

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

6 **WARNING**
7

8 **RISK OF INFECTIONS**
9

10 **TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT**
11 **CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER**
12 **OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS**
13 **RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE**
14 **WARNINGS).**

15
16 **PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION**
17 **WITH A TUBERCULIN SKIN TEST.¹ TREATMENT OF LATENT TUBERCULOSIS**
18 **INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.**
19
20

21 **DESCRIPTION**
22

23 REMICADE[®] is a chimeric IgG1. monoclonal antibody with an approximate molecular weight
24 of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab
25 binds specifically to human tumor necrosis factor alpha (TNF α) with an association constant of
26 10^{10} M^{-1} . Infliximab is produced by a recombinant cell line cultured by continuous perfusion and
27 is purified by a series of steps that includes measures to inactivate and remove viruses.
28

29 REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion.
30 Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is
31 approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg
32 polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium
33 phosphate, dihydrate. No preservatives are present.
34

35 **CLINICAL PHARMACOLOGY**
36

37 **General**
38

39 Infliximab neutralizes the biological activity of TNF α by binding with high affinity to the
40 soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors.^{2,3}
41 Infliximab does not neutralize TNF \downarrow (lymphotoxin α), a related cytokine that utilizes the same
42 receptors as TNF α . Biological activities attributed to TNF α include: induction of pro-
43 inflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration
44 by increasing endothelial layer permeability and expression of adhesion molecules by endothelial

45 cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of
46 acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by
47 synoviocytes and/or chondrocytes. Cells expressing transmembrane TNF α bound by infliximab
48 can be lysed *in vitro*³ or *in vivo*.⁴ Infliximab inhibits the functional activity of TNF α in a wide
49 variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T
50 lymphocytes and epithelial cells. Anti-TNF α antibodies reduce disease activity in the cotton-top
51 tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-
52 induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a
53 result of constitutive expression of human TNF α , and when administered after disease onset,
54 allows eroded joints to heal.

55

56 **Pharmacodynamics**

57

58 Elevated concentrations of TNF α have been found in involved tissues and fluids of patients with
59 rheumatoid arthritis, Crohn's disease and ankylosing spondylitis. In rheumatoid arthritis,
60 treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the
61 joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular
62 adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)],
63 chemoattraction [IL-8 and monocyte chemoattractant protein (MCP-1)] and tissue degradation
64 [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with REMICADE
65 reduced infiltration of inflammatory cells and TNF α production in inflamed areas of the
66 intestine, and reduced the proportion of mononuclear cells from the lamina propria able to
67 express TNF α and interferon. After treatment with REMICADE, patients with rheumatoid
68 arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein
69 (CRP) compared to baseline. Peripheral blood lymphocytes from REMICADE-treated patients
70 showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic
71 stimulation when compared to cells from untreated patients.

72

73 **Pharmacokinetics**

74

75 Single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between
76 the dose administered and the maximum serum concentration. The volume of distribution at
77 steady state was independent of dose and indicated that infliximab was distributed primarily
78 within the vascular compartment. Median pharmacokinetic results for doses of 3 mg/kg to
79 10 mg/kg in rheumatoid arthritis and 5 mg/kg in Crohn's disease indicate that the terminal half-
80 life of infliximab is 8.0 to 9.5 days.

81

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

92 A pediatric Crohn's disease pharmacokinetic study was conducted in 21 patients aged 11 to 17
93 years old. No notable differences in single-dose pharmacokinetic parameters were observed
94 between pediatric and adult Crohn's disease patients (see [PRECAUTIONS, Pediatric Use](#)).
95

96 **CLINICAL STUDIES**

98 **Rheumatoid Arthritis**

100 The safety and efficacy of infliximab were assessed in two multicenter, randomized, double-
101 blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of
102 stable doses of folic acid, oral corticosteroids (=10 mg/day) and/or non-steroidal anti-
103 inflammatory drugs was permitted.
104

105 Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis
106 despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease
107 duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were
108 on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4
109 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at
110 weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX.
111

112 Study RA II was a placebo-controlled study of three active treatment arms in 1004 MTX naive
113 patients of 3 or fewer years duration active rheumatoid arthritis. Patients enrolled had a median
114 age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint
115 count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At
116 randomization, all patients received MTX (optimized to 20 mg/wk by week 8) and either
117 placebo, 3mg/kg or 6 mg/kg REMICADE at weeks 0, 2, and 6 and every 8 weeks thereafter.
118

119 Data on use of REMICADE without concurrent MTX are limited (see [ADVERSE REACTIONS,](#)
120 [Immunogenicity](#)).^{5,6}
121

122 *Clinical response*

124 In Study RA I, all doses/schedules of REMICADE + MTX resulted in improvement in signs and
125 symptoms as measured by the American College of Rheumatology response criteria (ACR 20)
126 with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo +
127 MTX ([Table 1](#)). This improvement was observed at week 2 and maintained through week 102.
128 Greater effects on each component of the ACR 20 were observed in all patients treated with
129 REMICADE + MTX compared to placebo + MTX ([Table 2](#)). More patients treated with
130 REMICADE reached a major clinical response than placebo-treated patients ([Table 1](#)).
131

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

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

<u>Response</u>	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

137

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) ^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)

138

139 *Radiographic response*

140

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

145

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

149

150 In Study RA II, >90% of patients had at least two evaluable x-rays. Inhibition of progression of
151 structural damage was observed at weeks 30 and 54 (Table 3) in the REMICADE + MTX groups
152 compared to MTX alone. In an exploratory analysis of Study RA II, patients treated with
153 REMICADE + MTX demonstrated less progression of structural damage compared to MTX
154 alone, whether baseline acute phase reactants (ESR and CRP) were normal or elevated: patients
155 with elevated baseline acute phase reactants treated with MTX alone demonstrated a mean
156 progression in vdH-S score of 4.2 units compared to patients treated with REMICADE + MTX
157 who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants
158 treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared

159 to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving
 160 REMICADE + MTX, 59% had no progression (vdH-S score = 0 unit) of structural damage
 161 compared to 45% patients receiving MTX alone. In a subset of patients who began the study
 162 without erosions, REMICADE + MTX maintained an erosion free state at 1 year in a greater
 163 proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively (p<0.01).
 164 Fewer patients in the REMICADE + MTX groups (47%) developed erosions in uninvolved
 165 joints compared to MTX alone (59%).
 166

Table 3
RADIOGRAPHIC CHANGE
FROM BASELINE TO WEEK 54

	Study RA I			Study RA II		
	REMICADE + MTX			REMICADE + MTX		
	Placebo + MTX (n=64)	3 mg/kg q 8 wks (n=71)	10 mg/kg q 8 wks (n=77)	Placebo + MTX (n=282)	3 mg/kg q 8 wks (n=359)	6 mg/kg q 8 wks (n=363)
<i>Total Score</i>						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3 ^a	0.2 ^a	3.7	0.4 ^a	0.5 ^a
Median	4.0	0.5	0.5	0.4	0.0	0.0
<i>Erosion Score</i>						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8
Change from baseline						
Mean	4.1	0.2 ^a	0.2 ^a	3.0	0.3 ^a	0.1 ^a
Median	2.0	0.0	0.5	0.3	0.0	0.0
<i>JSN Score</i>						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1 ^a	0.0 ^a	0.6	0.1 ^a	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

^a P < 0.001 for each outcome against placebo.

168 *Physical function response*

169

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

172

173 In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater
174 improvement from baseline in HAQ and SF-36 physical component summary score averaged
175 over time through week 54 compared to placebo + MTX, and no worsening in the SF-36 mental
176 component summary score. The median (interquartile range) improvement from baseline to week
177 54 in HAQ was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for REMICADE +
178 MTX ($p < 0.001$). Both HAQ and SF-36 effects were maintained through week 102.
179 Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in the
180 trial through 102 weeks.

181

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

186

187 **Active Crohn's Disease**

188

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

195

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

201

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

209

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

213 Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg
 214 infliximab maintenance groups were in clinical remission and were able to discontinue
 215 corticosteroid use compared to patients in the placebo maintenance group at week 54 (Table 4).
 216

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

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

217
 218 ^a REMICADE at week 0
 219 ^b REMICADE 5 mg/kg administered at weeks 0, 2 and 6
 220 ^c p-values represent pairwise comparisons to placebo
 221 ^d Of those receiving corticosteroids at baseline
 222

223 Patients in the infliximab maintenance groups (5 mg/kg and 10 mg/kg) had a longer time to loss
 224 of response than patients in the placebo maintenance group (Figure 1). At weeks 30 and 54,
 225 significant improvement from baseline was seen among the 5 mg/kg and 10 mg/kg infliximab-
 226 treated groups compared to the placebo group in the disease specific inflammatory bowel disease
 227 questionnaire (IBDQ), particularly the bowel and systemic components, and in the physical
 228 component summary score of the general health-related quality of life questionnaire SF-36.
 229

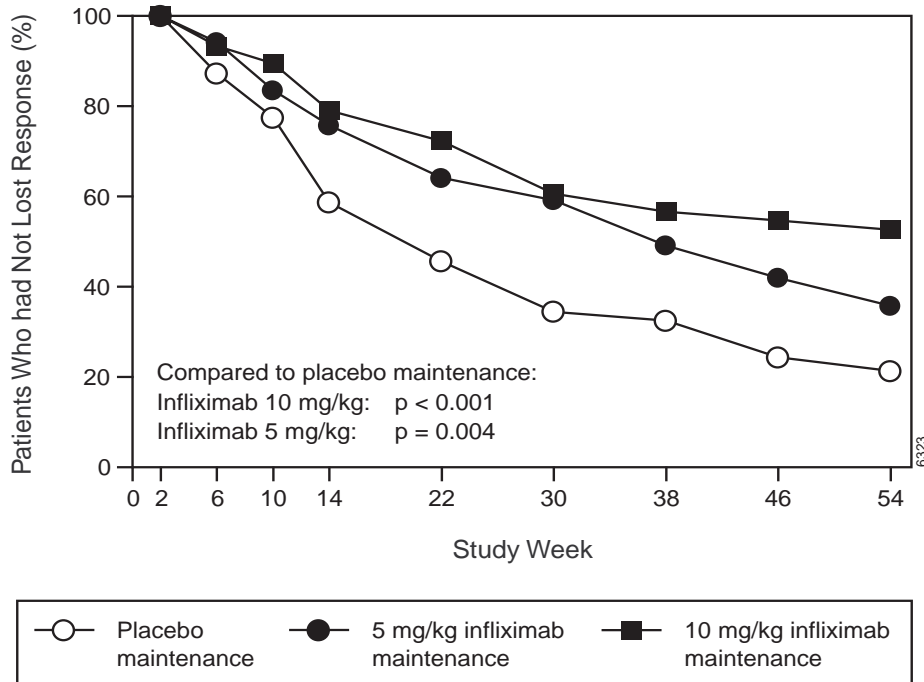


Figure 1
Kaplan-Meier estimate of the proportion of patients
who had not lost response through week 54

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 infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at week 10. Of the infliximab-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 infliximab 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 infliximab 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.

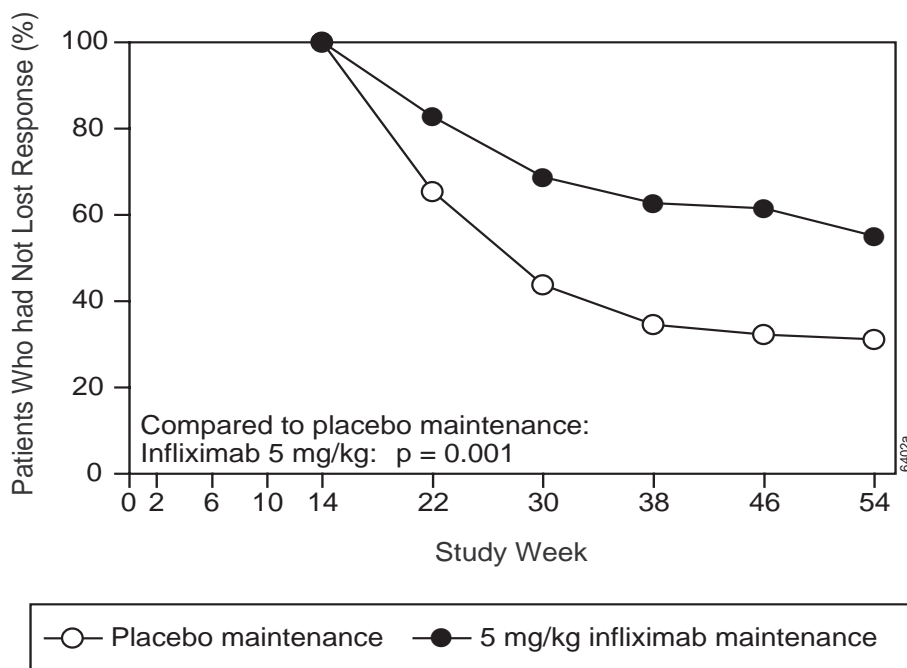
257 In the first trial,¹⁰ 94 patients received three doses of either placebo or REMICADE at weeks 0,
258 2 and 6. Fistula response (=50% reduction in number of enterocutaneous fistulas draining upon
259 gentle compression on at least two consecutive visits without an increase in medication or
260 surgery for Crohn's disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE
261 group (p=0.002) and 56% (18/32) of patients in the 10 mg/kg REMICADE group (p=0.021) vs.
262 26% (8/31) of patients in the placebo arm. The median time to onset of response and median
263 duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure
264 of all fistula was achieved in 52% of REMICADE-treated patients compared with 13% of
265 placebo-treated patients (p<0.001).

266
267 In the second trial (ACCENT II [Study Crohn's II]), patients who were enrolled had to have at
268 least one draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg
269 REMICADE at weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE
270 maintenance at week 14. Patients received maintenance doses at week 14 and then every eight
271 weeks through week 46. Patients who were in fistula response (fistula response was defined the
272 same as in the first trial) at both weeks 10 and 14 were randomized separately from those not in
273 response. The primary endpoint was time from randomization to loss of response among those
274 patients who were in fistula response.

275
276 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and
277 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of the
278 patients had received previous immunosuppressive and antibiotic therapy.

279
280 At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to
281 REMICADE maintenance had a longer time to loss of fistula response compared to the placebo
282 maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no
283 draining fistulas compared with 22% (20/90) of placebo-treated patients (p=0.02). Compared to
284 placebo maintenance, patients on REMICADE maintenance had a trend toward fewer
285 hospitalizations.

286



287
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292

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

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

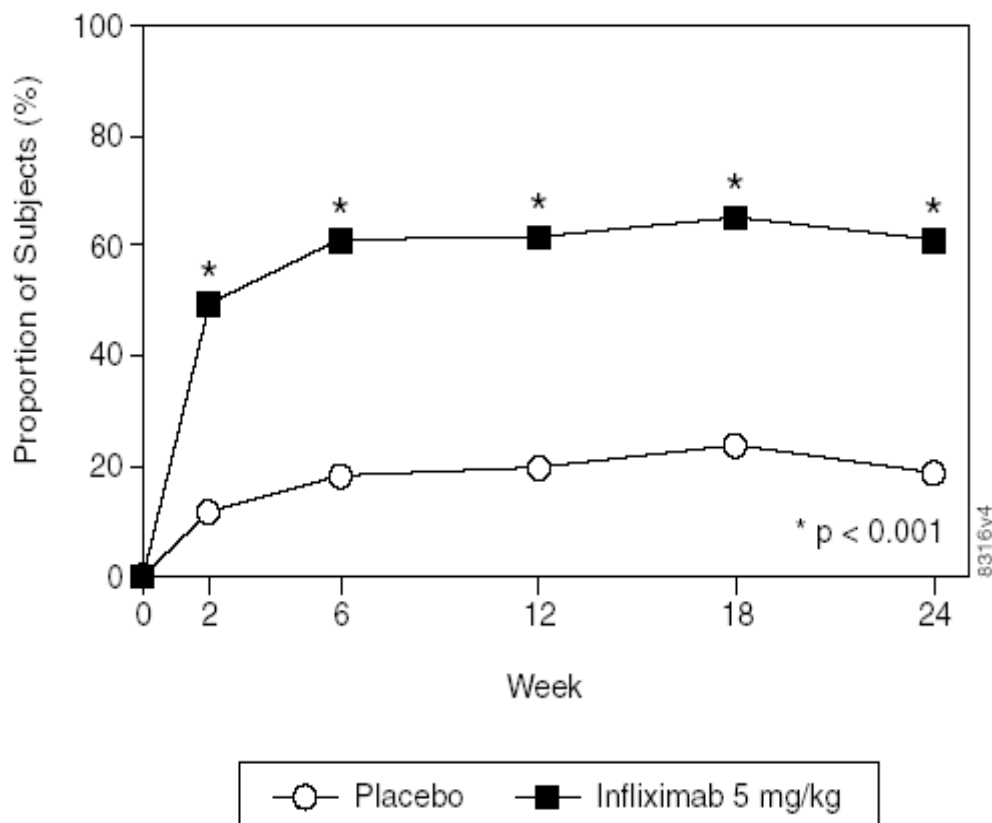
297
298 Patients who had not achieved a response by week 14 were unlikely to respond to additional
299 doses of REMICADE.

300
301 Similar proportions of patients in either group developed new fistulas (17% overall) and similar
302 numbers developed abscesses (15% overall).

303 304 **Ankylosing Spondylitis**

305
306 The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-
307 blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were
308 between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New
309 York criteria for Ankylosing Spondylitis.¹¹ Patients were to have had active disease as evidenced
310 by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible
311 range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with
312 complete ankylosis of the spine were excluded from study participation, and the use of Disease
313 Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited.
314 Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12
315 and 18.

316 At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by
 317 the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20),
 318 was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo
 319 group ($p < 0.001$). Improvement was observed at week 2 and maintained through week 24 (Figure
 320 3 and Table 5).
 321
 322



323
 324
 325 **Figure 3**
 326 **Proportion of patients achieving ASAS 20 response**
 327

328 At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs
 329 and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and
 330 ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE,
 331 compared to 9% and 4%, respectively, for patients receiving placebo ($p < 0.001$, REMICADE vs.
 332 placebo). A low level of disease activity (defined as a value < 20 [on a scale of 0-100 mm] in
 333 each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated
 334 patients vs. 1% in placebo-treated patients ($p < 0.001$).
 335
 336
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340

Table 5
Components of Ankylosing Spondylitis Disease Activity

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

341
342 The median improvement from baseline in the general health-related quality of life questionnaire
343 SF-36 physical component summary score at week 24 was 10.2 for the REMICADE group vs.
344 0.8 for the placebo group (p<0.001). There was no change in the SF-36 mental component
345 summary score in either the REMICADE group or the placebo group.

346
347 Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled
348 study of 70 patients with ankylosing spondylitis.

349
350 **INDICATIONS AND USAGE**

351
352 **Rheumatoid Arthritis**

353
354 REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms,
355 inhibiting the progression of structural damage, and improving physical function in patients with
356 moderately to severely active rheumatoid arthritis.

357

358 **Crohn's Disease**

359

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

363

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

366

367 **Ankylosing Spondylitis**

368

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

371

372 **CONTRAINDICATIONS**

373

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

380

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

383

384 **WARNINGS**

385

386 **RISK OF INFECTIONS**

387 (See [boxed WARNING](#))

388

389 **SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN**
390 **REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF**
391 **THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS**
392 **IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON**
393 **CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO**
394 **THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE**
395 **THEM TO INFECTIONS.**

396

397 **REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY**
398 **IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN**
399 **CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC**
400 **INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE**
401 **MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER**
402 **TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY**
403 **MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE**
404 **THERAPY SHOULD BE DISCONTINUED (see [ADVERSE REACTIONS, Infections](#)).**

405 **CASES OF HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS,**
406 **PNEUMOCYSTOSIS, TUBERCULOSIS, OTHER BACTERIAL, MYCOBACTERIAL**
407 **AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING**
408 **REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE**
409 **HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS**
410 **AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY**
411 **CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.**
412

413 **SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT**
414 **USE OF ANAKINRA AND ANOTHER TNF α -BLOCKING AGENT, ETANERCEPT,**
415 **WITH NO ADDED CLINICAL BENEFIT COMPARED TO ETANERCEPT ALONE.**
416 **BECAUSE OF THE NATURE OF THE ADVERSE EVENTS SEEN WITH**
417 **COMBINATION OF ETANERCEPT AND ANAKINRA THERAPY, SIMILAR**
418 **TOXICITIES MAY ALSO RESULT FROM THE COMBINATION OF ANAKINRA**
419 **AND OTHER TNF α -BLOCKING AGENTS. THEREFORE, THE COMBINATION OF**
420 **REMICADE AND ANAKINRA IS NOT RECOMMENDED.**
421

422 **Hepatotoxicity**

423

424 Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have
425 been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune
426 hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between
427 two weeks to more than a year after initiation of REMICADE; elevations in hepatic
428 aminotransferase levels were not noted prior to discovery of the liver injury in many of these
429 cases. Some of these cases were fatal or necessitated liver transplantation. Patients with
430 symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If
431 jaundice and/or marked liver enzyme elevations (e.g., ≥ 5 times the upper limit of normal)
432 develops, REMICADE should be discontinued, and a thorough investigation of the abnormality
433 should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been
434 associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e.,
435 surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and
436 monitored prior to the initiation of and during treatment with REMICADE. In clinical trials,
437 mild or moderate elevations of ALT and AST have been observed in patients receiving
438 REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS,
439 Hepatotoxicity).
440

441 **Patients with Heart Failure**

442

443 REMICADE has been associated with adverse outcomes in patients with heart failure, and
444 should be used in patients with heart failure only after consideration of other treatment options.
445 The results of a randomized study evaluating the use of REMICADE in patients with heart
446 failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10
447 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and
448 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without
449 identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-
450 marketing reports of new onset heart failure, including heart failure in patients without known
451 pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a

452 decision is made to administer REMICADE to patients with heart failure, they should be closely
453 monitored during therapy, and REMICADE should be discontinued if new or worsening
454 symptoms of heart failure appear. (See [CONTRAINDICATIONS](#) and [ADVERSE
455 REACTIONS, Patients with Heart Failure.](#))

456

457 **Hematologic Events**

458

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

467

468 **Hypersensitivity**

469

470 REMICADE has been associated with hypersensitivity reactions that vary in their time of onset
471 and required hospitalization in some cases. Most hypersensitivity reactions, which include
472 urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE
473 infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn's
474 disease patients 3 to 12 days after REMICADE therapy was reinstated following an extended
475 period without REMICADE treatment. Symptoms associated with these reactions include fever,
476 rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia.
477 These reactions were associated with marked increase in antibodies to infliximab, loss of
478 detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE
479 should be discontinued for severe reactions. Medications for the treatment of hypersensitivity
480 reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be
481 available for immediate use in the event of a reaction (see [ADVERSE REACTIONS, Infusion-
482 related Reactions](#)).

483

484 **Neurologic Events**

485

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

493

494 **Malignancies**

495

496 In the controlled portions of clinical trials of all the TNF α -blocking agents, more cases of
497 lymphoma have been observed among patients receiving a TNF blocker compared with control
498 patients. During the controlled portions of REMICADE trials in patients with moderately to

499 severely active rheumatoid arthritis and Crohn's disease, 1 patient developed lymphoma among
500 1389 REMICADE-treated patients versus 0 among 483 control patients (median duration of
501 follow-up 1.1 years). In the controlled and open-label portions of these clinical trials of
502 REMICADE, 3 patients developed lymphomas (1 patient with rheumatoid arthritis and 2 patients
503 with Crohn's disease) among 2410 patients (median duration of follow-up 1.1 years). In
504 rheumatoid arthritis patients, this is approximately 3-fold higher than expected in the general
505 population. In the combined clinical trial population for rheumatoid arthritis and Crohn's
506 disease, this is approximately 6-fold higher than expected in the general population. Rates in
507 clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF
508 blockers and may not predict rates observed in a broader patient population. Patients with
509 Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or
510 chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold)
511 than the general population for the development of lymphoma. The potential role of TNF α -
512 blocking therapy in the development of malignancies is not known (see [ADVERSE](#)
513 [REACTIONS, Malignancies](#)). No studies have been conducted that include patients with a
514 history of malignancy or that continue treatment in patients who develop malignancy while
515 receiving REMICADE; thus additional caution should be exercised in considering REMICADE
516 treatment of these patients.

517

518 **PRECAUTIONS**

519

520 **Autoimmunity**

521

522 Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the
523 development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like
524 syndrome following treatment with REMICADE, treatment should be discontinued (see
525 [ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome](#)).

526

527 **Vaccinations**

528

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

532

533 **Information for Patients**

534

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

540

541 **Drug Interactions**

542

543 Concurrent administration of etanercept (another TNF α -blocking agent) and anakinra (an
544 interleukin-1 antagonist) has been associated with an increased risk of serious infections, and
545 increased risk of neutropenia and no additional benefit compared to these medicinal products

546 alone. Other TNF α -blocking agents (including REMICADE) used in combination with anakinra
547 may also result in similar toxicities (see [WARNINGS, RISK OF INFECTIONS](#)).
548

549 Specific drug interaction studies, including interactions with MTX, have not been conducted.
550 The majority of patients in rheumatoid arthritis or Crohn's disease clinical studies received one
551 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides
552 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.
553 Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids,
554 6-MP/AZA and aminosalicylates. Patients with Crohn's disease who received
555 immunosuppressants tended to experience fewer infusion reactions compared to patients on no
556 immunosuppressants (see [ADVERSE REACTIONS, Immunogenicity](#) and [Infusion-related
557 Reactions](#)).
558

559 Serum infliximab concentrations appeared to be unaffected by baseline use of medications for
560 the treatment of Crohn's disease including corticosteroids, antibiotics (metronidazole or
561 ciprofloxacin) and aminosalicylates.
562

563 **Carcinogenesis, Mutagenesis and Impairment of Fertility** 564

565 A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF α to evaluate
566 tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNF α in mice.
567 Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly
568 for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the
569 human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause
570 tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the
571 *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.
572 Chromosomal aberrations were not observed in an assay performed using human lymphocytes.
573 The significance of these findings for human risk is unknown. It is not known whether infliximab
574 can impair fertility in humans. No impairment of fertility was observed in a fertility and general
575 reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic
576 toxicity study.
577

578 **Pregnancy Category B** 579

580 Since infliximab does not cross-react with TNF α in species other than humans and chimpanzees,
581 animal reproduction studies have not been conducted with REMICADE. No evidence of
582 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity
583 study conducted in mice using an analogous antibody that selectively inhibits the functional
584 activity of mouse TNF α . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the
585 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to
586 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not
587 known whether REMICADE can cause fetal harm when administered to a pregnant woman or
588 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if
589 clearly needed.
590

591 **Nursing Mothers**

592
593 It is not known whether infliximab is excreted in human milk or absorbed systemically after
594 ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because
595 of the potential for adverse reactions in nursing infants from REMICADE, a decision should be
596 made whether to discontinue nursing or to discontinue the drug, taking into account the
597 importance of the drug to the mother.

598
599 **Pediatric Use**

600
601 Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in
602 pediatric patients with Crohn's disease have not been established.

603
604 **Geriatric Use**

605
606 In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or
607 safety in 181 patients aged 65 or older compared to younger patients although the incidence of
608 serious adverse events in patients aged 65 or older was higher in both infliximab and control
609 groups compared to younger patients. In Crohn's disease and ankylosing spondylitis studies,
610 there were insufficient numbers of patients aged 65 and over to determine whether they respond
611 differently from patients aged 18 to 65. Because there is a higher incidence of infections in the
612 elderly population in general, caution should be used in treating the elderly (see [ADVERSE
613 REACTIONS, Infections](#)).

614
615 **ADVERSE REACTIONS**

616
617 The data described herein reflect exposure to REMICADE in 2629 patients, including 1484
618 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most common reason
619 for discontinuation of treatment was infusion-related reactions (e.g. dyspnea, flushing, headache
620 and rash). Adverse events have been reported in a higher proportion of rheumatoid arthritis
621 patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were
622 observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in
623 patients with Crohn's disease.

624
625 **Infusion-related Reactions**

626
627 *Acute infusion reactions*

628
629 An infusion reaction was defined in clinical trials as any adverse event occurring during an
630 infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated
631 patients in all clinical studies experienced an infusion reaction compared to approximately 10%
632 of placebo-treated patients. Among all REMICADE infusions, 3% were accompanied by
633 nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary
634 reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were
635 accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and
636 cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included
637 anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients

638 discontinued REMICADE because of infusion reactions, and all patients recovered with
639 treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial
640 infusion were not associated with a higher incidence of reactions.

641
642 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to
643 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant
644 immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and
645 infusion reactions (see [ADVERSE REACTIONS, Immunogenicity](#) and [PRECAUTIONS, Drug
646 Interactions](#)).

647
648 In post-marketing experience, cases of anaphylactic-like reactions, including
649 laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with
650 REMICADE administration.

651
652 *Reactions following readministration*

653
654 In a study where 37 of 41 patients with Crohn's disease were retreated with infliximab following
655 a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events
656 manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and
657 symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also
658 experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache.
659 Patients experiencing these adverse events had not experienced infusion-related adverse events
660 associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of
661 patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients
662 who received lyophilized formulation. The clinical data are not adequate to determine if
663 occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms
664 improved substantially or resolved with treatment in all cases. There are insufficient data on the
665 incidence of these events after drug-free intervals of 1 to 2 years. These events have been
666 observed only infrequently in clinical studies and post-marketing surveillance with retreatment
667 intervals up to 1 year.

668 **Infections**

669
670
671 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated
672 patients (average of 53 weeks of follow-up) and in 28% of placebo-treated patients (average of
673 47 weeks of follow-up). The infections most frequently reported were respiratory tract infections
674 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among
675 REMICADE-treated patients, **serious infections included pneumonia**, cellulitis, abscess, skin
676 ulceration, sepsis, and bacterial infection. In all clinical trials, three opportunistic infections were
677 reported; coccidioidomycosis (which resulted in death), nocardiosis and cytomegalovirus.
678 Tuberculosis was reported in six patients, one of whom died due to miliary tuberculosis. Other
679 cases of tuberculosis, including disseminated tuberculosis, also have been reported post-
680 marketing. Most of these cases of tuberculosis occurred within the first two months after
681 initiation of therapy with infliximab and may reflect recrudescence of latent disease (see
682 [WARNINGS, RISK OF INFECTIONS](#)). In the RA trials at 1 year, 5.3% of patients receiving
683 infliximab and MTX every 8 weeks developed serious infections as compared to 3.4% of
684 placebo patients receiving MTX. Of 924 patients receiving infliximab, 1.7% developed

685 pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm
686 respectively. During the 54 weeks Crohn's II Study, 15% of patients with fistulizing Crohn's
687 disease developed a new fistula-related abscess.

688
689 In post-marketing experience, infections have been observed with various pathogens including
690 viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems
691 and have been reported in patients receiving REMICADE alone or in combination with
692 immunosuppressive agents.

693 **Autoantibodies/Lupus-like Syndrome**

694
695
696 Approximately half of infliximab-treated patients in clinical trials who were antinuclear antibody
697 (ANA) negative at baseline developed a positive ANA during the trial compared with
698 approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected
699 in approximately one-fifth of infliximab-treated patients compared with 0% of placebo-treated
700 patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

701 **Malignancies**

702
703
704 Among 2410 patients with moderately to severely active rheumatoid arthritis and Crohn's disease
705 treated with REMICADE in clinical trials with a median of 1.1 years of follow-up, 3 patients
706 developed lymphomas, for a rate of 0.07 cases per 100 patient-years of follow-up in patients with
707 rheumatoid arthritis and 0.12 cases per 100 patient-years of follow up in the combined clinical
708 trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold
709 higher in the RA clinical trial population and 6-fold higher in the overall clinical trial population
710 than expected in an age-, gender-, and race-matched general population based on the
711 Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE
712 cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates
713 observed in a broader patient population. An increased rate of lymphoma up to several fold has
714 been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be
715 further increased in patients with more severe disease activity. Other than lymphoma, 13 patients
716 developed malignancies, which was similar in number to what would be expected in the general
717 population. Of these, the most common malignancies were breast, colorectal, and melanoma.
718 (See [WARNINGS, Malignancies.](#))

719
720 Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been
721 reported in patients receiving REMICADE during post-approval use.

722 **Patients with Heart Failure**

723
724
725 In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class
726 III/IV; left ventricular ejection fraction =35%), 150 patients were randomized to receive
727 treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks.
728 Higher incidences of mortality and hospitalization due to worsening heart failure were observed
729 in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg
730 REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the
731 placebo groups. There were trends towards increased dyspnea, hypotension, angina, and

732 dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo.
733 REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See
734 [CONTRAINDICATIONS](#) and [WARNINGS, Patients with Heart Failure.](#))

735

736 **Immunogenicity**

737

738 Treatment with REMICADE can be associated with the development of antibodies to infliximab.
739 The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed
740 by maintenance dosing was approximately 10% as assessed through one to two years of
741 REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's
742 disease patients receiving REMICADE after drug free intervals >16 weeks. The majority of
743 antibody-positive patients had low titers. Patients who were antibody-positive were more likely
744 to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see
745 [ADVERSE REACTIONS, Infusion-related Reactions](#)) than were patients who were antibody
746 negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease
747 patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

748

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

755

756 **Hepatotoxicity**

757

758 Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported
759 rarely in patients receiving REMICADE (see [WARNINGS, Hepatotoxicity](#)). Reactivation of
760 hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus
761 (i.e., surface antigen positive) (see [WARNINGS, Hepatotoxicity](#)).

762

763 In clinical trials in RA, Crohn's disease and ankylosing spondylitis, elevations of
764 aminotransferases were observed (ALT more common than AST) in a greater proportion of
765 patients receiving REMICADE than in controls, both when REMICADE was given as
766 monotherapy and when it was used in combination with other immunosuppressive agents. In
767 general, patients who developed ALT and AST elevations were asymptomatic, and the
768 abnormalities decreased or resolved with either continuation or discontinuation of REMICADE,
769 or modification of concomitant medications. ALT elevations =5 times the upper limit of normal
770 were observed in 1% of patients receiving REMICADE.

771

772 In rheumatoid arthritis clinical trials, 34% of patients who received REMICADE + MTX
773 experienced transient mild (<2 times the upper limit of normal) or moderate (=2 but <3 times the
774 upper limit of normal) elevations in ALT compared to 24% of patients treated with placebo +
775 MTX. ALT elevations =3 times the upper limit of normal were observed in 3.9% of patients
776 who received REMICADE + MTX compared with 3.2% of patients who received MTX alone
777 (median follow up approximately 1 year).

778

779 In Crohn's disease clinical trials (median follow up 54 weeks), 39% of patients receiving
780 REMICADE-maintenance experienced mild to moderate elevations in ALT, compared to 34% of
781 patients treated with placebo-maintenance. ALT elevations =3 times the upper limit of normal
782 were observed in 5.0% of patients who received REMICADE-maintenance compared with 4.0%
783 of patients who received placebo-maintenance.
784

785 In an ankylosing spondylitis clinical trial in which patients were not receiving MTX, 40% of
786 patients who received REMICADE experienced mild to moderate elevations in ALT compared
787 to 13% of patients treated with placebo. ALT elevations =3 times the upper limit of normal were
788 observed in 12 (6%) REMICADE-treated patients compared to none in placebo-treated patients.
789

790 **Other Adverse Reactions**

791
792 Safety data are available from 2629 REMICADE-treated patients, including 1304 with
793 rheumatoid arthritis, and 1106 with Crohn's disease, 202 with ankylosing spondylitis and 17
794 with other conditions. Adverse events reported in =5% of all patients with rheumatoid arthritis
795 receiving 4 or more infusions are in [Table 6](#). The types and frequencies of adverse reactions
796 observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis and
797 Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-
798 treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient
799 numbers and duration of follow-up for patients who never received REMICADE to provide
800 meaningful comparisons.

801
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804

Table 6
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%
Pruritis	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%

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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.

811 The most common serious adverse events observed in clinical trials were infections (see
812 [ADVERSE REACTIONS, Infections](#)). Other serious, medically relevant adverse events =0.2%
813 or clinically significant adverse events by body system were as follows:

814
815 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
816 *Blood:* pancytopenia
817 *Cardiovascular:* circulatory failure, hypotension, syncope
818 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,
819 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
820 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness
821 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia
822 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis
823 *Metabolic and Nutritional:* dehydration
824 *Musculoskeletal:* intervertebral disk herniation, tendon disorder
825 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction
826 *Platelet, Bleeding and Clotting:* thrombocytopenia
827 *Neoplasms:* basal cell, breast, lymphoma
828 *Psychiatric:* confusion, suicide attempt
829 *Red Blood Cell:* anemia, hemolytic anemia
830 *Reproductive:* menstrual irregularity
831 *Resistance Mechanism:* cellulitis, sepsis, serum sickness
832 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including
833 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
834 *Skin and Appendages:* increased sweating, ulceration
835 *Urinary:* renal calculus, renal failure
836 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis
837 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

838
839 The following adverse events have been reported during post-approval use of REMICADE:
840 neutropenia (see [WARNINGS, Hematologic Events](#)), interstitial pneumonitis/fibrosis, idiopathic
841 thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic
842 and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies
843 (additional neurologic events have also been observed, see [WARNINGS, Neurologic Events](#)).
844 Because these events are reported voluntarily from a population of uncertain size, it is not always
845 possible to reliably estimate their frequency or establish a causal relationship to REMICADE
846 exposure.

847 848 **OVERDOSAGE**

849
850 Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of
851 overdosage, it is recommended that the patient be monitored for any signs or symptoms of
852 adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

853

854 **DOSAGE AND ADMINISTRATION**

855

856 **Rheumatoid Arthritis**

857

858 The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed
859 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
860 thereafter. REMICADE should be given in combination with methotrexate. For patients who
861 have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or
862 treating as often as every 4 weeks.

863

864 **Crohn's Disease or Fistulizing Crohn's Disease**

865

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

872

873 **Ankylosing Spondylitis**

874

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

878

879 **Preparation and Administration Instructions**

880 **Use aseptic technique.**

881

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

888

889 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial
890 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE
891 solution required.

892

893 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a
894 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and
895 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center
896 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass
897 wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution
898 by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous
899 agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.
900 Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to

901 light yellow and opalescent, and the solution may develop a few translucent particles as
902 infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign
903 particles are present.

- 904
- 905 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with
906 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride
907 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium
908 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted
909 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.
910
 - 911 4. The infusion solution must be administered over a period of not less than 2 hours and must
912 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore
913 size of 1.2 μm or less). Any unused portion of the infusion solution should not be stored for
914 reuse.
915
 - 916 5. No physical biochemical compatibility studies have been conducted to evaluate the co-
917 administration of REMICADE with other agents. REMICADE should not be infused
918 concomitantly in the same intravenous line with other agents.
919
 - 920 6. Parenteral drug products should be inspected visually for particulate matter and
921 discoloration prior to administration, whenever solution and container permit. If visibly
922 opaque particles, discoloration or other foreign particulates are observed, the solution
923 should not be used.
924

925 **Storage**

926

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

929 **HOW SUPPLIED**

930

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

933

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

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985 **Rx Only**

986 **REMICADE® (infliximab)**
987 **Patient Information Sheet**

988
989 You should read this information sheet before you start using REMICADE® (pronounced rem-
990 eh-kaid) and before each time you are scheduled to receive REMICADE. This information sheet
991 does not take the place of talking with your doctor. You and your doctor should talk about your
992 health and how you are feeling before you start taking REMICADE, while you are taking it and
993 at regular checkups. If you do not understand any of the information in this sheet, you should ask
994 your doctor to explain what it means.

995
996 **What is REMICADE?**

997 REMICADE is a medicine that is used to treat adults with moderately to severely active
998 rheumatoid arthritis, Crohn's disease and ankylosing spondylitis. In Crohn's disease,
999 REMICADE is for people who have not responded well enough to other medicines.

1000
1001 **How does REMICADE work?**

1002 The medicine REMICADE is a type of protein that recognizes, attaches to and blocks the action
1003 of a substance in your body called tumor necrosis factor. Tumor necrosis factor (TNF) is made
1004 by certain blood cells in your body. REMICADE will not cure rheumatoid arthritis, Crohn's
1005 disease or ankylosing spondylitis, but blocking TNF with REMICADE may reduce the
1006 inflammation caused by too much TNF in your body. You should also know that REMICADE
1007 may help you feel better but can also cause serious side effects and can reduce your body's
1008 ability to fight infections (see below).

1009
1010 **What should I know about the immune system, and taking REMICADE for Rheumatoid**
1011 **Arthritis, Crohn's Disease or Ankylosing Spondylitis?**

1012 The immune system protects the body by responding to "invaders" like bacteria, viruses and
1013 other foreign matter that enter your body by producing antibodies and putting them into action to
1014 fight off the "invaders." In diseases like rheumatoid arthritis, Crohn's disease and ankylosing
1015 spondylitis, your body's immune system produces too much TNF. Too much TNF can cause
1016 your immune system to attack healthy tissues in your body and cause inflammation. If this
1017 condition is left untreated, it can cause permanent damage to the body's bones, cartilage and
1018 tissue.

1019
1020 While taking REMICADE can block the TNF that causes inflammation, it can also lower your
1021 body's ability to fight infections. So, taking REMICADE can make you more prone to getting
1022 infections or it can make an infection that you already have worse. You should call your doctor
1023 right away if you think you have an infection.

1024
1025 **What important information should I know about treatment with REMICADE?**

1026 REMICADE, like other medicines that affect your immune system, is a strong medicine that can
1027 cause serious side effects. Possible serious side effects include:

1028
1029 Serious Infections:

1030 Some patients have had serious infections while receiving REMICADE. Some of the patients
1031 have died from these infections. Serious infections include TB (tuberculosis), and infections

1032 caused by viruses, fungi or bacteria that have spread throughout the body. If you develop a
1033 fever, feel very tired, have a cough, or have flu-like symptoms, these could be signs that you
1034 may be getting an infection. If you have any of these symptoms while you are taking or after
1035 you have taken REMICADE, you should tell your doctor right away.

1036
1037 Heart Failure:

1038 If you have been told that you have a heart problem called congestive heart failure and you
1039 are currently being treated with REMICADE, you will need to be closely monitored by your
1040 doctor. If you develop new or worse symptoms that are related to your heart condition, such
1041 as shortness of breath or swelling of your ankles or feet, you must contact your doctor
1042 immediately.

1043
1044 Blood Problems:

1045 In some patients the body may fail to produce enough of the blood cells that help your body
1046 fight infections or help you stop bleeding. Some of the patients have died from this failure to
1047 produce blood cells. If you develop a fever that doesn't go away, bruise or bleed very easily
1048 or look very pale, call your doctor right away. Your doctor may decide to stop your
1049 treatment.

1050
1051 Allergic Reactions:

1052 Some patients have had severe allergic reactions to REMICADE. These reactions can happen
1053 while you are getting your REMICADE infusion or shortly afterwards. The symptoms of an
1054 allergic reaction may include hives (red, raised, itchy patches of skin), difficulty breathing,
1055 chest pain and high or low blood pressure. Your doctor may decide to stop REMICADE
1056 treatment and give you medicines to treat the allergic reaction.

1057 Some patients who have been taking REMICADE for Crohn's disease have had allergic
1058 reactions 3 to 12 days after receiving their REMICADE treatment. The symptoms of this
1059 type of delayed reaction may include fever, rash, headache and muscle or joint pain. Call
1060 your doctor right away if you develop any of these symptoms or any other unusual symptoms
1061 such as difficulty swallowing.

1062
1063 Nervous System Disorders:

1064 There have been rare cases where people taking REMICADE or other TNF blockers have
1065 developed disorders that affected their nervous system. Signs that you could be having a
1066 problem include: changes in your vision, weakness in your arms and/or legs, and numbness
1067 or tingling in any part of your body.

1068
1069 Malignancy

1070 Reports of a type of blood cancer called lymphoma in patients on REMICADE or other TNF
1071 blockers are rare but occur more often than expected for people in general. People who have
1072 been treated for rheumatoid arthritis, Crohn's disease or ankylosing spondylitis for a long
1073 time, particularly those with highly active disease may be more prone to develop lymphoma.
1074 If you take REMICADE or other TNF blockers, your risk for developing lymphoma may
1075 increase. You should also tell your doctor if you have had or develop lymphoma or other
1076 cancers while you are taking REMICADE.

1077
1078 Liver Injury

1079 There have been rare cases where people taking REMICADE have developed liver
1080 problems. Signs that you could be having a problem include: jaundice (skin and eyes turning
1081 yellow), dark brown-colored urine, right sided abdominal pain, fever, and severe fatigue
1082 (tiredness). You should contact your doctor immediately if you develop any of these
1083 symptoms.

1084 1085 **Other Important Information**

1086
1087 Some patients have developed symptoms that can resemble a disease called lupus. Lupus-like
1088 symptoms may include chest discomfort or pain that doesn't go away, shortness of breath, joint
1089 pain, or a rash on the cheeks or arms that gets worse in the sun. If you develop any of these
1090 symptoms your doctor may decide to stop your treatment with REMICADE.

1091 1092 **What are the more common side effects of REMICADE?**

1093 The more common side effects with REMICADE are respiratory infections (that may include
1094 sinus infections and sore throat), coughing and stomach pain.

1095 1096 **Who should not take REMICADE?**

1097 YOU SHOULD NOT take REMICADE if you have:

1098 Heart failure, unless your doctor has talked to you and decided that you are able to take
1099 REMICADE.

1100 Had an allergic reaction to REMICADE or any other product that was made with murine
1101 (mouse) proteins.

1102 1103 **What health concerns should I talk to my doctor about?**

1104 Before receiving your first treatment with REMICADE you should tell your doctor if you:

1105 Have or think you may have any kind of infection. The infection could be in only one place
1106 in your body (such as an open cut or sore), or an infection that affects your whole body (such
1107 as the flu). Having an infection could put you at risk for serious side effects from
1108 REMICADE.

1109 Have an infection that won't go away or a history of infection that keeps coming back.

1110 Have had TB (tuberculosis), or if you have recently been with anyone who might have TB.
1111 Your doctor will examine you for TB and perform a skin test. If your doctor feels that you
1112 are at risk for TB, he or she may start treating you for TB before you begin REMICADE
1113 therapy.

1114 Have lived in or visited an area of the country where an infection called histoplasmosis or
1115 coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common. If
1116 you don't know if the area you live in is one where histoplasmosis or coccidioidomycosis is
1117 common, ask your doctor.

1118 Have or have previously had heart failure or other heart conditions.

1119 Have or have had a condition that affects your nervous system, like multiple sclerosis, or
1120 Guillain-Barré syndrome, or if you experience any numbness, or tingling, or have had a
1121 seizure.

1122 Are pregnant or nursing.

1123 Have recently received or are scheduled to receive a vaccine.

1124

1125 **Can I take REMICADE while I am on other medicines?**

1126 Tell your doctor if you are taking any other medicines including over the counter medicines,
1127 supplements or herbal products before you are treated with REMICADE. If you start taking or
1128 plan to start taking any new medicine while you are taking REMICADE, tell your doctor.

1129
1130 REMICADE and KINERET should not be taken together.

1131
1132 **How will REMICADE be given to me?**

1133 REMICADE will be given to you by a healthcare professional. REMICADE will be given to you
1134 by an IV. This means that the medicine will be given to you through a needle placed in a vein in
1135 your arm. It will take about 2 hours to give you the full dose of medicine. During that time and for
1136 a period after you receive REMICADE, you will be monitored by a healthcare professional. Your
1137 doctor may ask you to take other medicines along with REMICADE.

1138
1139 Only a health care professional should prepare the medicine and administer it to you.

1140
1141 **How often will I receive REMICADE?**

1142 Rheumatoid Arthritis

1143 If you are receiving REMICADE for rheumatoid arthritis you will receive your first dose
1144 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose
1145 every 8 weeks. Your doctor will monitor your response to REMICADE and may change your
1146 dose or treat you more frequently (as often as every 4 weeks).

1147
1148 Crohn's Disease or Fistulizing Crohn's Disease

1149 If you are receiving REMICADE for active Crohn's disease or fistulizing Crohn's disease, you
1150 will receive your first dose followed by additional doses at 2 and 6 weeks after the first dose. You
1151 will then receive a dose every 8 weeks. Your doctor will monitor your response to REMICADE
1152 and may change your dose.

1153
1154 Ankylosing Spondylitis

1155 If you are receiving REMICADE for ankylosing spondylitis you will receive your first dose
1156 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose
1157 every 6 weeks.

1158
1159 **What if I still have questions?**

1160 If you have any questions, or problems, always talk first with your doctor. You can also visit the
1161 REMICADE internet site at www.remicade.com.

1162
1163 Product developed and manufactured by:

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1165 200 Great Valley Parkway
1166 Malvern, PA 19355

1167
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