

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

6 **WARNINGS**
7

8 **RISK OF INFECTIONS**
9

10 **TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT**
11 **CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER**
12 **OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS**
13 **RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE**
14 **WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH A**
15 **REACTIVE TUBERCULIN SKIN TEST REDUCES THE RISK OF TB**
16 **REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH REMICADE.**
17 **HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS**
18 **RECEIVING REMICADE WHO WERE TUBERCULIN SKIN TEST NEGATIVE**
19 **PRIOR TO RECEIVING REMICADE.**
20

21 **PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION**
22 **WITH A TUBERCULIN SKIN TEST.¹ TREATMENT OF LATENT TUBERCULOSIS**
23 **INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.**
24 **PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING REMICADE FOR SIGNS**
25 **AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE**
26 **TUBERCULIN SKIN TEST NEGATIVE.**
27

28 **HEPATOSPLENIC T-CELL LYMPHOMAS**
29

30 **RARE POSTMARKETING CASES OF HEPATOSPLENIC T-CELL LYMPHOMA**
31 **HAVE BEEN REPORTED IN ADOLESCENT AND YOUNG ADULT PATIENTS WITH**
32 **CROHN'S DISEASE TREATED WITH REMICADE. THIS RARE TYPE OF T-CELL**
33 **LYMPHOMA HAS A VERY AGGRESSIVE DISEASE COURSE AND IS USUALLY**
34 **FATAL. ALL OF THESE HEPATOSPLENIC T-CELL LYMPHOMAS WITH**
35 **REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT TREATMENT**
36 **WITH AZATHIOPRINE OR 6-MERCAPTOPYRIMIDINE.**
37

38
39 **DESCRIPTION**
40

41 **REMICADE®** is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight
42 of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab
43 binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of
44 10^{10} M^{-1} . Infliximab is produced by a recombinant cell line cultured by continuous perfusion and
45 is purified by a series of steps that includes measures to inactivate and remove viruses.
46

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

52

53 **CLINICAL PHARMACOLOGY**

54

55 **General**

56

57 Infliximab neutralizes the biological activity of TNF α by binding with high affinity to the
58 soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors.^{2,3}
59 Infliximab does not neutralize TNF β (lymphotoxin α), a related cytokine that utilizes the same
60 receptors as TNF α . Biological activities attributed to TNF α include: induction of pro-
61 inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration
62 by increasing endothelial layer permeability and expression of adhesion molecules by endothelial
63 cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of
64 acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by
65 synoviocytes and/or chondrocytes. Cells expressing transmembrane TNF α bound by infliximab
66 can be lysed *in vitro*³ or *in vivo*.⁴ Infliximab inhibits the functional activity of TNF α in a wide
67 variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T
68 lymphocytes and epithelial cells. The relationship of these biological response markers to the
69 mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNF α
70 antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis
71 and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease
72 in transgenic mice that develop polyarthritis as a result of constitutive expression of human
73 TNF α , and when administered after disease onset, allows eroded joints to heal.

74

75 **Pharmacodynamics**

76

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

95

96 **Pharmacokinetics**

97

98 In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship
99 between the dose administered and the maximum serum concentration. The volume of
100 distribution at steady state was independent of dose and indicated that infliximab was distributed
101 primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg
102 to 10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the median
103 terminal half-life of infliximab is 8.0 to 9.5 days.

104

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

115

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

119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159

CLINICAL STUDIES
Rheumatoid Arthritis

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

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

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

Data on use of REMICADE without concurrent MTX are limited (see ADVERSE REACTIONS, Immunogenicity).^{5,6}

Clinical response

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

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

REMICADE Psoriatic Arthritis sBLA FDA Labeling – August 11, 2006

Table 1

ACR RESPONSE (PERCENT OF PATIENTS)

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

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

^a p ≤ 0.001

^b p < 0.01

^c p < 0.05

160

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

| <u>Parameter (medians)</u> | <u>Placebo + MTX</u> | | <u>REMICADE + MTX^a</u> | |
|--|----------------------|----------------|-----------------------------------|----------------|
| | <u>(n=88)</u> | | <u>(n=340)</u> | |
| | <u>Baseline</u> | <u>Week 54</u> | <u>Baseline</u> | <u>Week 54</u> |
| No. of Tender Joints | 24 | 16 | 32 | 8 |
| No. of Swollen Joints | 19 | 13 | 20 | 7 |
| Pain ^b | 6.7 | 6.1 | 6.8 | 3.3 |
| Physician's Global Assessment ^b | 6.5 | 5.2 | 6.2 | 2.1 |
| Patient's Global Assessment ^b | 6.2 | 6.2 | 6.3 | 3.2 |
| Disability Index (HAQ-DI) ^c | 1.8 | 1.5 | 1.8 | 1.3 |
| CRP (mg/dL) | 3.0 | 2.3 | 2.4 | 0.6 |

^aAll doses/schedules of REMICADE + MTX

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

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

161

162 *Radiographic response*

163

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

168

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

172

173 In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of
174 structural damage was observed at weeks 30 and 54 (Table 3) in the REMICADE + MTX groups
175 compared to MTX alone. Patients treated with REMICADE + MTX demonstrated less
176 progression of structural damage compared to MTX alone, whether baseline acute phase
177 reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute phase
178 reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units
179 compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of
180 progression; patients with normal baseline acute phase reactants treated with MTX alone
181 demonstrated a mean progression in vdH-S score of 1.8 units compared to REMICADE + MTX
182 who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had

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

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> | | | | | | |
| <i>Baseline</i> | | | | | | |
| Mean | 79 | 78 | 65 | 11.3 | 11.6 | 11.2 |
| Median | 55 | 57 | 56 | 5.1 | 5.2 | 5.3 |
| <i>Change from baseline</i> | | | | | | |
| 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> | | | | | | |
| <i>Baseline</i> | | | | | | |
| Mean | 44 | 44 | 33 | 8.3 | 8.8 | 8.3 |
| Median | 25 | 29 | 22 | 3.0 | 3.8 | 3.8 |
| <i>Change from baseline</i> | | | | | | |
| 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> | | | | | | |
| <i>Baseline</i> | | | | | | |
| Mean | 36 | 34 | 31 | 3.0 | 2.9 | 2.9 |
| Median | 26 | 29 | 24 | 1.0 | 1.0 | 1.0 |
| <i>Change from baseline</i> | | | | | | |
| 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.

189

190 *Physical function response*

191

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

194

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

203

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

208

209 **Active Crohn's Disease**

210

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

217

218 In the single-dose trial⁸ of 108 patients, 16% (4/25) of placebo patients achieved a clinical
219 response (decrease in CDAI ≥ 70 points) at week 4 vs. 81% (22/27) of patients receiving 5 mg/kg
220 REMICADE ($p < 0.001$, two-sided, Fisher's Exact test). Additionally, 4% (1/25) of placebo
221 patients and 48% (13/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission
222 (CDAI < 150) at week 4.

223

224 In a multidose trial (ACCENT I [Study Crohn's I])⁹, 545 patients received 5 mg/kg at week 0
225 and were then randomized to one of three treatment groups; the placebo maintenance group
226 received placebo at weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group
227 received 5 mg/kg at weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance
228 group received 5 mg/kg at weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in
229 response at week 2 were randomized and analyzed separately from those not in response at week
230 2. Corticosteroid taper was permitted after week 6.

231

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

235

236 Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg
237 REMICADE maintenance groups were in clinical remission and were able to discontinue
238 corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).
239

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

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

240

241 ^a REMICADE at week 0

242 ^b REMICADE 5 mg/kg administered at weeks 0, 2 and 6

243 ^c p-values represent pairwise comparisons to placebo

244 ^d Of those receiving corticosteroids at baseline

245

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

252

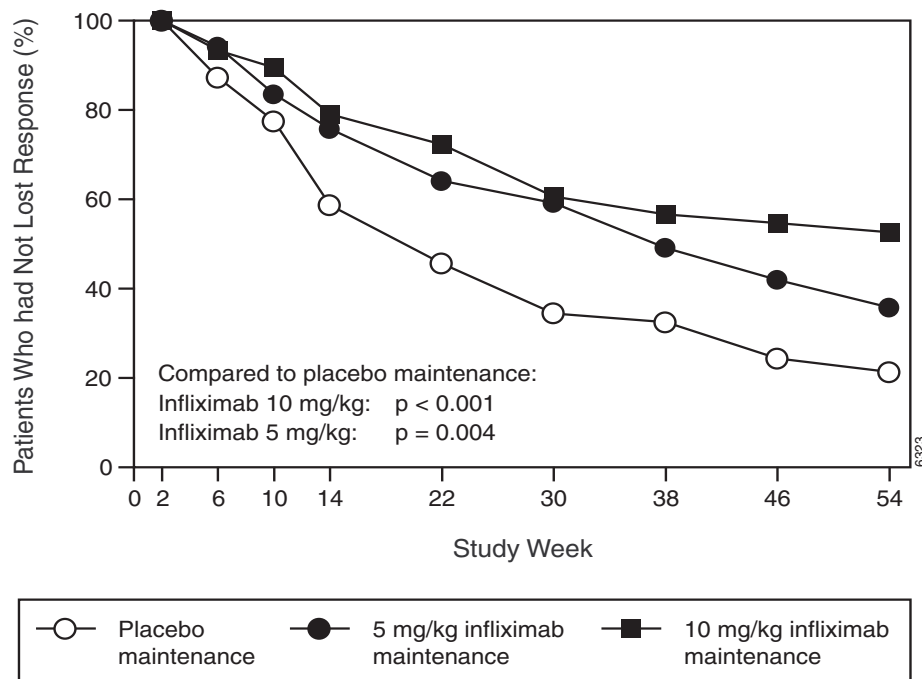


Figure 1
Kaplan-Meier estimate of the proportion of patients
who had not lost response through week 54

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

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

Fistulizing Crohn's Disease

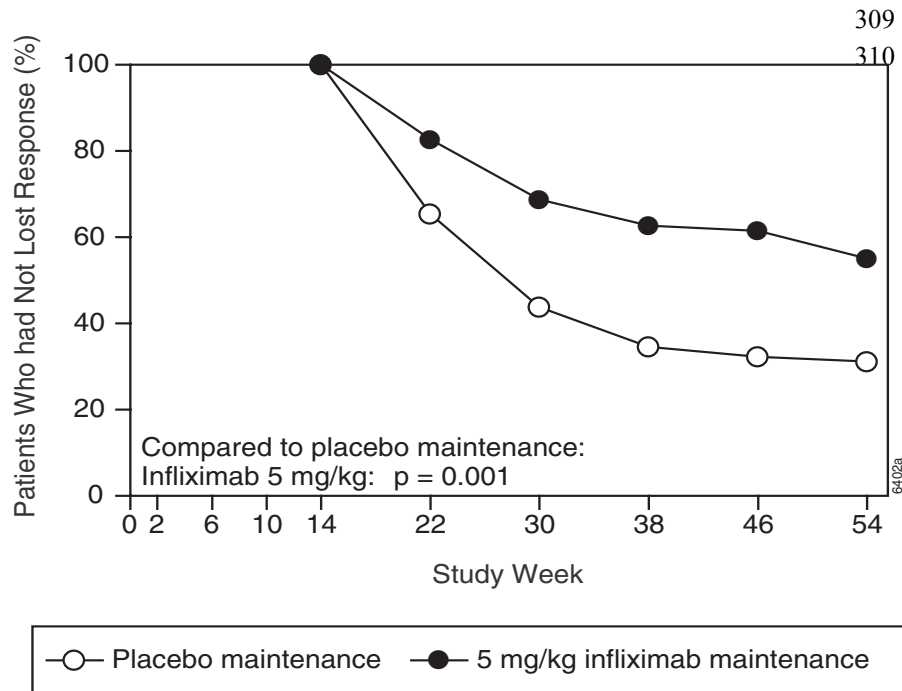
The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-aminosalicylates, antibiotics, MTX, 6-mercaptopurine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

280 In the first trial,¹⁰ 94 patients received three doses of either placebo or REMICADE at weeks 0,
281 2 and 6. Fistula response ($\geq 50\%$ reduction in number of enterocutaneous fistulas draining upon
282 gentle compression on at least two consecutive visits without an increase in medication or
283 surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE
284 group ($p=0.002$) and 56% (18/32) of patients in the 10 mg/kg REMICADE group ($p=0.021$) vs.
285 26% (8/31) of patients in the placebo arm. The median time to onset of response and median
286 duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure
287 of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of
288 placebo-treated patients ($p<0.001$).

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

298
299 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and
300 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of
301 the patients had received previous immunosuppressive and antibiotic therapy.

302
303 At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to
304 REMICADE maintenance had a longer time to loss of fistula response compared to the placebo
305 maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no
306 draining fistulas compared with 22% (20/90) of placebo-treated patients ($p=0.02$). Compared to
307 placebo maintenance, patients on REMICADE maintenance had a trend toward fewer
308 hospitalizations.



311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337

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.

338 All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. At Week
339 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given
340 either every 8 weeks or every 12 weeks.

341

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

345

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

350

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

356

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

362

363
 364
 365
 366
 367
 368
 369
 370
 371
 372
 373
 374
 375
 376
 377
 378
 379
 380
 381
 382
 383
 384
 385
 386
 387

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.

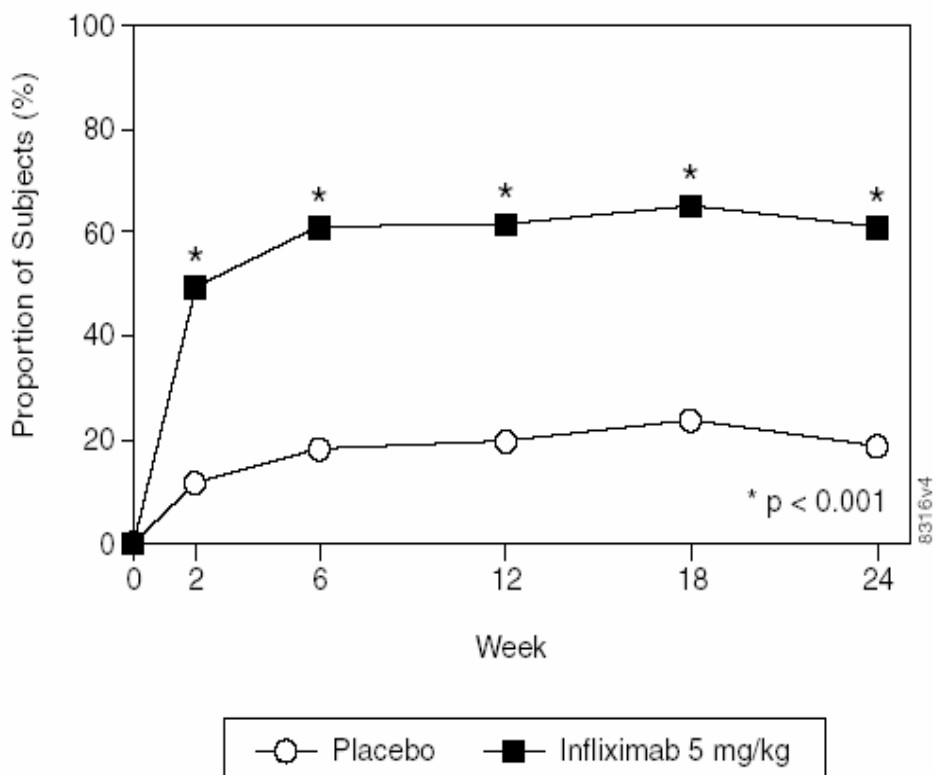
* p-value < 0.05

**p-value < 0.01

388 **Ankylosing Spondylitis**

389
390 The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-
391 blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were
392 between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New
393 York criteria for Ankylosing Spondylitis.¹¹ Patients were to have had active disease as evidenced
394 by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible
395 range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with
396 complete ankylosis of the spine were excluded from study participation, and the use of Disease
397 Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited.
398 Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12
399 and 18.

400
401 At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by
402 the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20),
403 was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo
404 group (p<0.001). Improvement was observed at week 2 and maintained through week 24
405 (Figure 3 and Table 6).



406
407
408
409
410

Figure 3
Proportion of patients achieving ASAS 20 response

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

418
419
420
421

Table 6
Components of Ankylosing Spondylitis Disease Activity

| | Placebo (n=78) | | REMICADE 5mg/kg (n=201) | | p-value |
|--|-------------------|-------------|----------------------------|-------------|---------|
| | Baseline | 24 Weeks | Baseline | 24 Weeks | |
| ASAS 20 response Criteria (Mean) | | | | | |
| Patient global assessment ^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

422
423
424
425
426
427
428
429
430
431
432
433
434

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

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

Psoriatic Arthritis

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

447
448 *Clinical response*

449
450 Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the
451 ACR criteria, with 58% of REMICADE-treated patients achieving ACR 20 at week 14,
452 compared with 11% of placebo-treated patients ($p < 0.001$). The response was similar regardless
453 of concomitant use of methotrexate. Improvement was observed as early as week 2. At 6
454 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of
455 patients receiving REMICADE compared to 16%, 4%, and 2%, respectively, of patients
456 receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic
457 arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with
458 peripheral arthritis subtypes.

459
460 Compared to placebo, treatment with REMICADE resulted in improvements in the components
461 of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 7). The clinical
462 response was maintained through week 54. Similar ACR responses were observed in an earlier
463 randomized, placebo-controlled study of 104 psoriatic arthritis patients, and the responses were
464 maintained through 98 weeks in an open label extension phase.

465

466

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 (n=100) ^a | |
|--|--------------------|---------|---|----------------------|
| | Baseline | Week 24 | Baseline | Week 24 ^a |
| 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

467

468

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

476

477 *Radiographic response*

478

479 Structural damage in both hands and feet was assessed radiographically by the change from
480 baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints.
481 The total modified vdH-S score is a composite score of structural damage that measures the
482 number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and
483 feet. At Week 24, REMICADE-treated patients had less radiographic progression than placebo-

484 treated patients (mean change of -0.70 vs. 0.82, $p < 0.001$). REMICADE-treated patients also had
485 less progression in their erosion scores (-0.56 vs. 0.51) and JSN scores (-0.14 vs. 0.31). The
486 patients in the REMICADE group demonstrated continued inhibition of structural damage at
487 week 54. Most patients showed little or no change in the vdH-S score during this 12-month
488 study (median change of 0 in both patients who initially received REMICADE or placebo).
489 More patients in the placebo group (12%) had readily apparent radiographic progression
490 compared with the REMICADE group (3%).

491

492 *Physical function*

493

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

499

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

505

506 **Ulcerative Colitis**

507

508 The safety and efficacy of REMICADE were assessed in two randomized, double-blind,
509 placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative
510 colitis (UC) (Mayo score¹² 6 to 12 [of possible range 0-12], Endoscopy subscore ≥ 2) with an
511 inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant
512 treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory
513 agents was permitted. Corticosteroid taper was permitted after week 8. In both studies, patients
514 were randomized to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE at
515 weeks 0, 2, 6, 14 and 22.

516

517 Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-
518 mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or
519 were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients
520 in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-
521 MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More
522 patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%,
523 respectively). Clinical response was defined as a decrease from baseline in the Mayo score by \geq
524 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal
525 bleeding subscore of 0 or 1.

526

527 In both studies, greater percentages of patients in both REMICADE groups achieved a clinical
528 response, a sustained clinical response (response at both weeks 8 and 30), clinical remission and
529 other assessed clinical outcomes than in the placebo group (Table 8). Of patients on

530 corticosteroids at baseline, greater proportions of patients in the REMICADE treatment groups
531 were in clinical remission and able to discontinue corticosteroids at week 30 compared with the
532 patients in the placebo treatment groups (22% in REMICADE treatment groups vs. 10% in
533 placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in placebo group in
534 Study UC II). The REMICADE-associated response was generally similar in the 5 mg/kg and 10
535 mg/kg dose groups.

536

Table 8
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 | | | | | | |
| Week 8 | 37% | 69%* | 62%* | 29% | 65%* | 69%* |
| Week 30 | 30% | 52%* | 51%** | 26% | 47%* | 60%* |
| Sustained Response (both Week 8 and 30) | | | | | | |
| | 23% | 49%* | 46%* | 15% | 41%* | 53%* |
| Clinical Remission ² | | | | | | |
| Week 8 | 15% | 39%* | 32%** | 6% | 34%* | 28%* |
| Week 30 | 16% | 34%* | 37%* | 11% | 26%** | 36%* |
| Sustained Remission (both Week 8 and 30) | | | | | | |
| | 8% | 23%* | 26%* | 2% | 15%* | 23%* |
| Mucosal Healing ³ | | | | | | |
| Week 8 | 34% | 62%* | 59%* | 31% | 60%* | 62%* |
| Week 30 | 25% | 50%* | 49%* | 30% | 46%** | 57%* |

537

538 * P < 0.001, ** P < 0.01

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

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

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

544
 545 The improvement with REMICADE was consistent across all Mayo subscores through week 30
 546 (study UC I shown in Table 9; Study UC II was similar).

547
 548 **Table 9**
 549 **Proportion of patients in Study UC I with Mayo subscores indicating**
 550 **inactive or mild disease through week 30**
 551

| | 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% |
| Rectal Bleeding | | | |
| Baseline | 54% | 40% | 48% |
| Week 8 | 74% | 86% | 80% |
| Week 30 | 65% | 74% | 71% |
| Physician's global assessment | | | |
| Baseline | 4% | 6% | 3% |
| Week 8 | 44% | 74% | 64% |
| Week 30 | 36% | 57% | 55% |
| Endoscopy findings | | | |
| Baseline | 0% | 0% | 0% |
| Week 8 | 34% | 62% | 59% |
| Week 30 | 26% | 51% | 52% |

552
 553 **INDICATIONS AND USAGE**

554
 555 **Rheumatoid Arthritis**

556
 557 REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms,
 558 inhibiting the progression of structural damage, and improving physical function in patients with
 559 moderately to severely active rheumatoid arthritis.

560
 561 **Crohn's Disease**

562
 563 REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical
 564 remission in adult and pediatric patients with moderately to severely active Crohn's disease who
 565 have had an inadequate response to conventional therapy (see Boxed WARNING, WARNINGS,
 566 and PRECAUTIONS-Pediatric Use).

567
 568 REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal
 569 fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

570

571 **Ankylosing Spondylitis**

572

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

575

576 **Psoriatic Arthritis**

577

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

581

582 **Ulcerative Colitis**

583

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

587

588 **CONTRAINDICATIONS**

589

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

596

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

599

600

601 **WARNINGS**

602

603 **RISK OF INFECTIONS**

604 (See boxed WARNING)

605

606 **SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN**
607 **REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF**
608 **THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS**
609 **IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON**
610 **CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO**
611 **THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS.**

612

613 **REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY**
614 **IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN**
615 **CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC**

616 **INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE**
617 **MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER**
618 **TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY**
619 **MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE**
620 **THERAPY SHOULD BE DISCONTINUED (see ADVERSE REACTIONS, Infections).**

621
622 **CASES OF TUBERCULOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS,**
623 **LISTERIOSIS, PNEUMOCYSTOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND**
624 **FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING**
625 **REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE**
626 **HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS**
627 **AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY**
628 **CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.**

629
630 **SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT**
631 **USE OF ANAKINRA AND ANOTHER TNF α -BLOCKING AGENT, ETANERCEPT,**
632 **WITH NO ADDED CLINICAL BENEFIT COMPARED TO ETANERCEPT ALONE.**
633 **BECAUSE OF THE NATURE OF THE ADVERSE EVENTS SEEN WITH**
634 **COMBINATION OF ETANERCEPT AND ANAKINRA THERAPY, SIMILAR**
635 **TOXICITIES MAY ALSO RESULT FROM THE COMBINATION OF ANAKINRA**
636 **AND OTHER TNF α -BLOCKING AGENTS. THEREFORE, THE COMBINATION OF**
637 **REMICADE AND ANAKINRA IS NOT RECOMMENDED.**

638
639 **HEPATOSPLENIC T-CELL LYMPHOMAS**
640 **(See boxed WARNING)**

641
642 **RARE POSTMARKETING CASES OF HEPATOSPLENIC T-CELL LYMPHOMAS**
643 **HAVE BEEN REPORTED IN ADOLESCENT AND YOUNG ADULT PATIENTS WITH**
644 **CROHN'S DISEASE TREATED WITH REMICADE. ALL OF THESE REPORTS**
645 **HAVE OCCURRED IN PATIENTS ON CONCOMITANT TREATMENT WITH**
646 **AZATHIOPRINE OR 6-MERCAPTOPURINE. THE CLINICAL COURSE OF THIS**
647 **DISEASE IS VERY AGGRESSIVE WITH A FATAL OUTCOME IN MOST PATIENTS**
648 **WITHIN 2 YEARS OF DIAGNOSIS.¹³ THE CAUSAL RELATIONSHIP OF**
649 **HEPATOSPLENIC T-CELL LYMPHOMA TO REMICADE THERAPY REMAINS**
650 **UNCLEAR.**

651
652 **Hepatotoxicity**

653
654 Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have
655 been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune
656 hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between
657 two weeks to more than a year after initiation of REMICADE; elevations in hepatic
658 aminotransferase levels were not noted prior to discovery of the liver injury in many of these
659 cases. Some of these cases were fatal or necessitated liver transplantation. Patients with
660 symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If
661 jaundice and/or marked liver enzyme elevations (e.g., ≥ 5 times the upper limit of normal)

662 develops, REMICADE should be discontinued, and a thorough investigation of the abnormality
663 should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been
664 associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e.,
665 surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and
666 monitored prior to the initiation of and during treatment with REMICADE. In clinical trials,
667 mild or moderate elevations of ALT and AST have been observed in patients receiving
668 REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS,
669 Hepatotoxicity).

670

671 **Patients with Heart Failure**

672

673 REMICADE has been associated with adverse outcomes in patients with heart failure, and
674 should be used in patients with heart failure only after consideration of other treatment options.
675 The results of a randomized study evaluating the use of REMICADE in patients with heart
676 failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10
677 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and
678 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without
679 identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-
680 marketing reports of new onset heart failure, including heart failure in patients without known
681 pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a
682 decision is made to administer REMICADE to patients with heart failure, they should be closely
683 monitored during therapy, and REMICADE should be discontinued if new or worsening
684 symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE
685 REACTIONS, Patients with Heart Failure).

686

687 **Hematologic Events**

688

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

697

698 **Hypersensitivity**

699

700 REMICADE has been associated with hypersensitivity reactions that vary in their time of onset
701 and required hospitalization in some cases. Most hypersensitivity reactions, which include
702 urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE
703 infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's
704 disease patients 3 to 12 days after REMICADE therapy was reinstated following an extended
705 period without REMICADE treatment. Symptoms associated with these reactions include fever,
706 rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia.
707 These reactions were associated with marked increase in antibodies to infliximab, loss of

708 detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE
709 should be discontinued for severe reactions. Medications for the treatment of hypersensitivity
710 reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be
711 available for immediate use in the event of a reaction (see ADVERSE REACTIONS, Infusion-
712 related Reactions).

713

714 **Neurologic Events**

715

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

723

724 **Malignancies**

725

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

737

738 In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of
739 lymphoma have been observed among patients receiving a TNF blocker compared with control
740 patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients
741 developed lymphomas among 4333 patients treated with REMICADE (median duration of
742 follow-up 1.0 years) vs. 0 lymphomas in 1266 control patients (median duration of follow-up 0.5
743 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per
744 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the
745 general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's
746 disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 5 lymphomas were
747 observed for a rate of 0.13 cases per 100 patient-years of follow-up, which is approximately 6-
748 fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid
749 arthritis, particularly patients with highly active disease and/or chronic exposure to
750 immunosuppressant therapies, may be at a higher risk (up to several fold) than the general
751 population for the development of lymphoma, even in the absence of TNF-blocking therapy.

752

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

759
760 The potential role of TNF-blocking therapy in the development of malignancies is not known
761 (see ADVERSE REACTIONS, Malignancies). Rates in clinical trials for REMICADE cannot be
762 compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a
763 broader patient population. Caution should be exercised in considering REMICADE treatment
764 in patients with a history of malignancy or in continuing treatment in patients who develop
765 malignancy while receiving REMICADE.

766

767 **PRECAUTIONS**

768

769 **Autoimmunity**

770

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

775

776 **Vaccinations**

777

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

781

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

785

786 **Information for Patients**

787

788 Patients or their caregivers should be provided the REMICADE Patient Information Sheet and
789 provided an opportunity to read it prior to each treatment infusion session. Because caution
790 should be exercised in administering REMICADE to patients with clinically important active
791 infections, it is important that the patient's overall health be assessed at each treatment visit and
792 any questions resulting from the patient's or caregiver's reading of the Patient Information Sheet
793 be discussed.

794

795 **Drug Interactions**

796

797 Concurrent administration of etanercept (another TNF α -blocking agent) and anakinra (an
798 interleukin-1 antagonist) has been associated with an increased risk of serious infections, and

799 increased risk of neutropenia and no additional benefit compared to these medicinal products
800 alone. Other TNF α -blocking agents (including REMICADE) used in combination with anakinra
801 may also result in similar toxicities (see WARNINGS, RISK OF INFECTIONS).

802
803 Specific drug interaction studies, including interactions with MTX, have not been conducted.
804 The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one
805 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides
806 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.
807 Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids,
808 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications
809 included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory
810 agents, folic acid and corticosteroids.

811
812 Patients with Crohn's disease who received immunosuppressants tended to experience fewer
813 infusion reactions compared to patients on no immunosuppressants (see ADVERSE
814 REACTIONS, Immunogenicity and Infusion-related Reactions). Serum infliximab
815 concentrations appeared to be unaffected by baseline use of medications for the treatment of
816 Crohn's disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and
817 aminosalicylates.

818

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

820

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

833

834 **Pregnancy Category B**

835

836 Since infliximab does not cross-react with TNF α in species other than humans and chimpanzees,
837 animal reproduction studies have not been conducted with REMICADE. No evidence of
838 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity
839 study conducted in mice using an analogous antibody that selectively inhibits the functional
840 activity of mouse TNF α . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the
841 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to
842 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not
843 known whether REMICADE can cause fetal harm when administered to a pregnant woman or
844 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if
845 clearly needed.

846

847 **Nursing Mothers**

848

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

855

856 **Pediatric Use**

857

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

864

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

868

869 Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and
870 pediatric patients with ulcerative colitis have not been established.

871

872

873 **Geriatric Use**

874

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

883

884 **ADVERSE REACTIONS**

885

886 The data described herein reflect exposure to REMICADE in 3406 adult patients (1304 patients
887 with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis,
888 293 with psoriatic arthritis, 484 with ulcerative colitis and 17 patients with other conditions),
889 including 1777 patients exposed beyond 30 weeks and 374 exposed beyond one year. (For
890 information on adverse reactions in pediatric patients see ADVERSE REACTIONS – Adverse
891 Reactions in Pediatric Crohn's Disease.) The most common reason for discontinuation of
892 treatment was infusion-related reactions (e.g. dyspnea, flushing, headache and rash). Adverse
893 events have been reported in a higher proportion of rheumatoid arthritis patients receiving the
894 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of
895 adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with Crohn's disease

896

897 **Infusion-related Reactions**

898

899 *Acute infusion reactions*

900

901 An infusion reaction was defined in clinical trials as any adverse event occurring during an
902 infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated
903 patients in all clinical studies experienced an infusion reaction compared to approximately 10%
904 of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by
905 nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary
906 reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were
907 accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and
908 cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included
909 anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients
910 discontinued REMICADE because of infusion reactions, and all patients recovered with
911 treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial
912 infusion were not associated with a higher incidence of reactions.

913

914 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to
915 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant
916 immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and
917 infusion reactions (see ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug
918 Interactions).

919
920 In post-marketing experience, cases of anaphylactic-like reactions, including
921 laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with
922 REMICADE administration.

923
924 *Reactions following readministration*

925
926 In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following
927 a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events
928 manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and
929 symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also
930 experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.
931 Patients experiencing these adverse events had not experienced infusion-related adverse events
932 associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of
933 patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients
934 who received lyophilized formulation. The clinical data are not adequate to determine if
935 occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms
936 improved substantially or resolved with treatment in all cases. There are insufficient data on the
937 incidence of these events after drug-free intervals of 1 to 2 years. These events have been
938 observed only infrequently in clinical studies and post-marketing surveillance with retreatment
939 intervals up to 1 year.

940
941 **Infections**

942
943 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated
944 patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of
945 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections
946 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among
947 REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin
948 ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were
949 reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was
950 fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was
951 reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis,
952 including disseminated tuberculosis, also have been reported post-marketing. Most of these cases
953 of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE
954 and may reflect recrudescence of latent disease (see WARNINGS, RISK OF INFECTIONS). In
955 the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE
956 every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients
957 receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4%
958 developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter
959 (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg
960 or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX,
961 serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3
962 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients
963 with fistulizing Crohn's disease developed a new fistula-related abscess.

964

965 In REMICADE clinical studies in patients with ulcerative colitis, infections treated with
966 antimicrobials were reported in 19% of REMICADE-treated patients (average of 27 weeks of
967 follow-up) and in 14% of placebo-treated patients (average 22 weeks of follow-up). The types of
968 infections, including serious infections, reported in patients with ulcerative colitis were similar to
969 those reported in other clinical studies.

970

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

975

976 **Autoantibodies/Lupus-like Syndrome**

977

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

983

984 **Malignancies**

985

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

988

989 In a randomized controlled clinical trial exploring the use of REMICADE in patients with
990 moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were
991 treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's
992 disease. Nine of these REMICADE-treated patients developed a malignancy, including 1
993 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of
994 follow-up 0.8 years; 95% CI 3.51 - 14.56). There was one reported malignancy among 77 control
995 patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up
996 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head
997 and neck.

998

999 Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been
1000 reported in patients receiving REMICADE during post-approval use.

1001

1002

1003 **Patients with Heart Failure**

1004

1005 In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class
1006 III/IV; left ventricular ejection fraction $\leq 35\%$), 150 patients were randomized to receive
1007 treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks.
1008 Higher incidences of mortality and hospitalization due to worsening heart failure were observed
1009 in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg
1010 REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the

1011 placebo groups. There were trends towards increased dyspnea, hypotension, angina, and
1012 dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo.
1013 REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See
1014 CONTRAINDICATIONS and WARNINGS, Patients with Heart Failure).
1015

1016 **Immunogenicity**

1017
1018 Treatment with REMICADE can be associated with the development of antibodies to infliximab.
1019 The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed
1020 by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE
1021 treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease
1022 patients receiving REMICADE after drug free intervals >16 weeks. In a study of psoriatic
1023 arthritis, where 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab
1024 occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients
1025 who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy
1026 and to experience an infusion reaction (see ADVERSE REACTIONS, Infusion-related
1027 Reactions) than were patients who were antibody negative. Antibody development was lower
1028 among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies
1029 such as 6-MP/AZA or MTX.
1030

1031 The data reflect the percentage of patients whose test results were positive for antibodies to
1032 infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the
1033 assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced
1034 by several factors including sample handling, timing of sample collection, concomitant
1035 medication, and underlying disease. For these reasons, comparison of the incidence of antibodies
1036 to infliximab with the incidence of antibodies to other products may be misleading.
1037

1038 **Hepatotoxicity**

1039
1040 Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported
1041 rarely in patients receiving REMICADE (see WARNINGS, Hepatotoxicity). Reactivation of
1042 hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus
1043 (i.e., surface antigen positive) (see WARNINGS, Hepatotoxicity).
1044

1045 In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis
1046 and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than
1047 AST) in a greater proportion of patients receiving REMICADE than in controls (Table 10), both
1048 when REMICADE was given as monotherapy and when it was used in combination with other
1049 immunosuppressive agents. In general, patients who developed ALT and AST elevations were
1050 asymptomatic, and the abnormalities decreased or resolved with either continuation or
1051 discontinuation of REMICADE, or modification of concomitant medications.
1052
1053

Table 10 Proportion of patients with elevated ALT in Clinical Trials

Proportion of patients with elevated ALT

| | <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% | 15% | 1% | 2% | <1% | <1% |
| Ankylosing spondylitis ⁴ | 13% | 40% | 0% | 6% | 0% | 2% |
| Psoriatic arthritis ⁵ | 16% | 42% | 0% | 5% | 0% | 2% |

1054 ¹Placebo patients received methotrexate while REMICADE patients received both REMICADE and
1055 methotrexate. Median follow-up was 58 weeks.

1056 ²Placebo patients in the 2 Phase III trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at
1057 study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo
1058 maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT
1059 analysis. Median follow-up was 54 weeks.

1060 ³Median follow-up was 30 weeks.

1061 ⁴Median follow-up was 24 weeks.

1062 ⁵Median follow-up was 24 weeks for REMICADE group and 18 weeks for placebo group.

1063

1064

1065 **Adverse Reactions in Pediatric Crohn's Disease**

1066

1067 There were some differences in the adverse reactions observed in the pediatric patients receiving
1068 REMICADE compared to those observed in adults with Crohn's disease. These differences are
1069 discussed in the following paragraphs.

1070

1071 The following adverse events were reported more commonly in 103 randomized pediatric
1072 Crohn's disease patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult
1073 Crohn's disease patients receiving a similar treatment regimen: anemia (11%), blood in stool
1074 (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture
1075 (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

1076

1077 Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in
1078 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more
1079 frequently for patients who received every 8 week as opposed to every 12 week infusions (74%
1080 and 38%, respectively), while serious infections were reported for 3 patients in the every 8 week
1081 and 4 patients in the every 12 week maintenance treatment group. The most commonly reported
1082 infections were upper respiratory tract infection and pharyngitis, and the most commonly
1083 reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8
1084 week and 1 in the every 12 week maintenance treatment groups). Herpes zoster was reported for
1085 2 patients in the every 8 week maintenance treatment group.

1086

1087 In Study Peds Crohn's, 18% of randomized patients experienced one or more infusion reactions,
1088 with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's,
1089 there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

1090

1091 Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn's.

1092

1093 Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric
1094 patients in Crohn's disease clinical trials; 4% had ALT elevations $\geq 3 \times$ ULN, and 1% had
1095 elevations $\geq 5 \times$ ULN. (Median follow-up was 53 weeks.)

1096

1097 The most common serious adverse events reported in the post-marketing experience in children
1098 were infections (some fatal) including opportunistic infections and tuberculosis, infusion
1099 reactions, and hypersensitivity reactions.

1100

1101 Serious adverse events in the post-marketing experience with REMICADE in the pediatric
1102 population have also included malignancies, including hepatosplenic T-cell lymphomas (see
1103 Boxed WARNING and WARNINGS), transient hepatic enzyme abnormalities, lupus-like
1104 syndromes, and the development of autoantibodies.

1105

1106 **Other Adverse Reactions**

1107

1108 Safety data are available from 3406 REMICADE-treated adult patients, including 1304 with
1109 rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing
1110 spondylitis, 293 with psoriatic arthritis, and 17 with other conditions. (For information on other
1111 adverse reactions in pediatric patients, see ADVERSE REACTIONS – Adverse Reactions in
1112 Pediatric Crohn's Disease). Adverse events reported in $\geq 5\%$ of all patients with rheumatoid
1113 arthritis receiving 4 or more infusions are in Table 11. The types and frequencies of adverse
1114 reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing
1115 spondylitis, psoriatic arthritis and Crohn's disease patients except for abdominal pain, which
1116 occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease
1117 studies, there were insufficient numbers and duration of follow-up for patients who never
1118 received REMICADE to provide meaningful comparisons.

1119
 1120
 1121
 1122

Table 11
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% |

1123
 1124
 1125
 1126
 1127
 1128

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.

1129 The most common serious adverse events observed in clinical trials were infections (see
1130 ADVERSE REACTIONS, Infections). Other serious, medically relevant adverse events $\geq 0.2\%$
1131 or clinically significant adverse events by body system were as follows:

1132

1133 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela

1134 *Blood:* pancytopenia

1135 *Cardiovascular:* circulatory failure, hypotension, syncope

1136 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,
1137 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia

1138 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness

1139 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia

1140 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis

1141 *Metabolic and Nutritional:* dehydration

1142 *Musculoskeletal:* intervertebral disk herniation, tendon disorder

1143 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction

1144 *Platelet, Bleeding and Clotting:* thrombocytopenia

1145 *Neoplasms:* basal cell, breast, lymphoma

1146 *Psychiatric:* confusion, suicide attempt

1147 *Red Blood Cell:* anemia, hemolytic anemia

1148 *Reproductive:* menstrual irregularity

1149 *Resistance Mechanism:* cellulitis, sepsis, serum sickness

1150 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including
1151 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency

1152 *Skin and Appendages:* increased sweating, ulceration

1153 *Urinary:* renal calculus, renal failure

1154 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis

1155 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

1156

1157 The following adverse events have been reported during post-approval use of REMICADE:
1158 neutropenia (see WARNINGS, Hematologic Events), interstitial pneumonitis/fibrosis, idiopathic
1159 thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic
1160 and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies
1161 (additional neurologic events have also been observed, see WARNINGS, Neurologic Events).
1162 Because these events are reported voluntarily from a population of uncertain size, it is not always
1163 possible to reliably estimate their frequency or establish a causal relationship to REMICADE
1164 exposure.

1165

1166 **OVERDOSAGE**

1167

1168 Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of
1169 overdose, it is recommended that the patient be monitored for any signs or symptoms of
1170 adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

1171

1172 **DOSAGE AND ADMINISTRATION**

1173

1174 **Rheumatoid Arthritis**

1175

1176 The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed
1177 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
1178 thereafter. REMICADE should be given in combination with methotrexate. For patients who
1179 have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or
1180 treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at
1181 higher doses (see ADVERSE REACTIONS, Infections).

1182

1183 **Crohn's Disease or Fistulizing Crohn's Disease**

1184

1185 The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at
1186 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the
1187 treatment of adults with moderately to severely active Crohn's disease or fistulizing Crohn's
1188 disease. For adult patients who respond and then lose their response, consideration may be given
1189 to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond
1190 with continued dosing and consideration should be given to discontinue REMICADE in these
1191 patients.

1192

1193 The recommended dose of REMICADE for children with moderately to severely active Crohn's
1194 disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a
1195 maintenance regimen of 5 mg/kg every 8 weeks.

1196

1197 **Ankylosing Spondylitis**

1198

1199 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed
1200 with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks
1201 thereafter.

1202

1203 **Psoriatic Arthritis**

1204

1205 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed
1206 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
1207 thereafter. REMICADE can be used with or without methotrexate.

1208

1209 **Ulcerative Colitis**

1210

1211 The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6
1212 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment
1213 of moderately to severely active ulcerative colitis.

1214

1215 **Preparation and Administration Instructions**

1216 **Use aseptic technique.**

1217

1218 REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after
1219 reconstitution should be used immediately, not re-entered or stored. The diluent to be used for
1220 reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted
1221 product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The
1222 infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE
1223 infusion should begin within 3 hours of preparation.

1224

1225 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial
1226 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE
1227 solution required.

1228

1229 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a
1230 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and
1231 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center
1232 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass
1233 wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution
1234 by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous
1235 agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.
1236 Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to
1237 light yellow and opalescent, and the solution may develop a few translucent particles as
1238 infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign
1239 particles are present.

1240

1241 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with
1242 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride
1243 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium
1244 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted
1245 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.

1246

1247 4. The infusion solution must be administered over a period of not less than 2 hours and must
1248 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore
1249 size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for
1250 reuse.

1251

1252 5. No physical biochemical compatibility studies have been conducted to evaluate the co-
1253 administration of REMICADE with other agents. REMICADE should not be infused
1254 concomitantly in the same intravenous line with other agents.

1255

1256 6. Parenteral drug products should be inspected visually for particulate matter and
1257 discoloration prior to administration, whenever solution and container permit. If visibly
1258 opaque particles, discoloration or other foreign particulates are observed, the solution
1259 should not be used.

1260

1261 **Storage**

1262

1263 Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do
1264 not use beyond the expiration date. This product contains no preservative.

1265

1266 **HOW SUPPLIED**

1267

1268 REMICADE lyophilized concentrate for IV injection is supplied in individually-boxed single-
1269 use vials in the following strength:

1270

1271 NDC 57894-030-01 100 mg infliximab in a 20 mL vial

1272

1273 **REFERENCES**

1274

1275 1. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin
1276 testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*
1277 2000;161:S221-S247.

1278

1279 2. Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human
1280 chimeric anti-TNF antibody. *Molec Immunol* 1993;30:1443-1453.

1281

1282 3. Scallon BJ, Moore MA, Trinh H, et al. Chimeric anti-TNF α monoclonal antibody cA2 binds
1283 recombinant transmembrane TNF α and activates immune effector functions. *Cytokine*
1284 1995;7:251-259.

1285

1286 4. ten Hove T, van Montfrans C, Peppelenbosch MP, et al. Infliximab treatment induces
1287 apoptosis of lamina propria T lymphocytes in Crohn's disease. *Gut* 2002;50:206-211.

1288

1289 5. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous
1290 infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose
1291 weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41(9):1552-1563.

1292

1293 6. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric
1294 monoclonal antibody to tumour necrosis factor alpha (cA2) vs. placebo in rheumatoid
1295 arthritis. *Lancet* 1994;344(8930):1105-1110.

1296

1297 7. Van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic
1298 assessments of hands and feet in a three-year prospective follow-up of patients with early
1299 rheumatoid arthritis. *Arthritis Rheum* 1992;35(1):26-34.

1300

1301 8. Targan SR, Hanauer SR, van Deventer SJH, et al. A short-term study of chimeric monoclonal
1302 antibody cA2 to tumor necrosis factor α for Crohn's disease. *N Engl J Med*
1303 1997;337(15):1029-1035.

1304

1305 9. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's
1306 disease: the ACCENT I randomized trial. *Lancet* 2002; 359:1541-1549.

1307

1308 10. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients
1309 with Crohn's disease. *N Engl J Med* 1999;340:1398-1405.

1310

1311 11. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing
1312 spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.*
1313 1984;27(4):361-368.

1314

1315 12. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for
1316 mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.*
1317 1987;317(26):1625-1629.

1318

1319 13. Belhadj K, Reyes F, Farcet JP, et al. Hepatosplenic $\gamma\delta$ T-cell lymphoma is a rare
1320 clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood*
1321 2003;102(13):4261-4269.

1322

1323

1324

1325

1326 ©Centocor, Inc. 2006

1327 Malvern, PA 19355, USA

1328 1-800-457-6399

1329

License #1242

August 2006

1330

1331 **Rx Only**

1332

REMICADE® (Rem-eh-kaid)

1333

(infliximab)

1334

Patient Information Sheet

1335

1336 Read the Patient Information Sheet that comes with REMICADE before you receive the first
1337 treatment, and before each time you get a treatment of REMICADE. This information sheet does
1338 not take the place of talking with your doctor about your medical condition or treatment.

1339

1340 **What is the most important information I should know about REMICADE?**

1341

1342 REMICADE is a medicine that affects your immune system. It can cause serious side effects
1343 including:

1344

1345 Serious Infections

1346 • Some patients have had serious infections while receiving REMICADE. These serious
1347 infections include TB (tuberculosis), and infections caused by viruses, fungi or bacteria
1348 that have spread throughout the body. Some patients have died from these infections.

1349 • Tell your doctor right away if you have any of the following signs of an infection while
1350 taking or after taking REMICADE:

1351

• a fever

1352

• feel very tired

1353

• have a cough

1354

• have flu-like symptoms

1355

1356 Cancer

1357 • Some children and young adults with Crohn's disease who have received REMICADE
1358 have developed a rare type of cancer called Hepatosplenic T-cell Lymphoma. This type
1359 of cancer often results in death. These patients were also receiving drugs known as
1360 azathioprine or 6-mercaptopurine.

1361

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

1362

1363 See also, "**What are the possible side effects of REMICADE?**" below.

1364

1365 **What is REMICADE?**

1366

1367 REMICADE is a prescription medicine that is approved for patients with:

1368 • Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis,
1369 along with the medicine methotrexate

1370 • Crohn's Disease - children over the age of 6 and adults with Crohn's disease who have not
1371 responded well enough to other medicines

1372

• Ankylosing Spondylitis

1373

• Psoriatic Arthritis

- 1374
- Ulcerative Colitis - patients with moderately to severely active ulcerative colitis who have not responded well enough to other medicines.
- 1375
- 1376

1377 REMICADE blocks the action of a protein in your body called tumor necrosis factor-alpha
1378 (TNF-alpha). TNF-alpha is made by your body's immune system. People with certain
1379 diseases have too much TNF-alpha that can cause the immune system to attack normal
1380 healthy parts of the body. REMICADE can block the damage caused by too much TNF-
1381 alpha.

1382

1383 **Who should not receive REMICADE?**

1384

1385 You should not receive REMICADE if you have:

- heart failure, unless your doctor has examined you and decided that you are able to take REMICADE. Talk to your doctor about your heart failure.
 - had an allergic reaction to REMICADE or any of the other ingredients in REMICADE. See the end of this information sheet for a complete list of ingredients in REMICADE.
- 1386
- 1387
- 1388
- 1389
- 1390

1391 **What should I tell my doctor before starting treatment with REMICADE?**

1392

1393 Your doctor will assess your health before each treatment.

1394

1395 Tell your doctor about all of your medical conditions, including if you:

- have any kind of infection even if it is very minor (such as an open cut or sore). REMICADE affects the body's immune system and makes you less able to fight infections.
 - have an infection that won't go away or a history of infection that keeps coming back.
 - have had TB (tuberculosis), or if you have recently been near anyone who might have TB. Even if you do not have active TB, if you have been near someone with TB and have the TB germ in your body, you can get a serious TB infection while taking REMICADE. Sometimes these serious TB infections can cause death.
 - live or have lived in certain parts of the country where there is more risk for certain kinds of fungal infections (histoplasmosis or coccidioidomycosis). These infections may develop or become more severe if you take REMICADE. If you don't know if you have lived in an area where histoplasmosis or coccidioidomycosis is common, ask your doctor.
 - have or had hepatitis B. If you are a chronic carrier of the virus that causes hepatitis B, taking REMICADE could cause the hepatitis B virus to become an active infection again.
 - have other liver problems including liver failure.
 - have heart failure or other heart conditions. If you have heart failure, it may get worse while you take REMICADE.
 - have or have had any type of cancer.
 - have COPD (Chronic Obstructive Pulmonary Disease), a specific type of lung disease. Patients with COPD may have an increased risk of getting cancer while taking REMICADE.
 - have or have had a condition that affects your nervous system such as
 - multiple sclerosis, or Guillain-Barré syndrome, or
- 1396
- 1397
- 1398
- 1399
- 1400
- 1401
- 1402
- 1403
- 1404
- 1405
- 1406
- 1407
- 1408
- 1409
- 1410
- 1411
- 1412
- 1413
- 1414
- 1415
- 1416
- 1417
- 1418

- 1419 • if you experience any numbness or tingling, or
- 1420 • if you have had a seizure.
- 1421 • have recently received or are scheduled to receive a vaccine. **Adults and children**
- 1422 **should not receive a live vaccine while taking REMICADE.** Children with Crohn's
- 1423 disease should have all of their vaccines brought up to date before starting treatment with
- 1424 REMICADE.
- 1425 • are pregnant or planning to become pregnant. It is not known if REMICADE harms your
- 1426 unborn baby. REMICADE should be given to a pregnant woman only if clearly needed.
- 1427 Talk to your doctor about stopping REMICADE if you are pregnant or planning to
- 1428 become pregnant.
- 1429 • are breast-feeding or planning to breast-feed. It is not known whether REMICADE
- 1430 passes into your breast milk. Talk to your doctor about the best way to feed your baby
- 1431 while taking REMICADE. You should not breast-feed while taking REMICADE.
- 1432

1433 **How should I receive REMICADE?**

- 1434
- 1435 • You will be given REMICADE through a needle placed in a vein (IV or intravenous
- 1436 infusion) in your arm.
- 1437 • REMICADE will be given to you over a period of about 2 hours.
- 1438 • Your doctor will determine the right dose of REMICADE for you and how often you
- 1439 should receive it. Make sure to discuss with your doctor when you will receive infusions
- 1440 and to come in for all your infusions and follow-up appointments.
- 1441 • A healthcare professional will monitor you during the REMICADE infusion and for a
- 1442 period of time afterward for side effects.
- 1443 • Only a healthcare professional should prepare the medicine and administer it to you.
- 1444 • Your doctor may do certain tests while you are taking REMICADE to monitor you for
- 1445 side effects and to see how well you respond to the treatment.
- 1446

1447 **What should I avoid while receiving REMICADE?**

1448

1449 Do not take REMICADE and the medication KINERET (Anakinra) together.

1450

1451 **Tell your doctor about all the medicines you take**, including prescription and non-prescription

1452 medicines, vitamins, and herbal supplements.

1453

1454 Know the medicines you take. Keep a list of your medicines and show them to your doctor and

1455 pharmacist when you get a new medicine.

1456

1457 **What are the possible side effects of REMICADE?**

1458

1459 Serious and sometimes fatal side effects have been reported in patients taking REMICADE (see

1460 also "**What is the most important information I should know about REMICADE?**"). These

1461 include:

1462

1463 Serious Infections

- 1464 • Some patients get serious infections while being treated with REMICADE. Serious
1465 infections include tuberculosis (TB) and infections caused by viruses, fungi, or bacteria
1466 that spread throughout the body. Some patients die from these infections.
- 1467 • Your doctor will examine you for TB and perform a skin test to see if you have TB. If
1468 your doctor feels that you are at risk for TB, you may be treated with medicine for TB
1469 before you begin treatment with REMICADE and during treatment with REMICADE.
- 1470 • Even if your TB test is negative your doctor should carefully monitor you for TB
1471 infections while you are taking REMICADE.
- 1472 • Tell your doctor right away if you have any of the following signs of an infection while
1473 taking or after taking REMICADE:
 - 1474 • a fever
 - 1475 • feel very tired
 - 1476 • have a cough
 - 1477 • have flu-like symptoms
- 1478 • If you are a chronic carrier of the hepatitis B virus, the virus can become active while you
1479 are being treated with REMICADE. Your doctor may do a blood test before you start
1480 treatment with REMICADE and occasionally while you are being treated. Tell your
1481 doctor if you have any of the following symptoms:
 - 1482 • feel unwell
 - 1483 • poor appetite
 - 1484 • tiredness (fatigue)
 - 1485 • fever, skin rash and/or joint pain

1487 Cancer

- 1488 • Some children and young adults with Crohn's disease who have received REMICADE
1489 have developed a rare type of cancer called Hepatosplenic T-cell Lymphoma. This type
1490 of cancer often results in death. These patients were also receiving drugs known as
1491 azathiaprine or 6-mercaptopurine.
- 1492 • People who have been treated for rheumatoid arthritis, Crohn's disease, ankylosing
1493 spondylitis, or psoriatic arthritis for a long time may be more likely to develop lymphoma.
1494 This is especially true for people with very active disease.
- 1495 • Patients with COPD (a specific type of lung disease) may have an increased risk for
1496 getting cancer while being treated with REMICADE.
- 1497 • If you take REMICADE, your chances of getting lymphoma or other cancers may
1498 increase.

1500 Heart Failure

1501 If you have a heart problem called congestive heart failure, your doctor should check you closely
1502 while you are taking REMICADE. Your congestive heart failure may get worse while you are
1503 taking REMICADE. Be sure to tell your doctor of any new or worse symptoms including:

- 1504 • Shortness of breath
- 1505 • Swelling of ankles or feet
- 1506 • Sudden weight gain

1507 Treatment with REMICADE may need to be stopped if you get new or worse congestive heart
1508 failure.

1509

1510 Liver Injury

1511 In rare cases, some patients taking REMICADE have developed serious liver problems. Tell
1512 your doctor if you have

- 1513 • Jaundice (skin and eyes turning yellow)
- 1514 • Dark brown-colored urine
- 1515 • Pain on the right side of your stomach area (right-sided abdominal pain)
- 1516 • Fever
- 1517 • Extreme tiredness (severe fatigue)

1518

1519 Blood Problems

1520 In some patients taking REMICADE, the body may not make enough of the blood cells that help
1521 fight infections or help stop bleeding. Tell your doctor if you

- 1522 • Have a fever that does not go away
- 1523 • Bruise or bleed very easily
- 1524 • Look very pale

1525

1526 Nervous System Disorders

1527 In rare cases, patients taking REMICADE have developed problems with their nervous system.
1528 Tell your doctor if you have

- 1529 • Changes in your vision
- 1530 • Weakness in your arms and/or legs
- 1531 • Numbness or tingling in any part of your body
- 1532 • Seizures

1533

1534 Allergic Reactions

1535 Some patients have had severe allergic reactions to REMICADE. These reactions can happen
1536 while you are getting your REMICADE treatment or shortly afterwards. Your doctor may need
1537 to stop treatment with REMICADE and give you medicines to treat the allergic reaction. Signs
1538 of an allergic reaction can include:

- 1539 • Hives (red, raised, itchy patches of skin)
- 1540 • Difficulty breathing
- 1541 • Chest pain
- 1542 • High or low blood pressure
- 1543 • Fever
- 1544 • Chills

1545 Some patients treated with REMICADE for Crohn's disease have had delayed allergic reactions.
1546 The delayed reactions occurred 3 to 12 days after receiving treatment with REMICADE. Tell
1547 your doctor right away if you have any of these signs of delayed allergic reaction to
1548 REMICADE:

- 1549 • Fever
- 1550 • Rash
- 1551 • Headache
- 1552 • Sore throat
- 1553 • Muscle or joint pain

- 1554 • Swelling of the face and hands
- 1555 • Difficulty swallowing

1556

1557 Lupus-like Syndrome

1558 Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any
1559 of the following symptoms your doctor may decide to stop your treatment with REMICADE.

- 1560 • Chest discomfort or pain that does not go away
- 1561 • Shortness of breath
- 1562 • Joint pain
- 1563 • Rash on the cheeks or arms that gets worse in sun

1564

1565 **The most common side effects of REMICADE are**

- 1566 • Respiratory infections, such as sinus infections and sore throat)
- 1567 • Headache
- 1568 • Rash
- 1569 • Coughing
- 1570 • Stomach pain

1571 Children who took REMICADE in studies for Crohn's disease, showed some differences in side
1572 effects compared with adults who took REMICADE for Crohn's disease. The side effects that
1573 happened more in children were: anemia (low red blood cells), blood in stool, leukopenia (low
1574 white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils,
1575 the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions
1576 of the breathing tract.

1577 Tell your doctor about any side effect that bothers you or does not go away.

1578 These are not all of the side effects with REMICADE. Ask your doctor or pharmacist for more
1579 information.

1580

1581 **General information about REMICADE**

1582 Medicines are sometimes prescribed for purposes that are not mentioned in patient information
1583 sheets. Do not use REMICADE for a condition for which it was not prescribed.

1584

1585 This information sheet summarizes the most important information about REMICADE. You can
1586 ask your doctor or pharmacist for information about REMICADE that is written for health
1587 professionals.

1588

1589 For more information go to www.remicade.com or call 1-800-457-6399.

1590

1591

1592

1593 **What are the ingredients in REMICADE?**

1594

1595 The active ingredient is Infliximab.

1596 The inactive ingredients in REMICADE include: sucrose, polysorbate 80, monobasic sodium
1597 phosphate monohydrate, and dibasic sodium phosphate dihydrate. No Preservatives are present.

1598

1599 Produced developed and manufactured by:

1600 Centocor, Inc.

1601 200 Great Valley Parkway

1602 Malvern, PA 19355

1603

1604 Rx only

1605

1606 Revised August 2006