

1 **REMICADE®**
2 **(infliximab)**
3 **for IV Injection**
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6 **WARNINGS**
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8 **RISK OF INFECTIONS**
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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.**

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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.**
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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-MERCAPTOPYRINE.**
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39 **DESCRIPTION**

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41 REMICADE[®] is a chimeric IgG1 κ 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 (TNF α) 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.

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53 **CLINICAL PHARMACOLOGY**

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55 **General**

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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. Anti-TNF α antibodies reduce disease activity in the cotton-top
69 tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-
70 induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a
71 result of constitutive expression of human TNF α , and when administered after disease onset,
72 allows eroded joints to heal.

73

74 Pharmacodynamics

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

94 Pharmacokinetics

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

103
104 Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in
105 predictable concentration-time profiles following each treatment. No systemic accumulation of
106 infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 8-
107 week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8
108 weeks after a maintenance dose of 3 to 10 mg/kg of REMICADE, median infliximab serum
109 concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations
110 were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab.
111 No major differences in clearance or volume of distribution were observed in patient subgroups
112 defined by age, weight, or gender. It is not known if there are differences in clearance or volume
113 of distribution in patients with marked impairment of hepatic or renal function.

114
115 Infliximab peak and trough concentrations were similar in pediatric (aged 6 to 17 years old) and
116 adult patients with Crohn’s disease following the administration of the recommended regimen
117 (see [DOSAGE AND ADMINISTRATION, Crohn’s Disease or Fistulizing Crohn’s Disease](#)).

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CLINICAL STUDIES

Rheumatoid Arthritis

The safety and efficacy of REMICADE were assessed in two multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤ 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](#)).

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

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

| <u>Parameter (medians)</u> | <u>Placebo + MTX</u> | | <u>REMICADE + MTX^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)

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161 *Radiographic response*

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

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

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

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

Table 3
RADIOGRAPHIC CHANGE FROM BASELINE TO WEEK 54

| | Study RA I | | | Study RA II | | |
|-------------------------|----------------------------|---------------------------------|----------------------------------|-----------------------------|----------------------------------|----------------------------------|
| | Placebo + MTX (n=64) | REMICADE + MTX | | Placebo + MTX (n=282) | REMICADE + MTX | |
| | | 3 mg/kg q 8 wks (n=71) | 10 mg/kg q 8 wks (n=77) | | 3 mg/kg q 8 wks (n=359) | 6 mg/kg q 8 wks (n=363) |
| <i>Total Score</i> | | | | | | |
| Baseline | | | | | | |
| Mean | 79 | 78 | 65 | 11.3 | 11.6 | 11.2 |
| Median | 55 | 57 | 56 | 5.1 | 5.2 | 5.3 |
| Change from baseline | | | | | | |
| Mean | 6.9 | 1.3 ^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.

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190 *Physical function response*

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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**

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

Table 4
CLINICAL REMISSION AND STEROID WITHDRAWAL

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

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240 ^a REMICADE at week 0241 ^b REMICADE 5 mg/kg administered at weeks 0, 2 and 6242 ^c p-values represent pairwise comparisons to placebo243 ^d Of those receiving corticosteroids at baseline

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

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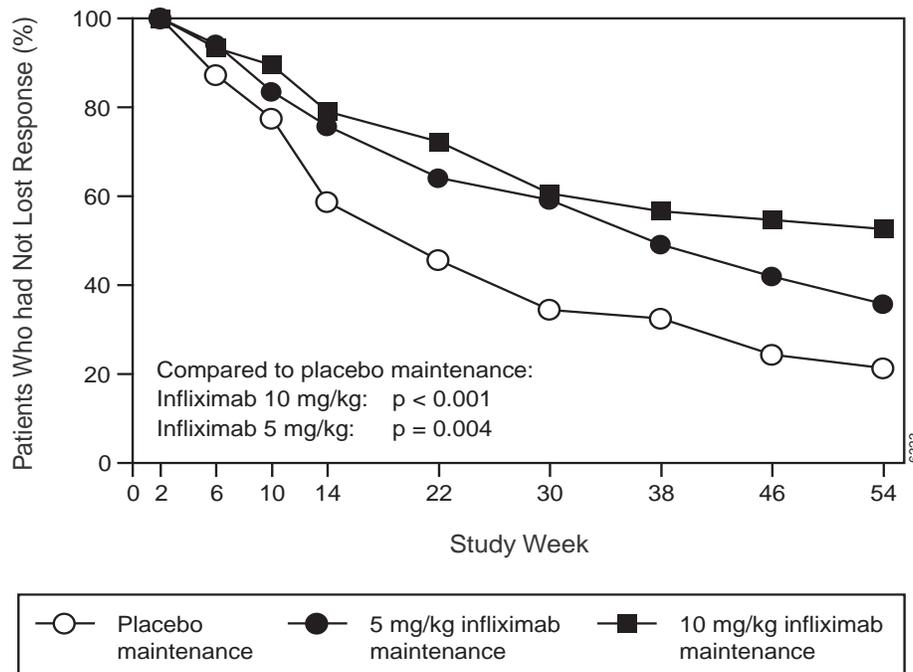


Figure 1
Kaplan-Meier estimate of the proportion of patients
who had not lost response through week 54

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

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

Fistulizing Crohn’s Disease

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

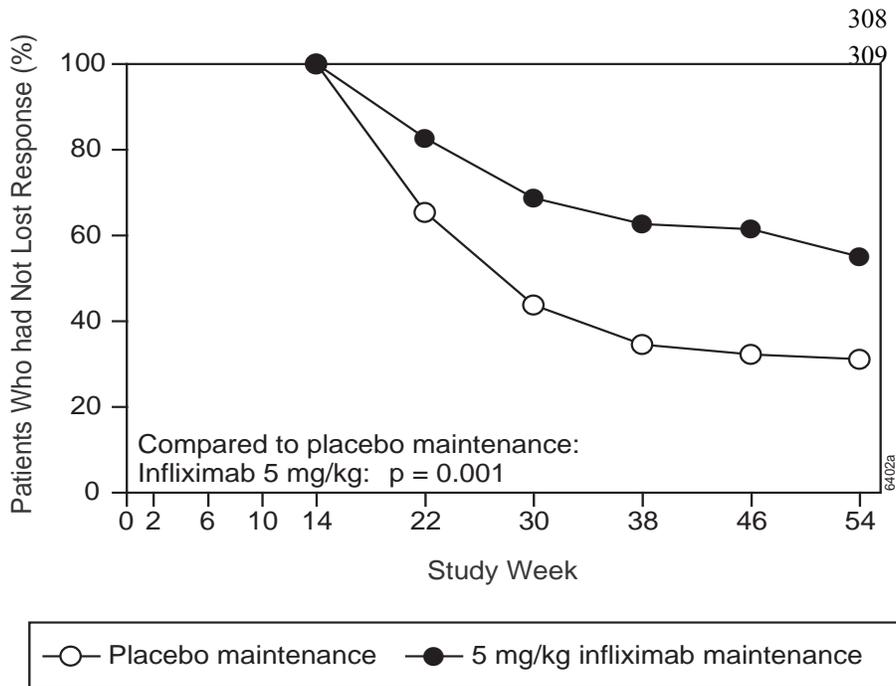
279 In the first trial,¹⁰ 94 patients received three doses of either placebo or REMICADE at weeks 0,
280 2 and 6. Fistula response ($\geq 50\%$ reduction in number of enterocutaneous fistulas draining upon
281 gentle compression on at least two consecutive visits without an increase in medication or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

288
289 In the second trial (ACCENT II [Study Crohn’s II]), patients who were enrolled had to have at
290 least one draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg
291 REMICADE at weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE
292 maintenance at week 14. Patients received maintenance doses at week 14 and then every eight
293 weeks through week 46. Patients who were in fistula response (fistula response was defined the
294 same as in the first trial) at both weeks 10 and 14 were randomized separately from those not in
295 response. The primary endpoint was time from randomization to loss of response among those
296 patients who were in fistula response.

297
298 Among the randomized patients (273 of the 296 initially enrolled), 87% had perianal fistulas and
299 14% had abdominal fistulas. Eight percent also had rectovaginal fistulas. Greater than 90% of
300 the patients had received previous immunosuppressive and antibiotic therapy.

301
302 At week 14, 65% (177/273) of patients were in fistula response. Patients randomized to
303 REMICADE maintenance had a longer time to loss of fistula response compared to the placebo
304 maintenance group (Figure 2). At week 54, 38% (33/87) of REMICADE-treated patients had no
305 draining fistulas compared with 22% (20/90) of placebo-treated patients ($p=0.02$). Compared to
306 placebo maintenance, patients on REMICADE maintenance had a trend toward fewer
307 hospitalizations.

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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).

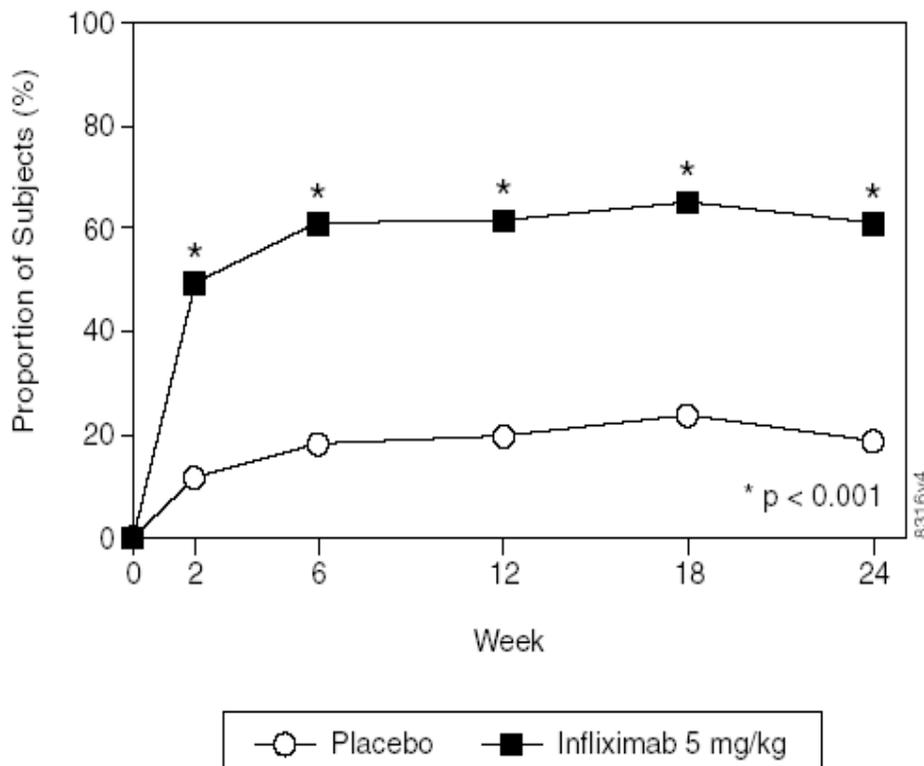
329 **Ankylosing Spondylitis**

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

341

342 At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by
 343 the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20),
 344 was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo
 345 group ($p < 0.001$). Improvement was observed at week 2 and maintained through week 24 (Figure
 346 3 and Table 5).



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Figure 3
Proportion of patients achieving ASAS 20 response

351
 352 At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs
 353 and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and
 354 ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE,
 355 compared to 9% and 4%, respectively, for patients receiving placebo (p<0.001, REMICADE vs.
 356 placebo). A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in
 357 each of the four ASAS response parameters) was achieved in 22% of REMICADE-treated
 358 patients vs. 1% in placebo-treated patients (p<0.001).

359
 360 **Table 5**
 361 **Components of Ankylosing Spondylitis Disease Activity**
 362

| | <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

363
 364 The median improvement from baseline in the general health-related quality of life questionnaire
 365 SF-36 physical component summary score at week 24 was 10.2 for the REMICADE group vs.
 366 0.8 for the placebo group (p<0.001). There was no change in the SF-36 mental component
 367 summary score in either the REMICADE group or the placebo group.

368
 369 Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled
 370 study of 70 patients with ankylosing spondylitis.

371
 372
 373

Psoriatic Arthritis

373
374
375 Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-
376 controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID
377 therapy (≥ 5 swollen joints and ≥ 5 tender joints) with one or more of the following subtypes:
378 arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis
379 (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients
380 also had plaque psoriasis with a qualifying target lesion ≥ 2 cm in diameter. Forty-six percent of
381 patients continued on stable doses of methotrexate (≤ 25 mg/week). During the 24-week double-
382 blind phase, patients received either 5 mg/kg REMICADE or placebo at weeks 0, 2, 6, 14, and 22
383 (100 patients in each group). At week 16, placebo patients with $< 10\%$ improvement from
384 baseline in both swollen and tender joint counts were switched to REMICADE induction (early
385 escape).

386
387 Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the
388 ACR criteria, with 58% of REMICADE-treated patients achieving ACR 20 at week 14,
389 compared with 11% of placebo-treated patients ($p < 0.001$). The response was similar regardless
390 of concomitant use of methotrexate. Improvement was observed as early as week 2. At 6
391 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of
392 patients receiving REMICADE compared to 16%, 4%, and 2%, respectively, of patients
393 receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic
394 arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with
395 peripheral arthritis subtypes.

396
397 Compared to placebo, treatment with REMICADE resulted in improvements in the components
398 of the ACR response criteria, as well as in dactylitis and enthesopathy ([Table 6](#)).

399
400 The results of this study were similar to those seen in an earlier multicenter, randomized,
401 placebo-controlled study of 104 patients with psoriatic arthritis.

402

402

Table 6
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

| Parameter (medians) | Placebo (n=100) | | REMICADE 5mg/kg ^a (n=100) | |
|---|--------------------|---------|---|---------|
| | Baseline | Week 24 | Baseline | Week 24 |
| 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

^b Scale 0-68

^c Scale 0-66

^d Visual Analog Scale (0=best, 10=worst)

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

^f Normal range 0-0.6 mg/dL

403

404 Improvement in PASI in patients with baseline body surface area (BSA) \geq 3% (n=87 placebo,
405 n=83 REMICADE) was achieved at week 14, regardless of concomitant methotrexate use, with
406 64% of REMICADE-treated patients achieving at least 75% improvement from baseline vs. 2%
407 of placebo-treated patients; improvement was observed as early as week 2. At 6 months, the
408 PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients
409 receiving REMICADE compared to 1% and 0%, respectively, of patients receiving placebo.

410

411 **Ulcerative Colitis**

412

413 The safety and efficacy of REMICADE were assessed in two randomized, double-blind,
414 placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative
415 colitis (UC) (Mayo score¹² 6 to 12 [of possible range 0-12], Endoscopy subscore \geq 2) with an
416 inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant
417 treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory
418 agents was permitted. Corticosteroid taper was permitted after week 8. In both studies, patients

419 were randomized to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE at
420 weeks 0, 2, 6, 14 and 22.

421
422 Patients in Study UC I had failed to respond or were intolerant to oral corticosteroids, 6-
423 mercaptopurine (6-MP), or azathioprine (AZA). Patients in Study UC II had failed to respond or
424 were intolerant to the above treatments and/or aminosalicylates. Similar proportions of patients
425 in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-
426 MP/azathioprine (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More
427 patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%,
428 respectively). Clinical response was defined as a decrease from baseline in the Mayo score by \geq
429 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal
430 bleeding subscore of 0 or 1.

431
432 In both studies, greater percentages of patients in both REMICADE groups achieved a clinical
433 response, a sustained clinical response (response at both weeks 8 and 30), clinical remission and
434 other assessed clinical outcomes than in the placebo group (Table 7). Of patients on
435 corticosteroids at baseline, greater proportions of patients in the REMICADE treatment groups
436 were in clinical remission and able to discontinue corticosteroids at week 30 compared with the
437 patients in the placebo treatment groups (22% in REMICADE treatment groups vs. 10% in
438 placebo group in Study UC I; 23% in REMICADE treatment groups vs. 3% in placebo group in
439 Study UC II). The REMICADE-associated response was generally similar in the 5 mg/kg and 10
440 mg/kg dose groups.

441

441

Table 7
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%* |

442

443 * P < 0.001, ** P < 0.01

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

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

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

449
450 The improvement with REMICADE was consistent across all Mayo subscores through week 30
451 (study UC I shown in [Table 8](#); Study UC II was similar).
452

453 **Table 8**
454 **Proportion of patients in Study UC I with Mayo subscores indicating**
455 **inactive or mild disease through week 30**
456

| | Placebo (n=121) | Study UC I REMICADE | |
|-------------------------------|--------------------|------------------------|---------------------|
| | | 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% |

457
458 **INDICATIONS AND USAGE**

459
460 **Rheumatoid Arthritis**

461
462 REMICADE, in combination with methotrexate, is indicated for reducing signs and symptoms,
463 inhibiting the progression of structural damage, and improving physical function in patients with
464 moderately to severely active rheumatoid arthritis.
465

466 **Crohn’s Disease**

467
468 REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical
469 remission in adult and pediatric patients with moderately to severely active Crohn’s disease who
470 have had an inadequate response to conventional therapy (see [Boxed WARNING, WARNINGS,](#)
471 [and PRECAUTIONS-Pediatric Use](#)).
472

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

475

476 **Ankylosing Spondylitis**

477

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

480

481 **Psoriatic Arthritis**

482

483 REMICADE is indicated for reducing signs and symptoms of active arthritis in patients with
484 psoriatic arthritis.

485

486 **Ulcerative Colitis**

487

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

491

492 **CONTRAINDICATIONS**

493

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

500

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

503

504 **WARNINGS**

505

506 **RISK OF INFECTIONS**

507 (See [boxed WARNING](#))

508

509 **SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN**
510 **REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF**
511 **THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS**
512 **IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON**
513 **CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO**
514 **THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS.**

515

516 **REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY**
517 **IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN**

518 **CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC**
519 **INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE**
520 **MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER**
521 **TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY**
522 **MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE**
523 **THERAPY SHOULD BE DISCONTINUED (see [ADVERSE REACTIONS, Infections](#)).**

524
525 **CASES OF TUBERCULOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS,**
526 **LISTERIOSIS, PNEUMOCYSTOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND**
527 **FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING**
528 **REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE**
529 **HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS**
530 **AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY**
531 **CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.**

532
533 **SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT**
534 **USE OF ANAKINRA AND ANOTHER TNF α -BLOCKING AGENT, ETANERCEPT,**
535 **WITH NO ADDED CLINICAL BENEFIT COMPARED TO ETANERCEPT ALONE.**
536 **BECAUSE OF THE NATURE OF THE ADVERSE EVENTS SEEN WITH**
537 **COMBINATION OF ETANERCEPT AND ANAKINRA THERAPY, SIMILAR**
538 **TOXICITIES MAY ALSO RESULT FROM THE COMBINATION OF ANAKINRA**
539 **AND OTHER TNF α -BLOCKING AGENTS. THEREFORE, THE COMBINATION OF**
540 **REMICADE AND ANAKINRA IS NOT RECOMMENDED.**

541 **HEPATOSPLENIC T-CELL LYMPHOMAS**

542 **(See [boxed WARNING](#))**

543
544
545 **RARE POSTMARKETING CASES OF HEPATOSPLENIC T-CELL LYMPHOMAS**
546 **HAVE BEEN REPORTED IN ADOLESCENT AND YOUNG ADULT PATIENTS WITH**
547 **CROHN’S DISEASE TREATED WITH REMICADE. ALL OF THESE REPORTS**
548 **HAVE OCCURRED IN PATIENTS ON CONCOMITANT TREATMENT WITH**
549 **AZATHIOPRINE OR 6-MERCAPTOPYRIMIDINE. THE CLINICAL COURSE OF THIS**
550 **DISEASE IS VERY AGGRESSIVE WITH A FATAL OUTCOME IN MOST PATIENTS**
551 **WITHIN 2 YEARS OF DIAGNOSIS.¹³ THE CAUSAL RELATIONSHIP OF**
552 **HEPATOSPLENIC T-CELL LYMPHOMA TO REMICADE THERAPY REMAINS**
553 **UNCLEAR.**

Hepatotoxicity

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

Patients with Heart Failure

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

Hematologic Events

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

608 Hypersensitivity

609
610 REMICADE has been associated with hypersensitivity reactions that vary in their time of onset
611 and required hospitalization in some cases. Most hypersensitivity reactions, which include
612 urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE
613 infusion. However, in some cases, serum sickness-like reactions have been observed in Crohn’s
614 disease patients 3 to 12 days after REMICADE therapy was reinstated following an extended
615 period without REMICADE treatment. Symptoms associated with these reactions include fever,
616 rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia.
617 These reactions were associated with marked increase in antibodies to infliximab, loss of
618 detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE
619 should be discontinued for severe reactions. Medications for the treatment of hypersensitivity
620 reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be
621 available for immediate use in the event of a reaction (see [ADVERSE REACTIONS, Infusion-](#)
622 [related Reactions](#)).

623 Neurologic Events

624
625
626 REMICADE and other agents that inhibit TNF have been associated in rare cases with optic
627 neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic
628 evidence of central nervous system demyelinating disorders, including multiple sclerosis, and
629 CNS manifestation of systemic vasculitis. Prescribers should exercise caution in considering the
630 use of REMICADE in patients with pre-existing or recent onset of central nervous system
631 demyelinating or seizure disorders. Discontinuation of REMICADE should be considered in
632 patients who develop significant central nervous system adverse reactions.

633 Malignancies

634
635
636 In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE,
637 more malignancies have been observed in patients receiving those TNF-blockers compared with
638 control patients. During the controlled portions of REMICADE trials in patients with moderately
639 to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis,
640 and ulcerative colitis, 14 patients were diagnosed with malignancies among 2897 REMICADE-
641 treated patients vs. 1 among 1262 control patients (at a rate of 0.65/100 patient-years among
642 REMICADE-treated patients vs. a rate of 0.13/100 patient-years among control patients), with
643 median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for
644 control patients. Of these, the most common malignancies were breast, colorectal, and
645 melanoma. The rate of malignancies among REMICADE-treated patients was similar to that
646 expected in the general population whereas the rate in control patients was lower than expected.

647
648 In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of
649 lymphoma have been observed among patients receiving a TNF blocker compared with control
650 patients. In the controlled and open-label portions of REMICADE clinical trials, 4 patients
651 developed lymphomas among 4292 patients treated with REMICADE (median duration of
652 follow-up 1.0 years) vs. 0 lymphomas in 1265 control patients (median duration of follow-up 0.5

653 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per
654 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the
655 general population. In the combined clinical trial population for rheumatoid arthritis, Crohn’s
656 disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 4 lymphomas were
657 observed for a rate of 0.11 cases per 100 patient-years of follow-up, which is approximately 5-
658 fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid
659 arthritis, particularly patients with highly active disease and/or chronic exposure to
660 immunosuppressant therapies, may be at a higher risk (up to several fold) than the general
661 population for the development of lymphoma, even in the absence of TNF-blocking therapy.

662
663 In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic
664 obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and
665 neck origin, were reported in REMICADE-treated patients compared with control patients. All
666 patients had a history of heavy smoking (see [ADVERSE REACTIONS, Malignancies](#)).
667 Prescribers should exercise caution when considering the use of REMICADE in patients with
668 moderate to severe COPD.

669
670 The potential role of TNF-blocking therapy in the development of malignancies is not known
671 (see [ADVERSE REACTIONS, Malignancies](#)). Rates in clinical trials for REMICADE cannot be
672 compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a
673 broader patient population. Caution should be exercised in considering REMICADE treatment
674 in patients with a history of malignancy or in continuing treatment in patients who develop
675 malignancy while receiving REMICADE.

676 677 **PRECAUTIONS**

678 679 **Autoimmunity**

680
681 Treatment with REMICADE may result in the formation of autoantibodies and, rarely, in the
682 development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-
683 like syndrome following treatment with REMICADE, treatment should be discontinued (see
684 [ADVERSE REACTIONS, Autoantibodies/Lupus-like Syndrome](#)).

685 686 **Vaccinations**

687
688 No data are available on the response to vaccination with live vaccines or on the secondary
689 transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is
690 recommended that live vaccines not be given concurrently.

691
692 It is recommended that all pediatric Crohn’s disease patients be brought up to date with all
693 vaccinations prior to initiating REMICADE therapy. The interval between vaccination and
694 initiation of REMICADE therapy should be in accordance with current vaccination guidelines.

695
696
697

698 **Information for Patients**

699
700 Patients or their caregivers should be provided the REMICADE Patient Information Sheet and
701 provided an opportunity to read it prior to each treatment infusion session. Because caution
702 should be exercised in administering REMICADE to patients with clinically important active
703 infections, it is important that the patient's overall health be assessed at each treatment visit and
704 any questions resulting from the patient's or caregiver’s reading of the Patient Information Sheet
705 be discussed.

706
707 **Drug Interactions**

708
709 Concurrent administration of etanercept (another TNF α -blocking agent) and anakinra (an
710 interleukin-1 antagonist) has been associated with an increased risk of serious infections, and
711 increased risk of neutropenia and no additional benefit compared to these medicinal products
712 alone. Other TNF α -blocking agents (including REMICADE) used in combination with anakinra
713 may also result in similar toxicities (see [WARNINGS, RISK OF INFECTIONS](#)).

714
715 Specific drug interaction studies, including interactions with MTX, have not been conducted.
716 The majority of patients in rheumatoid arthritis or Crohn’s disease clinical studies received one
717 or more concomitant medications. In rheumatoid arthritis, concomitant medications besides
718 MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids and/or narcotics.
719 Concomitant Crohn’s disease medications were antibiotics, antivirals, corticosteroids,
720 6-MP/AZA and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications
721 included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory
722 agents, folic acid and corticosteroids.

723
724 Patients with Crohn’s disease who received immunosuppressants tended to experience fewer
725 infusion reactions compared to patients on no immunosuppressants (see [ADVERSE](#)
726 [REACTIONS, Immunogenicity](#) and [Infusion-related Reactions](#)). Serum infliximab
727 concentrations appeared to be unaffected by baseline use of medications for the treatment of
728 Crohn’s disease including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and
729 aminosalicylates.

730
731 **Carcinogenesis, Mutagenesis and Impairment of Fertility**

732
733 A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF α to evaluate
734 tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNF α in mice.
735 Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly
736 for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the
737 human dose of 5 mg/kg for Crohn’s disease. Results indicated that cV1q did not cause
738 tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the
739 *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively.
740 Chromosomal aberrations were not observed in an assay performed using human lymphocytes.
741 The significance of these findings for human risk is unknown. It is not known whether infliximab
742 can impair fertility in humans. No impairment of fertility was observed in a fertility and general

743 reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic
744 toxicity study.

745

746 **Pregnancy Category B**

747

748 Since infliximab does not cross-react with TNF α in species other than humans and chimpanzees,
749 animal reproduction studies have not been conducted with REMICADE. No evidence of
750 maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity
751 study conducted in mice using an analogous antibody that selectively inhibits the functional
752 activity of mouse TNF α . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the
753 anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to
754 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. It is not
755 known whether REMICADE can cause fetal harm when administered to a pregnant woman or
756 can affect reproduction capacity. REMICADE should be given to a pregnant woman only if
757 clearly needed.

758

759 **Nursing Mothers**

760

761 It is not known whether REMICADE is excreted in human milk or absorbed systemically after
762 ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because
763 of the potential for adverse reactions in nursing infants from REMICADE, a decision should be
764 made whether to discontinue nursing or to discontinue the drug, taking into account the
765 importance of the drug to the mother.

766

767 **Pediatric Use**

768

769 REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical
770 remission in pediatric patients with moderately to severely active Crohn’s disease who have had
771 an inadequate response to conventional therapy (see [Boxed WARNING](#), [WARNINGS](#),
772 [INDICATIONS AND USAGE](#), [PRECAUTIONS-Vaccinations](#), and [DOSAGE AND](#)
773 [ADMINISTRATION](#)).

774

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

778

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

781

782 **Active Crohn’s Disease in Pediatric Patients**

783

784 The safety and efficacy of REMICADE were assessed in a randomized, open-label study (Study
785 Peds Crohn’s) in 112 pediatric patients 6 to 17 years old with moderately to severely active
786 Crohn’s disease and an inadequate response to conventional therapies. The median age was 13
787 years and the median Pediatric Crohn’s Disease Activity Index (PCDAI) was 40 (on a scale of 0

788 to 100). All patients were required to be on a stable dose of 6-mercaptopurine, azathioprine, or
789 methotrexate; 35% were also receiving corticosteroids at baseline.

790

791 All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. At Week
792 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given
793 either every 8 weeks or every 12 weeks.

794

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

798

799 The proportion of pediatric patients achieving clinical response at Week 10 compared favorably
800 with the proportion of adults achieving a clinical response in Study Crohn’s I. The study
801 definition of clinical response in Study Peds Crohn’s was based on the PCDAI score, whereas
802 the CDAI score was used in the adult Study Crohn’s I.

803

804 At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the
805 every 8 week treatment group than in the every 12 week treatment group (73% vs. 47% at Week
806 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in
807 clinical remission was also greater in the every 8 week treatment group than in the every 12
808 week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54), ([Table 9](#)).

809

810 For patients in Study Peds Crohn’s receiving corticosteroids at baseline, the proportion of
811 patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every
812 8 week maintenance group and 33% for the every 12 week maintenance group. At Week 54, the
813 proportion of patients able to discontinue corticosteroids while in remission was 46% for the
814 every 8 week maintenance group and 17% for the every 12 week maintenance group.

815

Table 9
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

Adverse Reactions in Pediatric Crohn’s Disease

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

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

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

862 week and 1 in the every 12 week maintenance treatment groups). Herpes zoster was reported for
863 2 patients in the every 8 week maintenance treatment group.

864
865 In Study Peds Crohn’s, 18% of randomized patients experienced one or more infusion reactions,
866 with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn’s,
867 there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

868
869 Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn’s.

870
871 Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric
872 patients in Crohn’s disease clinical trials; 4% had ALT elevations $\geq 3 \times$ ULN, and 1% had
873 elevations $\geq 5 \times$ ULN. (Median follow-up was 53 weeks.)

874
875 The most common serious adverse events reported in the post-marketing experience in children
876 were infections (some fatal) including opportunistic infections and tuberculosis, infusion
877 reactions, and hypersensitivity reactions.

878
879 Serious adverse events in the post-marketing experience with REMICADE in the pediatric
880 population have also included malignancies, including hepatosplenic T-cell lymphomas (see
881 [Boxed WARNING](#) and [WARNINGS](#)), transient hepatic enzyme abnormalities, lupus-like
882 syndromes, and the development of autoantibodies.

883 884 **Geriatric Use**

885
886 In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or
887 safety in 181 patients aged 65 or older compared to younger patients although the incidence of
888 serious adverse events in patients aged 65 or older was higher in both REMICADE and control
889 groups compared to younger patients. In Crohn’s disease, ulcerative colitis, ankylosing
890 spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and
891 over to determine whether they respond differently from patients aged 18 to 65. Because there is
892 a higher incidence of infections in the elderly population in general, caution should be used in
893 treating the elderly (see [ADVERSE REACTIONS, Infections](#)).

894 895 **ADVERSE REACTIONS**

896
897 The data described herein reflect exposure to REMICADE in 3263 adult patients (1304 patients
898 with rheumatoid arthritis, 1106 patients with Crohn’s disease, 202 with ankylosing spondylitis,
899 150 with psoriatic arthritis, 484 with ulcerative colitis and 17 patients with other conditions),
900 including 1484 patients exposed beyond 30 weeks and 296 exposed beyond one year. (For
901 information on adverse reactions in pediatric patients see [PRECAUTIONS-Pediatric Use](#).) The
902 most common reason for discontinuation of treatment was infusion-related reactions (e.g.
903 dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion
904 of rheumatoid arthritis patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no
905 differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10
906 mg/kg dose in patients with Crohn’s disease

907 Infusion-related Reactions

908

909 Acute infusion reactions

910

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

923

924 Patients who became positive for antibodies to infliximab were more likely (approximately 2- to
925 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant
926 immunosuppressant agents appeared to reduce the frequency of antibodies to infliximab and
927 infusion reactions (see [ADVERSE REACTIONS, Immunogenicity](#) and [PRECAUTIONS, Drug
928 Interactions](#)).

929

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

933

934 Reactions following readministration

935

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

950

951

Infections

951
952
953 In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated
954 patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of
955 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections
956 (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among
957 REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin
958 ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were
959 reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was
960 fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was
961 reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis,
962 including disseminated tuberculosis, also have been reported post-marketing. Most of these cases
963 of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE
964 and may reflect recrudescence of latent disease (see **WARNINGS, RISK OF INFECTIONS**). In
965 the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE
966 every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients
967 receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4%
968 developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter
969 (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg
970 or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX,
971 serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3
972 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn’s II Study, 15% of patients
973 with fistulizing Crohn’s disease developed a new fistula-related abscess.

974
975 In REMICADE clinical studies in patients with ulcerative colitis, infections treated with
976 antimicrobials were reported in 19% of REMICADE-treated patients (average of 27 weeks of
977 follow-up) and in 14% of placebo-treated patients (average 22 weeks of follow-up). The types of
978 infections, including serious infections, reported in patients with ulcerative colitis were similar to
979 those reported in other clinical studies.

980
981 In post-marketing experience, infections have been observed with various pathogens including
982 viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems
983 and have been reported in patients receiving REMICADE alone or in combination with
984 immunosuppressive agents.

Autoantibodies/Lupus-like Syndrome

985
986
987
988 Approximately half of REMICADE-treated patients in clinical trials who were antinuclear
989 antibody (ANA) negative at baseline developed a positive ANA during the trial compared with
990 approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected
991 in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated
992 patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.

993
994

994 Malignancies

995
996 In controlled trials, more REMICADE-treated patients developed malignancies than placebo-
997 treated patients. (See [WARNINGS, Malignancies](#).)
998

999 In a randomized controlled clinical trial exploring the use of REMICADE in patients with
1000 moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were
1001 treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn’s
1002 disease. Nine of these REMICADE-treated patients developed a malignancy, including 1
1003 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of
1004 follow-up 0.8 years; 95% CI 3.51 - 14.56). There was one reported malignancy among 77 control
1005 patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up
1006 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head
1007 and neck.
1008

1009 Malignancies, including non-Hodgkin’s lymphoma and Hodgkin’s disease, have also been
1010 reported in patients receiving REMICADE during post-approval use.
1011

1012 Patients with Heart Failure

1013
1014 In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class
1015 III/IV; left ventricular ejection fraction $\leq 35\%$), 150 patients were randomized to receive
1016 treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks.
1017 Higher incidences of mortality and hospitalization due to worsening heart failure were observed
1018 in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg
1019 REMICADE group had died compared with 4 deaths each in the 5 mg/kg REMICADE and the
1020 placebo groups. There were trends towards increased dyspnea, hypotension, angina, and
1021 dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo.
1022 REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II). (See
1023 [CONTRAINDICATIONS](#) and [WARNINGS, Patients with Heart Failure](#).)
1024

1025 Immunogenicity

1026
1027 Treatment with REMICADE can be associated with the development of antibodies to infliximab.
1028 The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed
1029 by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE
1030 treatment. A higher incidence of antibodies to infliximab was observed in Crohn’s disease
1031 patients receiving REMICADE after drug free intervals >16 weeks. The majority of antibody-
1032 positive patients had low titers. Patients who were antibody-positive were more likely to have
1033 higher rates of clearance, reduced efficacy and to experience an infusion reaction (see
1034 [ADVERSE REACTIONS, Infusion-related Reactions](#)) than were patients who were antibody
1035 negative. Antibody development was lower among rheumatoid arthritis and Crohn’s disease
1036 patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.
1037

1038 The data reflect the percentage of patients whose test results were positive for antibodies to
 1039 infliximab in an ELISA assay, and are highly dependent on the sensitivity and specificity of the
 1040 assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced
 1041 by several factors including sample handling, timing of sample collection, concomitant
 1042 medication, and underlying disease. For these reasons, comparison of the incidence of antibodies
 1043 to infliximab with the incidence of antibodies to other products may be misleading.

1044

1045 **Hepatotoxicity**

1046

1047 Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported
 1048 rarely in patients receiving REMICADE (see [WARNINGS, Hepatotoxicity](#)). Reactivation of
 1049 hepatitis B has occurred in patients receiving REMICADE who are chronic carriers of this virus
 1050 (i.e., surface antigen positive) (see [WARNINGS, Hepatotoxicity](#)).

1051

1052 In clinical trials in rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis
 1053 and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than
 1054 AST) in a greater proportion of patients receiving REMICADE than in controls (Table 10), both
 1055 when REMICADE was given as monotherapy and when it was used in combination with other
 1056 immunosuppressive agents. In general, patients who developed ALT and AST elevations were
 1057 asymptomatic, and the abnormalities decreased or resolved with either continuation or
 1058 discontinuation of REMICADE, or modification of concomitant medications.

1059

1060

Table 10 Proportion of patients with elevated ALT in Clinical Trials

| | <u>Proportion of patients with elevated ALT</u> | | | | | |
|-------------------------------------|---|----------|-----------------|----------|-----------------|----------|
| | <u>>1 to <3 x ULN</u> | | <u>≥3 x ULN</u> | | <u>≥5 x ULN</u> | |
| | Placebo | REMICADE | Placebo | REMICADE | Placebo | REMICADE |
| Rheumatoid arthritis ¹ | 24% | 34% | 3% | 4% | <1% | <1% |
| Crohn’s disease ² | 34% | 39% | 4% | 5% | 0% | 2% |
| Ulcerative colitis ³ | 12% | 15% | 1% | 2% | <1% | <1% |
| Ankylosing spondylitis ⁴ | 13% | 40% | 0% | 6% | 0% | 2% |
| Psoriatic arthritis ⁵ | 16% | 42% | 0% | 5% | 0% | 2% |

1061 ¹Placebo patients received methotrexate while REMICADE patients received both REMICADE and
 1062 methotrexate. Median follow-up was 58 weeks.

1063 ²Placebo patients in the 2 Phase III trials in Crohn’s disease received an initial dose of 5 mg/kg REMICADE at
 1064 study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo
 1065 maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT
 1066 analysis. Median follow-up was 54 weeks.

1067 ³Median follow-up was 30 weeks.

1068 ⁴Median follow-up was 24 weeks.

1069 ⁵Median follow-up was 24 weeks for REMICADE group and 18 weeks for placebo group.

1070

Other Adverse Reactions

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Safety data are available from 3263 REMICADE-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn’s disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, and 17 with other conditions. (For information on other adverse reactions in pediatric patients, see [PRECAUTIONS-Pediatric Use](#).) Adverse events reported in $\geq 5\%$ of all patients with rheumatoid arthritis receiving 4 or more infusions are in [Table 11](#). The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn’s disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

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1086

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% |

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1091

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.

1092
1093 The most common serious adverse events observed in clinical trials were infections (see
1094 [ADVERSE REACTIONS, Infections](#)). Other serious, medically relevant adverse events $\geq 0.2\%$
1095 or clinically significant adverse events by body system were as follows:

1096
1097 *Body as a whole:* allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela
1098 *Blood:* pancytopenia
1099 *Cardiovascular:* circulatory failure, hypotension, syncope
1100 *Gastrointestinal:* constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction,
1101 intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia
1102 *Central & Peripheral Nervous:* meningitis, neuritis, peripheral neuropathy, dizziness
1103 *Heart Rate and Rhythm:* arrhythmia, bradycardia, cardiac arrest, tachycardia
1104 *Liver and Biliary:* biliary pain, cholecystitis, cholelithiasis, hepatitis
1105 *Metabolic and Nutritional:* dehydration
1106 *Musculoskeletal:* intervertebral disk herniation, tendon disorder
1107 *Myo-, Endo-, Pericardial and Coronary Valve:* myocardial infarction
1108 *Platelet, Bleeding and Clotting:* thrombocytopenia
1109 *Neoplasms:* basal cell, breast, lymphoma
1110 *Psychiatric:* confusion, suicide attempt
1111 *Red Blood Cell:* anemia, hemolytic anemia
1112 *Reproductive:* menstrual irregularity
1113 *Resistance Mechanism:* cellulitis, sepsis, serum sickness
1114 *Respiratory:* adult respiratory distress syndrome, lower respiratory tract infection (including
1115 pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency
1116 *Skin and Appendages:* increased sweating, ulceration
1117 *Urinary:* renal calculus, renal failure
1118 *Vascular (Extracardiac):* brain infarction, pulmonary embolism, thrombophlebitis
1119 *White Cell and Reticuloendothelial:* leukopenia, lymphadenopathy

1120
1121 The following adverse events have been reported during post-approval use of REMICADE:
1122 neutropenia (see [WARNINGS, Hematologic Events](#)), interstitial pneumonitis/fibrosis, idiopathic
1123 thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic
1124 and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies
1125 (additional neurologic events have also been observed, see [WARNINGS, Neurologic Events](#)).
1126 Because these events are reported voluntarily from a population of uncertain size, it is not always
1127 possible to reliably estimate their frequency or establish a causal relationship to REMICADE
1128 exposure.

1129 **OVERDOSAGE**

1130
1131
1132 Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of
1133 overdosage, it is recommended that the patient be monitored for any signs or symptoms of
1134 adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

1135

1136 **DOSAGE AND ADMINISTRATION**

1137

1138 **Rheumatoid Arthritis**

1139

1140 The recommended dose of REMICADE is 3 mg/kg given as an intravenous infusion followed
1141 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
1142 thereafter. REMICADE should be given in combination with methotrexate. For patients who
1143 have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or
1144 treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at
1145 higher doses (see [ADVERSE REACTIONS, Infections](#)).

1146

1147 **Crohn’s Disease or Fistulizing Crohn’s Disease**

1148

1149 The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at
1150 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the
1151 treatment of adults with moderately to severely active Crohn’s disease or fistulizing Crohn’s
1152 disease. For adult patients who respond and then lose their response, consideration may be given
1153 to treatment with 10 mg/kg. Patients who do not respond by week 14 are unlikely to respond
1154 with continued dosing and consideration should be given to discontinue REMICADE in these
1155 patients.

1156

1157 The recommended dose of REMICADE for children with moderately to severely active Crohn’s
1158 disease is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a
1159 maintenance regimen of 5 mg/kg every 8 weeks.

1160

1161 **Ankylosing Spondylitis**

1162

1163 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed
1164 with additional similar doses at 2 and 6 weeks after the first infusion, then every 6 weeks
1165 thereafter.

1166

1167 **Psoriatic Arthritis**

1168

1169 The recommended dose of REMICADE is 5 mg/kg given as an intravenous infusion followed
1170 with additional similar doses at 2 and 6 weeks after the first infusion then every 8 weeks
1171 thereafter. REMICADE can be used with or without methotrexate.

1172

1173 **Ulcerative Colitis**

1174

1175 The recommended dose of REMICADE is 5 mg/kg given as an induction regimen at 0, 2 and 6
1176 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment
1177 of moderately to severely active ulcerative colitis.

1178

1179 Preparation and Administration Instructions**1180 Use aseptic technique.**

1181

1182 REMICADE vials do not contain antibacterial preservatives. Therefore, the vials after
1183 reconstitution should be used immediately, not re-entered or stored. The diluent to be used for
1184 reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted
1185 product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The
1186 infusion concentration should range between 0.4 mg/mL and 4 mg/mL. The REMICADE
1187 infusion should begin within 3 hours of preparation.

1188

1189 1. Calculate the dose and the number of REMICADE vials needed. Each REMICADE vial
1190 contains 100 mg of infliximab. Calculate the total volume of reconstituted REMICADE
1191 solution required.

1192

1193 2. Reconstitute each REMICADE vial with 10 mL of Sterile Water for Injection, USP, using a
1194 syringe equipped with a 21-gauge or smaller needle. Remove the flip-top from the vial and
1195 wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center
1196 of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass
1197 wall of the vial. Do not use the vial if the vacuum is not present. Gently swirl the solution
1198 by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous
1199 agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual.
1200 Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to
1201 light yellow and opalescent, and the solution may develop a few translucent particles as
1202 infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign
1203 particles are present.

1204

1205 3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with
1206 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride
1207 Injection, USP, equal to the volume of reconstituted REMICADE from the 0.9% Sodium
1208 Chloride Injection, USP, 250 mL bottle or bag. Slowly add the total volume of reconstituted
1209 REMICADE solution to the 250 mL infusion bottle or bag. Gently mix.

1210

1211 4. The infusion solution must be administered over a period of not less than 2 hours and must
1212 use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore
1213 size of 1.2 µm or less). Any unused portion of the infusion solution should not be stored for
1214 reuse.

1215

1216 5. No physical biochemical compatibility studies have been conducted to evaluate the co-
1217 administration of REMICADE with other agents. REMICADE should not be infused
1218 concomitantly in the same intravenous line with other agents.

1219

1220 6. Parenteral drug products should be inspected visually for particulate matter and
1221 discoloration prior to administration, whenever solution and container permit. If visibly
1222 opaque particles, discoloration or other foreign particulates are observed, the solution
1223 should not be used.

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Storage

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

HOW SUPPLIED

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

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

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1294 **Rx Only**1295 **REMICADE® (infliximab)**
1296 **Patient Information Sheet**
1297

1298 You should read this information sheet before you start using REMICADE® (pronounced rem-
1299 eh-kaid) and before each time you are scheduled to receive REMICADE. This information sheet
1300 does not take the place of talking with your doctor. You and your doctor should talk about your
1301 health and how you are feeling before you start taking REMICADE, while you are taking it and
1302 at regular checkups. If you do not understand any of the information in this sheet, you should ask
1303 your doctor to explain what it means.
1304

1305 **What is REMICADE?**

1306 REMICADE is a medicine that is used to treat adults with moderately to severely active
1307 rheumatoid arthritis, Crohn’s disease and ulcerative colitis. REMICADE is also used to treat
1308 children with Crohn’s disease. In Crohn’s disease and ulcerative colitis, REMICADE is for
1309 people who have not responded well enough to other medicines. REMICADE is also used to
1310 treat active ankylosing spondylitis and psoriatic arthritis.
1311

1312 **How does REMICADE work?**

1313 The medicine REMICADE is a type of protein that recognizes, attaches to and blocks the action
1314 of a substance in your body called tumor necrosis factor. Tumor necrosis factor (TNF) is made
1315 by certain blood cells in your body. REMICADE will not cure rheumatoid arthritis, Crohn’s
1316 disease, ulcerative colitis, ankylosing spondylitis or psoriatic arthritis, but blocking TNF with
1317 REMICADE may reduce the inflammation caused by TNF in your body. You should also know
1318 that REMICADE may help you feel better but can also cause serious side effects and can reduce
1319 your body’s ability to fight infections (see below).
1320

1321 **What should I know about the immune system, and taking REMICADE for Rheumatoid**
1322 **Arthritis, Crohn’s Disease, Ulcerative Colitis, Ankylosing Spondylitis or Psoriatic**
1323 **Arthritis?**

1324 The immune system protects the body by responding to “invaders” like bacteria, viruses and
1325 other foreign matter that enter your body by producing antibodies and putting them into action to
1326 fight off the “invaders.” In diseases like rheumatoid arthritis, Crohn’s disease, ulcerative colitis,
1327 ankylosing spondylitis and psoriatic arthritis, TNF can cause your immune system to attack
1328 healthy tissues in your body and cause inflammation and damage. If these diseases are untreated,
1329 it can cause permanent damage to the body’s bones, cartilage and tissue.
1330

1331 While taking REMICADE can block the TNF that causes inflammation, it can also lower your
1332 body’s ability to fight infections. So, taking REMICADE can make you more prone to getting
1333 infections or it can make an infection that you already have worse. You should call your doctor
1334 right away if you think you have an infection.
1335

1336 **What important information should I know about treatment with REMICADE?**

1337 REMICADE, like other medicines that affect your immune system, is a strong medicine that can
1338 cause serious side effects. Possible serious side effects include:

1339

1340 Serious Infections:

- 1341 • Some patients have had serious infections while receiving REMICADE. Some of the patients
1342 have died from these infections. Serious infections include TB (tuberculosis), and infections
1343 caused by viruses, fungi or bacteria that have spread throughout the body. If you develop a
1344 fever, feel very tired, have a cough, or have flu-like symptoms, these could be signs that you
1345 may be getting an infection. If you have any of these symptoms while you are taking or after
1346 you have taken REMICADE, you should tell your doctor right away.

1347

1348 Heart Failure:

- 1349 • If you have been told that you have a heart problem called congestive heart failure and you
1350 are currently being treated with REMICADE, you will need to be closely monitored by your
1351 doctor. If you develop new or worse symptoms that are related to your heart condition, such
1352 as shortness of breath or swelling of your ankles or feet, you must contact your doctor
1353 immediately.

1354

1355 Blood Problems:

- 1356 • In some patients the body may fail to produce enough of the blood cells that help your body
1357 fight infections or help you stop bleeding. Some of the patients have died from this failure to
1358 produce blood cells. If you develop a fever that doesn't go away, bruise or bleed very easily
1359 or look very pale, call your doctor right away. Your doctor may decide to stop your
1360 treatment.

1361

1362 Allergic Reactions:

- 1363 • Some patients have had severe allergic reactions to REMICADE. These reactions can happen
1364 while you are getting your REMICADE infusion or shortly afterwards. The symptoms of an
1365 allergic reaction may include hives (red, raised, itchy patches of skin), difficulty breathing,
1366 chest pain and high or low blood pressure. Your doctor may decide to stop REMICADE
1367 treatment and give you medicines to treat the allergic reaction.
- 1368 • Some patients who have been taking REMICADE for Crohn’s disease have had allergic
1369 reactions 3 to 12 days after receiving their REMICADE treatment. The symptoms of this
1370 type of delayed reaction may include fever, rash, headache and muscle or joint pain. Call
1371 your doctor right away if you develop any of these symptoms or any other unusual symptoms
1372 such as difficulty swallowing.

1373

1374 Nervous System Disorders:

- 1375 • There have been rare cases where people taking REMICADE or other TNF blockers have
1376 developed disorders that affected their nervous system. Signs that you could be having a
1377 problem include: changes in your vision, weakness in your arms and/or legs, and numbness
1378 or tingling in any part of your body.

1379

1380 Cancer:

- 1381 • Reports of a type of blood cancer called lymphoma in patients on REMICADE or other TNF
1382 blockers are rare but occur more often than expected for people in general. People who have
1383 been treated for rheumatoid arthritis, Crohn’s disease, ankylosing spondylitis or psoriatic

1384 arthritis for a long time, particularly those with highly active disease may be more prone to
1385 develop lymphoma. Children and young adults who have been treated for Crohn’s disease
1386 with REMICADE have developed a rare type of lymphoma that often results in death. These
1387 patients also were receiving drugs known as azathioprine or 6-mercaptopurine. Cancers, other
1388 than lymphoma, have also been reported. If you take REMICADE or other TNF blockers,
1389 your risk for developing lymphoma or other cancers may increase. You should also tell your
1390 doctor if you have had or develop lymphoma or other cancers while you are taking
1391 REMICADE. Patients with a specific type of lung disease called COPD (Chronic Obstructive
1392 Pulmonary Disease) may be at increased risk for cancer with REMICADE treatment. If you
1393 have COPD you should discuss with your doctor whether REMICADE is appropriate for you.
1394

1395 Liver Injury:

- 1396 • There have been rare cases where people taking REMICADE have developed serious liver
1397 problems, some fatal. Signs that you could be having a problem include: jaundice (skin and
1398 eyes turning yellow), dark brown-colored urine, right sided abdominal pain, fever, and
1399 severe fatigue (tiredness). You should contact your doctor immediately if you develop any
1400 of these symptoms.

1401 **Other Important Information**

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1403
1404 Some patients have developed symptoms that can resemble a disease called lupus. Lupus-like
1405 symptoms may include chest discomfort or pain that doesn’t go away, shortness of breath, joint
1406 pain, or a rash on the cheeks or arms that gets worse in the sun. If you develop any of these
1407 symptoms your doctor may decide to stop your treatment with REMICADE.
1408

1409 **What are the more common side effects of REMICADE?**

1410 The more common side effects with REMICADE are respiratory infections (that may include
1411 sinus infections and sore throat), coughing and stomach pain.
1412

1413 **Who should not take REMICADE?**

1414 YOU SHOULD NOT take REMICADE if you have:

- 1415 • Heart failure, unless your doctor has talked to you and decided that you are able to take
1416 REMICADE.
- 1417 • Had an allergic reaction to REMICADE or any other product that was made with murine
1418 (mouse) proteins.

1419 **What health concerns should I talk to my doctor about?**

1420 Before receiving your first treatment with REMICADE you should tell your doctor if you:

- 1421 • Have or think you may have any kind of infection. The infection could be in only one place
1422 in your body (such as an open cut or sore), or an infection that affects your whole body (such
1423 as the flu). Having an infection could put you at risk for serious side effects from
1424 REMICADE.
- 1425 • Have an infection that won’t go away or a history of infection that keeps coming back.
- 1426 • Have had TB (tuberculosis), or if you have recently been with anyone who might have TB.
1427 Your doctor will examine you for TB and perform a skin test. If your doctor feels that you
1428

1429 are at risk for TB, he or she may start treating you for TB before you begin REMICADE
1430 therapy.

- 1431 • Have lived in or visited an area of the country where an infection called histoplasmosis or
1432 coccidioidomycosis (an infection caused by a fungus that affects the lungs) is common. If
1433 you don’t know if the area you live in is one where histoplasmosis or coccidioidomycosis is
1434 common, ask your doctor.
- 1435 • Have or have previously had heart failure or other heart conditions.
- 1436 • Have or have had a condition that affects your nervous system, like multiple sclerosis, or
1437 Guillain-Barré syndrome, or if you experience any numbness, or tingling, or have had a
1438 seizure.
- 1439 • Are pregnant or nursing.
- 1440 • Have recently received or are scheduled to receive a vaccine.

1441

1442 **Can I take REMICADE while I am on other medicines?**

1443 Tell your doctor if you are taking any other medicines including over the counter medicines,
1444 supplements or herbal products before you are treated with REMICADE. If you start taking or
1445 plan to start taking any new medicine while you are taking REMICADE, tell your doctor.

1446

1447 REMICADE and KINERET should not be taken together.

1448

1449 **How will REMICADE be given to me?**

1450 REMICADE will be given to you by a healthcare professional. REMICADE will be given to you
1451 by an IV. This means that the medicine will be given to you through a needle placed in a vein in
1452 your arm. It will take about 2 hours to give you the full dose of medicine. During that time and for
1453 a period after you receive REMICADE, you will be monitored by a healthcare professional. Your
1454 doctor may ask you to take other medicines along with REMICADE.

1455

1456 Only a health care professional should prepare the medicine and administer it to you.

1457

1458 **How often will I receive REMICADE?**

1459 Rheumatoid Arthritis

1460 If you are receiving REMICADE for rheumatoid arthritis you will receive your first dose
1461 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose
1462 every 8 weeks. Your doctor will monitor your response to REMICADE and may change your
1463 dose or treat you more frequently (as often as every 4 weeks).

1464

1465 Crohn’s Disease or Fistulizing Crohn’s Disease

1466 If you are an adult or child receiving REMICADE for active Crohn's disease or an adult receiving
1467 REMICADE for fistulizing Crohn’s disease, you will receive your first dose followed by
1468 additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8 weeks.
1469 Your doctor will monitor your response to REMICADE and may change your dose.

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1474 Ulcerative Colitis

1475 If you are receiving REMICADE for ulcerative colitis, you will receive your first dose followed
1476 by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8
1477 weeks and your doctor will monitor your response to REMICADE.

1478
1479 Ankylosing Spondylitis

1480 If you are receiving REMICADE for ankylosing spondylitis you will receive your first dose
1481 followed by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose
1482 every 6 weeks.

1483
1484 Psoriatic Arthritis

1485 If you are receiving REMICADE for psoriatic arthritis you will receive your first dose followed
1486 by additional doses at 2 and 6 weeks after the first dose. You will then receive a dose every 8
1487 weeks.

1488
1489 **What if I still have questions?**

1490 If you have any questions, or problems, always talk first with your doctor. You can also visit the
1491 REMICADE internet site at www.remicade.com.

1492
1493 Product developed and manufactured by:

1494 Centocor, Inc.
1495 200 Great Valley Parkway
1496 Malvern, PA 19355

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