374
1106 exposed beyond one year. (For information on adverse reactions in pediatric patients see
1107 ADVERSE REACTIONS – Adverse Reactions in Pediatric Crohn's Disease.) One of the most
1108 common reasons for discontinuation of treatment was infusion-related reactions (e.g. dyspnea,
1109 flushing, headache and rash). Adverse events have been reported in a higher proportion of
1110 rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no
1111 differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10
1112 mg/kg dose in patients with Crohn's disease.

1113
1114 **Infusion-related Reactions**1115 *Infusion reactions*

1116
1117 An infusion reaction was defined in clinical trials as any adverse event occurring during an
1118 infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated
1119 patients in all clinical studies experienced an infusion reaction compared to approximately 10%
1120 of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by
1121 nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary
1122 reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were
1123 accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and
1124 cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included
1125 anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients
1126 discontinued REMICADE because of infusion reactions, and all patients recovered with
1127 treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial
1128 infusion were not associated with a higher incidence of reactions. The infusion reaction rates
1129 remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates
1130 were variable over time and somewhat higher following the final infusion than after the initial
1131 infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion

1132 reactions (i.e. an adverse event occurring within 1 to 2 hours) was 7% in the 3 mg/kg group, 4%
1133 in the 5 mg/kg group, and 1% in the placebo group.

1134
1135 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to
1136 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant
1137 immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and
1138 infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug
1139 Interactions).

1140
1141 In post-marketing experience, cases of anaphylactic-like reactions, including
1142 laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with
1143 REMICADE administration.

1144
1145 *Delayed Reactions/Reactions following readministration*
1146 *Plaque Psoriasis*
1147 In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible
1148 delayed hypersensitivity reaction, generally reported as serum sickness or a combination of
1149 arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within two
1150 weeks after repeat infusion.

1151
1152 *Crohn's disease*
1153 In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following
1154 a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events
1155 manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and
1156 symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also
1157 experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.
1158 Patients experiencing these adverse events had not experienced infusion-related adverse events
1159 associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of
1160 patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients
1161 who received lyophilized formulation. The clinical data are not adequate to determine if
1162 occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms
1163 improved substantially or resolved with treatment in all cases. There are insufficient data on the
1164 incidence of these events after drug-free intervals of 1 to 2 years. These events have been
1165 observed only infrequently in clinical studies and post-marketing surveillance with retreatment
1166 intervals up to 1 year.

1167
1168 **Infections**

1169
1170 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated
1171 patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of
1172 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections
1173 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among
1174 REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin
1175 ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were
1176 reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was

1177 fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was
1178 reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis,
1179 including disseminated tuberculosis, also have been reported post-marketing. Most of these cases
1180 of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE
1181 and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). In
1182 the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE
1183 every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients
1184 receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4%
1185 developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter
1186 (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg
1187 or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX,
1188 serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3
1189 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients
1190 with fistulizing Crohn's disease developed a new fistula-related abscess.

1191
1192 In REMICADE clinical studies in patients with ulcerative colitis, infections treated with
1193 antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of
1194 follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of
1195 infections, including serious infections, reported in patients with ulcerative colitis were similar to
1196 those reported in other clinical studies.

1197
1198 In post-marketing experience in the various indications, infections have been observed with
1199 various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have
1200 been noted in all organ systems and have been reported in patients receiving REMICADE alone
1201 or in combination with immunosuppressive agents.

1202
1203 The onset of serious infections may be preceded by constitutional symptoms such as fever, chills,
1204 weight loss, and fatigue. The majority of serious infections, however, may also be preceded by
1205 signs or symptoms localized to the site of the infection.

1206

1207 **Autoantibodies/Lupus-like Syndrome**

1208
1209 Approximately half of REMICADE-treated patients in clinical trials who were antinuclear
1210 antibody (ANA) negative at baseline developed a positive ANA during the trial compared with
1211 approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected
1212 in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated
1213 patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

1214

1215 **Malignancies**

1216
1217 In controlled trials, more REMICADE-treated patients developed malignancies than placebo-
1218 treated patients. (See WARNINGS, Malignancies.)

1219
1220 In a randomized controlled clinical trial exploring the use of REMICADE in patients with
1221 moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were

1222 treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's
1223 disease. Nine of these REMICADE-treated patients developed a malignancy, including 1
1224 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of
1225 follow-up 0.8 years; 95% CI 3.51 - 14.56). There was one reported malignancy among 77 control
1226 patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up
1227 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head
1228 and neck.

1229
1230 Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been
1231 reported in patients receiving REMICADE during post-approval use.
1232

1233 **Patients with Heart Failure**

1234

1235 In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class
1236 III/IV; left ventricular ejection fraction $\leq 35\%$), 150 patients were randomized to receive
1237 treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks.
1238 Higher incidences of mortality and hospitalization due to worsening heart failure were observed
1239 in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg
1240 REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the
1241 placebo groups. There were trends towards increased dyspnea, hypotension, angina, and
1242 dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo.
1243 REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See
1244 CONTRAINDICATIONS and WARNINGS, Patients with Heart Failure.)
1245

1246 **Immunogenicity**

1247

1248 Treatment with REMICADE can be associated with the development of antibodies to infliximab.
1249 The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed
1250 by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE
1251 treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease
1252 patients receiving REMICADE after drug free intervals >16 weeks. In a study of psoriatic
1253 arthritis, where 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab
1254 occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients
1255 who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy
1256 and to experience an infusion reaction (see ADVERSE REACTIONS: Infusion-related
1257 Reactions) than were patients who were antibody negative. Antibody development was lower
1258 among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies
1259 such as 6-MP/AZA or MTX.
1260

1261 In the psoriasis Study II, which included both the 5 mg/kg and 3 mg/kg doses, antibodies were
1262 observed in 36% of patients treated with 5 mg/kg every 8 weeks for 1 year, and in 51% of
1263 patients treated with 3 mg/kg every 8 weeks for 1 year. In the psoriasis Study III, which also
1264 included both the 5 mg/kg and 3 mg/kg doses, antibodies were observed in 20% of patients
1265 treated with 5 mg/kg induction (weeks 0, 2 and 6), and in 27% of patients treated with 3 mg/kg
1266 induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and

1267 II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for one year
 1268 and in Study III in patients treated with 5 mg/kg induction (14.1%-23.0%) and serious infusion
 1269 reaction rates (<1%) were similar to those observed in other study populations. The clinical
 1270 significance of apparent increased immunogenicity on efficacy and infusion reactions in
 1271 psoriasis patients as compared to patients with other diseases treated with REMICADE over the
 1272 long term is not known.

1273
 1274 The data reflect the percentage of patients whose test results were positive for antibodies to
 1275 infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the
 1276 assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced
 1277 by several factors including sample handling, timing of sample collection, concomitant
 1278 medication, and underlying disease. For these reasons, comparison of the incidence of antibodies
 1279 to infliximab with the incidence of antibodies to other products may be misleading.

1280

1281 **Hepatotoxicity**

1282

1283 Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported
 1284 rarely in patients receiving REMICADE (see WARNINGS, Hepatotoxicity). Reactivation of
 1285 hepatitis B virus has occurred in patients receiving TNF-blocking agents, including
 1286 REMICADE, who are chronic carriers of this virus (see WARNINGS, Hepatitis B Virus
 1287 Reactivation).

1288

1289 In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing
 1290 spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were
 1291 observed (ALT more common than AST) in a greater proportion of patients receiving
 1292 REMICADE than in controls (Table 11), both when REMICADE was given as monotherapy and
 1293 when it was used in combination with other immunosuppressive agents. In general, patients who
 1294 developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or
 1295 resolved with either continuation or discontinuation of REMICADE, or modification of
 1296 concomitant medications.

1297

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	13%	40%	0%	6%	0%	2%
Psoriatic arthritis ⁵	16%	42%	0%	5%	0%	2%
Plaque psoriasis ⁶	24%	49%	<1%	8%	0%	3%

1298 ¹Placebo patients received methotrexate while REMICADE patients received both REMICADE and
1299 methotrexate. Median follow-up was 58 weeks.

1300 ²Placebo patients in the 2 Phase III trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at
1301 study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo
1302 maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT
1303 analysis. Median follow-up was 54 weeks.

1304 ³Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and
1305 31 weeks for REMICADE.

1306 ⁴Median follow-up was 24 weeks.

1307 ⁵Median follow-up was 24 weeks for REMICADE group and 18 weeks for placebo group.

1308 ⁶ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and
1309 16 weeks for placebo.

1310

1311

1312 **Adverse Reactions in Pediatric Crohn's Disease**

1313

1314 There were some differences in the adverse reactions observed in the pediatric patients receiving
1315 REMICADE compared to those observed in adults with Crohn's disease. These differences are
1316 discussed in the following paragraphs.

1317

1318 The following adverse events were reported more commonly in 103 randomized pediatric
1319 Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult
1320 Crohn's disease patients receiving a similar treatment regimen: anemia (11%), blood in stool
1321 (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture
1322 (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

1323

1324 Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in
1325 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more
1326 frequently for patients who received every 8 week as opposed to every 12 week infusions (74%
1327 and 38%, respectively), while serious infections were reported for 3 patients in the every 8 week
1328 and 4 patients in the every 12 week maintenance treatment group. The most commonly reported
1329 infections were upper respiratory tract infection and pharyngitis, and the most commonly
1330 reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8
1331 week and 1 in the every 12 week maintenance treatment groups). Herpes zoster was reported for
1332 2 patients in the every 8 week maintenance treatment group.

1333

1334 In Study Peds Crohn's, 18% of randomized patients experienced one or more infusion reactions,
1335 with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's,
1336 there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

1337

1338 Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn's.

1339

1340 Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric
1341 patients in Crohn's disease clinical trials; 4% had ALT elevations $\geq 3 \times$ ULN, and 1% had
1342 elevations $\geq 5 \times$ ULN. (Median follow-up was 53 weeks.)

1343

1344

1345 **Adverse Reactions in Psoriasis Studies**

1346
1347 During the placebo-controlled portion across the three clinical trials up to week 16, the
1348 proportion of patients who experienced at least 1 SAE (defined as resulting in death, life
1349 threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7%
1350 in the 3 mg/kg REMICADE group, 3.2% in the placebo group, and 3.9% in the 5 mg/kg
1351 REMICADE group.

1352
1353 Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every
1354 8 weeks through one year of maintenance treatment experienced at least 1 SAE in Study I. In
1355 Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks,
1356 respectively, through one year of maintenance treatment experienced at least 1 SAE.

1357
1358 One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg
1359 REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients
1360 receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment
1361 experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving
1362 REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least
1363 1 serious infection. The most common serious infection (requiring hospitalization) were
1364 abscesses (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg
1365 REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after
1366 starting REMICADE.

1367
1368 In placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received
1369 REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients
1370 who received placebo.

1371
1372 In the psoriasis studies, 1% (15/1373) of patients experienced serum sickness or a combination
1373 of arthralgia and/or myalgia with fever, and/or rash, usually early in the treatment course. Of
1374 these patients, 6 required hospitalization due to fever, severe myalgia, arthralgia, swollen joints,
1375 and immobility.

1376
1377 **Other Adverse Reactions**

1378
1379 Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with
1380 rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing
1381 spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions.
1382 (For information on other adverse reactions in pediatric patients, see ADVERSE REACTIONS –
1383 Adverse Reactions in Pediatric Crohn's Disease). Adverse events reported in $\geq 5\%$ of all patients
1384 with rheumatoid arthritis receiving 4 or more infusions are in Table 12. The types and
1385 frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid
1386 arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients
1387 except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's
1388 disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-
1389 up for patients who never received REMICADE to provide meaningful comparisons.

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%

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.

1399
 1400 The most common serious adverse events observed in clinical trials were infections (see
 1401 ADVERSE REACTIONS, Infections). Other serious, medically relevant adverse events $\geq 0.2\%$
 1402 or clinically significant adverse events by body system were as follows:

1403
 1404 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
 1405 *Blood:* pancytopenia
 1406 *Cardiovascular:* circulatory failure, hypotension, syncope
 1407 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,
 1408 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
 1409 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness
 1410 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia
 1411 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis
 1412 *Metabolic and Nutritional:* dehydration
 1413 *Musculoskeletal:* intervertebral disk herniation, tendon disorder
 1414 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction
 1415 *Platelet, Bleeding and Clotting:* thrombocytopenia
 1416 *Neoplasms:* basal cell, breast, lymphoma
 1417 *Psychiatric:* confusion, suicide attempt
 1418 *Red Blood Cell:* anemia, hemolytic anemia
 1419 *Reproductive:* menstrual irregularity
 1420 *Resistance Mechanism:* cellulitis, sepsis, serum sickness
 1421 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including
 1422 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
 1423 *Skin and Appendages:* increased sweating, ulceration
 1424 *Urinary:* renal calculus, renal failure
 1425 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis
 1426 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

1427 1428 **Post-marketing Adverse Events**

1429
 1430 The following adverse events have been reported during post-approval use of REMICADE:
 1431 neutropenia (see WARNINGS, Hematologic Events), interstitial pneumonitis/fibrosis, idiopathic
 1432 thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic
 1433 and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal
 1434 necrolysis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional
 1435 neurologic events have also been observed, see WARNINGS, Neurologic Events) and acute liver
 1436 failure, jaundice, hepatitis, and cholestasis (see WARNINGS, Hepatotoxicity). Because these
 1437 events are reported voluntarily from a population of uncertain size, it is not always possible to
 1438 reliably estimate their frequency or establish a causal relationship to REMICADE exposure.

1439
 1440 The following serious adverse events have been reported in the post-marketing experience in
 1441 children: infections (some fatal) including opportunistic infections and tuberculosis, infusion
 1442 reactions, and hypersensitivity reactions.

1443

1444 Serious adverse events in the post-marketing experience with REMICADE in the pediatric
1445 population have also included malignancies, including hepatosplenic T-cell lymphomas (see
1446 Boxed WARNINGS and WARNINGS), transient hepatic enzyme abnormalities, lupus-like
1447 syndromes, and the development of autoantibodies.

1448

1449 **OVERDOSAGE**

1450

1451 Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of
1452 overdosage, it is recommended that the patient be monitored for any signs or symptoms of
1453 adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

1454

1455 **DOSAGE AND ADMINISTRATION**

1456

1457 **Rheumatoid Arthritis**

1458

1459 The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed
1460 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
1461 thereafter. REMICADE should be given in combination with methotrexate. For patients who
1462 have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or
1463 treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at
1464 higher doses (see ADVERSE REACTIONS, Infections).

1465

1466 **Crohn's Disease or Fistulizing Crohn's Disease**

1467

1468 The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at
1469 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the
1470 treatment of adults with moderately to severely active Crohn's disease or fistulizing Crohn's
1471 disease. For adult patients who respond and then lose their response, consideration may be given
1472 to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond
1473 with continued dosing and consideration should be given to discontinue REMICADE in these
1474 patients.

1475

1476 The recommended dose of REMICADE for children with moderately to severely active Crohn's
1477 disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a
1478 maintenance regimen of 5 mg/kg every 8 weeks.

1479

1480 **Ankylosing Spondylitis**

1481

1482 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed
1483 with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks
1484 thereafter.

1485

1486 **Psoriatic Arthritis**

1487
1488 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed
1489 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
1490 thereafter. REMICADE can be used with or without methotrexate.

1491
1492 **Plaque Psoriasis**

1493
1494 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion, followed
1495 by additional doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

1496
1497 **Ulcerative Colitis**

1498
1499 The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6
1500 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment
1501 of moderately to severely active ulcerative colitis.

1502
1503 **Administration Instructions Regarding Infusion Reactions**

1504
1505 Adverse effects during administration of REMICADE have included flu-like symptoms,
1506 headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin
1507 rashes. Anaphylaxis might occur at any time during REMICADE infusion. Approximately 20%
1508 of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared
1509 with 10% of placebo-treated patients (see ADVERSE REACTIONS, Infusion-related Reactions).
1510 Prior to infusion with REMICADE, premedication may be administered at the physician's
1511 discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen
1512 and/or corticosteroids.

1513
1514 During infusion, mild to moderate infusion reactions may improve following slowing or
1515 suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion
1516 rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids.
1517 For patients that do not tolerate the infusion following these interventions, REMICADE should
1518 be discontinued.

1519
1520 During or following infusion, patients that have severe infusion-related hypersensitivity reactions
1521 should be discontinued from further REMICADE treatment. The management of severe infusion
1522 reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel
1523 and medication should be available to treat anaphylaxis if it occurs.

1524

1525 **Preparation and Administration Instructions**1526 **Use aseptic technique.**

1527
1528 REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after
1529 reconstitution should be used immediately, not re-entered or stored. The diluent to be used for
1530 reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted
1531 product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The
1532 infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE
1533 infusion should begin within 3 hours of preparation.

- 1534
- 1535 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial
1536 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE
1537 solution required.
 - 1538
 - 1539 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a
1540 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and
1541 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center
1542 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass
1543 wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution
1544 by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous
1545 agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.
1546 Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to
1547 light yellow and opalescent, and the solution may develop a few translucent particles as
1548 infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign
1549 particles are present.
 - 1550
 - 1551 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with
1552 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride
1553 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium
1554 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted
1555 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.
 - 1556
 - 1557 4. The infusion solution must be administered over a period of not less than 2 hours and must
1558 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore
1559 size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for
1560 reuse.
 - 1561
 - 1562 5. No physical biochemical compatibility studies have been conducted to evaluate the co-
1563 administration of REMICADE with other agents. REMICADE should not be infused
1564 concomitantly in the same intravenous line with other agents.
 - 1565
 - 1566 6. Parenteral drug products should be inspected visually for particulate matter and
1567 discoloration prior to administration, whenever solution and container permit. If visibly
1568 opaque particles, discoloration or other foreign particulates are observed, the solution
1569 should not be used.

1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614

Storage

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

HOW SUPPLIED

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

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

REFERENCES

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

- 1615
1616 9. Targan SR, Hanauer SB, van Deventer SJH, et al. A short-term study of chimeric
1617 monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. *N Engl J Med*
1618 1997;337(15):1029-1035.
1619
1620 10. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's
1621 disease: the ACCENT I randomized trial. *Lancet* 2002; 359:1541-1549.
1622
1623 11. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients
1624 with Crohn's disease. *N Engl J Med* 1999;340:1398-1405.
1625
1626 12. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for
1627 ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis*
1628 *Rheum.* 1984;27(4):361-368.
1629
1630 13. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for
1631 mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.*
1632 1987;317(26):1625-1629.
1633
1634 14. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumor necrosis factor agents and
1635 tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis*
1636 2003;3:148-155.
1637
1638 15. Belhadj K, Reyes F, Farcet JP, et al. Hepatosplenic $\gamma\delta$ T-cell lymphoma is a rare
1639 clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood*
1640 2003;102(13):4261-4269.

1641
1642
1643
1644
1645
1646
1647
1648

©Centocor, Inc. 2006
Malvern, PA 19355, USA
1-800-457-6399

License #1242
April 2007

1649 **Rx Only**

1650 **MEDICATION GUIDE**
1651 **REMICADE® (Rem-eh-kaid)**
1652 **(infliximab)**

1653
1654 Read the Medication Guide that comes with REMICADE before you receive the first treatment,
1655 and before each time you get a treatment of REMICADE. This Medication Guide does not take
1656 the place of talking with your doctor about your medical condition or treatment.

1657

1658 **What is the most important information I should know about REMICADE?**

1659

1660 REMICADE is a medicine that affects your immune system. It can cause serious side effects
1661 including:

1662

1663 Serious Infections

- 1664 • Patients treated with REMICADE and other medicines that block TNF have an increased
1665 risk for infections. Some patients have had serious infections while receiving
1666 REMICADE. In some cases, the infections got worse (progressed) and became serious
1667 enough that patients needed to be in the hospital for treatment. These serious infections
1668 include TB (tuberculosis), and infections caused by viruses, fungi or bacteria that have
1669 spread throughout the body. Some patients have died from these infections.
- 1670 • Tell your doctor right away if you have any of the following symptoms, which may be
1671 early signs of a serious infection, while taking or after taking REMICADE:
- 1672 • a fever
 - 1673 • feel very tired
 - 1674 • have a cough
 - 1675 • have flu-like symptoms
 - 1676 • warm, red, or painful skin
- 1677 These may be early signs of a serious infection.

1678

1679 Cancer

- 1680 • Some children and young adults with Crohn's disease who have received REMICADE
1681 have developed a rare type of cancer called Hepatosplenic T-cell Lymphoma. This type
1682 of cancer often results in death. These patients were also receiving drugs known as
1683 azathioprine or 6-mercaptopurine.
- 1684 • Tell your doctor if you have ever had any type of cancer.

1685

1686 See also, "What are the possible side effects of REMICADE?" below.

1687

1688 **What is REMICADE?**

1689

1690 REMICADE is a prescription medicine that is approved for patients with:

- 1691 • Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis,
1692 along with the medicine methotrexate

- 1693 • Crohn's Disease - children over the age of 6 and adults with Crohn's disease who have not
- 1694 responded well enough to other medicines
- 1695 • Ankylosing Spondylitis
- 1696 • Psoriatic Arthritis
- 1697 • Plaque Psoriasis - adult patients with plaque psoriasis that is chronic (doesn't go away)
- 1698 severe, extensive, and/or disabling.
- 1699 • Ulcerative Colitis - adults with moderately to severely active ulcerative colitis who have
- 1700 not responded well enough to other medicines.

1701
 1702 REMICADE blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-
 1703 alpha). TNF-alpha is made by your body's immune system. People with certain diseases have
 1704 too much TNF-alpha that can cause the immune system to attack normal healthy parts of the
 1705 body. REMICADE can block the damage caused by too much TNF-alpha.

1706 1707 **Who should not receive REMICADE?**

1708
 1709 You should not receive REMICADE if you have:

- 1710 • heart failure, unless your doctor has examined you and decided that you are able to take
- 1711 REMICADE. Talk to your doctor about your heart failure.
- 1712 • had an allergic reaction to REMICADE, or any of the other ingredients in REMICADE.
- 1713 See the end of this Medication Guide for a complete list of ingredients in REMICADE.

1714 1715 **What should I tell my doctor before starting treatment with REMICADE?**

1716
 1717 Your doctor will assess your health before each treatment.

1718
 1719 Tell your doctor about all of your medical conditions, including if you:

- 1720 • have any kind of infection even if it is very minor (such as an open cut or sore).
- 1721 REMICADE affects the body's immune system and makes you less able to fight
- 1722 infections.
- 1723 • have an infection that won't go away or a history of infection that keeps coming back.
- 1724 • have had TB (tuberculosis), or if you have recently been near anyone who might have TB.
- 1725 If you have been near someone with TB and have the TB germ in your body, even if you
- 1726 don't have symptoms of an infection, you can get a serious TB infection while taking
- 1727 REMICADE. Sometimes these serious TB infections can cause death.
- 1728 • were born in, lived in or traveled to countries where there is more risk for getting TB.
- 1729 Ask your doctor if you are not sure.
- 1730 • live or have lived in certain parts of the country where there is more risk for certain kinds
- 1731 of fungal infections (histoplasmosis or coccidioidomycosis). These infections may
- 1732 develop or become more severe if you take REMICADE. If you don't know if you have
- 1733 lived in an area where histoplasmosis or coccidioidomycosis is common, ask your doctor.
- 1734 • have or had hepatitis B. If you are a chronic carrier of the virus that causes hepatitis B,
- 1735 taking REMICADE could cause the hepatitis B virus to become an active infection again.
- 1736 • have other liver problems including liver failure.

- 1737 • have heart failure or other heart conditions. If you have heart failure, it may get worse
- 1738 while you take REMICADE.
- 1739 • have or have had any type of cancer.
- 1740 • have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine
- 1741 to make your skin sensitive to light) for psoriasis. You may have a higher chance of
- 1742 getting skin cancer while receiving REMICADE.
- 1743 • have COPD (Chronic Obstructive Pulmonary Disease), a specific type of lung disease.
- 1744 Patients with COPD may have an increased risk of getting cancer while taking
- 1745 REMICADE.
- 1746 • have or have had a condition that affects your nervous system such as
- 1747 • multiple sclerosis, or Guillain-Barré syndrome, or
- 1748 • if you experience any numbness or tingling, or
- 1749 • if you have had a seizure.
- 1750 • have recently received or are scheduled to receive a vaccine. **Adults and children**
- 1751 **should not receive a live vaccine while taking REMICADE.** Children with Crohn's
- 1752 disease should have all of their vaccines brought up to date before starting treatment with
- 1753 REMICADE.
- 1754 • are pregnant or planning to become pregnant. It is not known if REMICADE harms your
- 1755 unborn baby. REMICADE should be given to a pregnant woman only if clearly needed.
- 1756 Talk to your doctor about stopping REMICADE if you are pregnant or planning to
- 1757 become pregnant.
- 1758 • are breast-feeding or planning to breast-feed. It is not known whether REMICADE
- 1759 passes into your breast milk. Talk to your doctor about the best way to feed your baby
- 1760 while taking REMICADE. You should not breast-feed while taking REMICADE.

1761

1762 **How should I receive REMICADE?**

1763

- 1764 • You will be given REMICADE through a needle placed in a vein (IV or intravenous
- 1765 infusion) in your arm.
- 1766 • Your doctor may decide to give you medicine before starting the REMICADE infusion to
- 1767 prevent or lessen side effects.
- 1768 • Only a healthcare professional should prepare the medicine and administer it to you.
- 1769 • REMICADE will be given to you over a period of about 2 hours.
- 1770 • If you have side effects from REMICADE, the infusion may need to be adjusted or
- 1771 stopped. In addition, your healthcare professional may decide to treat your symptoms.
- 1772 • A healthcare professional will monitor you during the REMICADE infusion and for a
- 1773 period of time afterward for side effects. Your doctor may do certain tests while you are
- 1774 taking REMICADE to monitor you for side effects and to see how well you respond to
- 1775 the treatment.
- 1776 • Your doctor will determine the right dose of REMICADE for you and how often you
- 1777 should receive it. Make sure to discuss with your doctor when you will receive infusions
- 1778 and to come in for all your infusions and follow-up appointments.

1779

1780 **What should I avoid while receiving REMICADE?**

1781

1782 Do not take REMICADE and the medication KINERET (Anakinra) together.

1783

1784 **Tell your doctor about all the medicines you take**, including prescription and non-prescription
1785 medicines, vitamins, and herbal supplements.

1786

1787 Know the medicines you take. Keep a list of your medicines and show them to your doctor and
1788 pharmacist when you get a new medicine.

1789

1790 **What are the possible side effects of REMICADE?**

1791

1792 Serious and sometimes fatal side effects have been reported in patients taking REMICADE (see
1793 also **“What is the most important information I should know about REMICADE?”**). These
1794 include:

1795

1796 Serious Infections

1797

1798 • Some patients have had serious infections while receiving REMICADE. These serious
1799 infections include tuberculosis (TB) and infections caused by viruses, fungi, or bacteria
1800 that have spread throughout the body. Some patients die from these infections. If you get
1801 an infection while receiving treatment with REMICADE your doctor will treat your
infection and may need to stop your REMICADE treatment.1802 • Tell your doctor right away if you have any of the following signs of an infection while
1803 taking or after taking REMICADE:

1804

1805 • a fever

1806

1807 • feel very tired

1808

1809 • have a cough

1810

1811 • have flu-like symptoms

1812

1813 • warm, red, or painful skin

1814

1815 • Your doctor will examine you for TB and perform a test to see if you have TB. If your
1816 doctor feels that you are at risk for TB, you may be treated with medicine for TB before
1817 you begin treatment with REMICADE and during treatment with REMICADE.1818 • Even if your TB test is negative your doctor should carefully monitor you for TB
1819 infections while you are taking REMICADE. Patients who had a **negative** TB skin test
before receiving REMICADE have developed active TB.

1820

1821 • If you are a chronic carrier of the hepatitis B virus, the virus can become active while you
1822 are being treated with REMICADE. In some cases patients have died as a result of
1823 hepatitis B virus being reactivated. Your doctor may do a blood test before you start
1824 treatment with REMICADE and occasionally while you are being treated. Tell your
doctor if you have any of the following symptoms:

1820

1821 • feel unwell

1822

1823 • poor appetite

1824

1825 • tiredness (fatigue)

1826 • fever, skin rash and/or joint pain

1825 Cancer

- 1826 • In clinical studies, more cancers were seen in patients who took REMICADE and other
1827 medicines that block TNF than patients who did not receive these treatments.
1828 • Some children and young adults with Crohn's disease who have received REMICADE
1829 have developed a rare type of cancer called Hepatosplenic T-cell Lymphoma. This type
1830 of cancer often results in death. These patients were also receiving drugs known as
1831 azathioprine or 6-mercaptopurine.
1832 • People who have been treated for rheumatoid arthritis, Crohn's disease, ankylosing
1833 spondylitis, psoriatic arthritis and plaque psoriasis for a long time may be more likely to
1834 develop lymphoma. This is especially true for people with very active disease.
1835 • Patients with COPD (a specific type of lung disease) may have an increased risk for
1836 getting cancer while being treated with REMICADE.
1837 • If you take REMICADE, your chances of getting lymphoma or other cancers may
1838 increase.

1839

1840 Heart Failure

1841 If you have a heart problem called congestive heart failure, your doctor should check you closely
1842 while you are taking REMICADE. Your congestive heart failure may get worse while you are
1843 taking REMICADE. Be sure to tell your doctor of any new or worse symptoms including:

- 1844 • Shortness of breath
1845 • Swelling of ankles or feet
1846 • Sudden weight gain

1847 Treatment with REMICADE may need to be stopped if you get new or worse congestive heart
1848 failure.

1849

1850 Liver Injury

1851 In rare cases, some patients taking REMICADE have developed serious liver problems. Tell
1852 your doctor if you have

- 1853 • Jaundice (skin and eyes turning yellow)
1854 • Dark brown-colored urine
1855 • Pain on the right side of your stomach area (right-sided abdominal pain)
1856 • Fever
1857 • Extreme tiredness (severe fatigue)

1858

1859 Blood Problems

1860 In some patients taking REMICADE, the body may not make enough of the blood cells that help
1861 fight infections or help stop bleeding. Tell your doctor if you

- 1862 • Have a fever that does not go away
1863 • Bruise or bleed very easily
1864 • Look very pale

1865

1866 Nervous System Disorders

1867 In rare cases, patients taking REMICADE have developed problems with their nervous system.
1868 Tell your doctor if you have

- 1869 • Changes in your vision
- 1870 • Weakness in your arms and/or legs
- 1871 • Numbness or tingling in any part of your body
- 1872 • Seizures

1873

1874 Allergic Reactions

1875 Some patients have had allergic reactions to REMICADE. Some of these reactions were severe.
1876 These reactions can happen while you are getting your REMICADE treatment or shortly
1877 afterwards. Your doctor may need to stop or pause your treatment with REMICADE and may
1878 give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:

- 1879 • Hives (red, raised, itchy patches of skin)
- 1880 • Difficulty breathing
- 1881 • Chest pain
- 1882 • High or low blood pressure
- 1883 • Fever
- 1884 • Chills

1885 Some patients treated with REMICADE have had delayed allergic reactions. The delayed
1886 reactions occurred 3 to 12 days after receiving treatment with REMICADE. Tell your doctor
1887 right away if you have any of these signs of delayed allergic reaction to REMICADE:

- 1888 • Fever
- 1889 • Rash
- 1890 • Headache
- 1891 • Sore throat
- 1892 • Muscle or joint pain
- 1893 • Swelling of the face and hands
- 1894 • Difficulty swallowing

1895

1896 Lupus-like Syndrome

1897 Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any
1898 of the following symptoms your doctor may decide to stop your treatment with REMICADE.

- 1899 • Chest discomfort or pain that does not go away
- 1900 • Shortness of breath
- 1901 • Joint pain
- 1902 • Rash on the cheeks or arms that gets worse in sun

1903

1904 **The most common side effects of REMICADE are**

1905

- 1906 • Respiratory infections, such as sinus infections and sore throat)
- 1907 • Headache
- 1908 • Rash
- 1909 • Coughing
- 1910 • Stomach pain

1911 Children who took REMICADE in studies for Crohn's disease, showed some differences in side
1912 effects compared with adults who took REMICADE for Crohn's disease. The side effects that
1913 happened more in children were: anemia (low red blood cells), blood in stool, leukopenia (low
1914 white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils,
1915 the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions
1916 of the breathing tract.

1917 Tell your doctor about any side effect that bothers you or does not go away.

1918 These are not all of the side effects with REMICADE. Ask your doctor or pharmacist for more
1919 information.

1920

1921 **General information about REMICADE**

1922

1923 Medicines are sometimes prescribed for purposes that are not mentioned in Medication Guides or
1924 patient information sheets. Do not use REMICADE for a condition for which it was not
1925 prescribed.

1926

1927 This information sheet summarizes the most important information about REMICADE. You can
1928 ask your doctor or pharmacist for information about REMICADE that is written for health
1929 professionals.

1930

1931 For more information go to www.remicade.com or call 1-800-457-6399.

1932

1933 **What are the ingredients in REMICADE?**

1934

1935 The active ingredient is Infliximab.

1936 The inactive ingredients in REMICADE include: sucrose, polysorbate 80, monobasic sodium
1937 phosphate monohydrate, and dibasic sodium phosphate dihydrate. No Preservatives are present.

1938

1939 Product developed and manufactured by:

1940 Centocor, Inc.

1941 200 Great Valley Parkway

1942 Malvern, PA 19355

1943

1944 Revised April 2007

1945

1946 This Medication Guide has been approved by the U.S. Food and Drug Administration.