REMICADE (infliximab)

Lyophilized Concentrate for Injection, for Intravenous Use

Initial U.S. Approval: 1998

These highlights do not include all the information needed to use REMICADE® safely and effectively. See full prescribing information for REMICADE.

HIGHLIGHTS OF PRESCRIBING INFORMATION

See full prescribing information for complete boxed warning.

• Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens.

• Discontinue REMICADE if a patient develops a serious infection.

• Perform test for latent TB; if positive, start treatment for TB prior to starting REMICADE. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)

• Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including REMICADE.

• Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers including REMICADE. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of REMICADE cases were reported in patients with Crohn’s disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)

DOSE FORMS AND STRENGTHS

100 mg of lyophilized infliximab in a 20 mL vial for intravenous infusion. (3)

ADVERSE REACTIONS

Most common adverse reactions (>10%) = infections (e.g. upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Use with anakinra or abatacept = increased risk of serious infections (7.1)

REMICADE® (infliximab)

Pediatric Ulcerative Colitis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.4)

Rheumatoid Arthritis: In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks. (2.5)

Ankylosing Spondylitis: 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks. (2.6)

Psoriatic Arthritis and Plaque Psoriasis: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.7) and (2.8)
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**WARNING: SERIOUS INFECTIONS and MALIGNANCY**

Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

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

Reported infections include:

- **Active tuberculosis**, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before REMICADE use and during therapy. Treatment for latent infection should be initiated prior to REMICADE use.
- **Invasive fungal infections**, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

**Serious Infections**

- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

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

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

**Malignancy**

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including REMICADE [see Warnings and Precautions (5.2)].

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMICADE cases have occurred in patients with Crohn’s disease or ulcerative colitis and most were in adolescent and young adult males.
1 INDICATIONS AND USAGE

1.1 Crohn’s Disease
REMICADE® is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. REMICADE is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn’s disease.

1.2 Pediatric Crohn’s Disease
REMICADE® is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy.

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

1.4 Pediatric Ulcerative Colitis
REMICADE® is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

1.5 Rheumatoid Arthritis
REMICADE®, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with rheumatoid arthritis.

1.6 Ankylosing Spondylitis
REMICADE® is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

1.7 Psoriatic Arthritis
REMICADE® is indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

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

2 DOSAGE AND ADMINISTRATION

2.1 Crohn’s Disease
The recommended dose of REMICADE® is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of active ankylosing spondylitis.

2.2 Pediatric Crohn’s Disease
The recommended dose of REMICADE® for pediatric patients 6 years and older with moderately to severely active Crohn’s disease is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

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

2.4 Pediatric Ulcerative Colitis
The recommended dose of REMICADE® for pediatric patients 6 years and older with moderately to severely active ulcerative colitis is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks.

2.5 Rheumatoid Arthritis
The recommended dose of REMICADE® is 3 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active rheumatoid arthritis. REMICADE® should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses.

2.6 Ankylosing Spondylitis
The recommended dose of REMICADE® is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of active ankylosing spondylitis.

2.7 Psoriatic Arthritis
The recommended dose of REMICADE® is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of psoriatic arthritis. REMICADE® can be used with or without methotrexate.

2.8 Plaque Psoriasis
The recommended dose of REMICADE® is 5 mg/kg given as an intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of chronic severe (i.e., extensive and/or disabling) plaque psoriasis.

2.9 Monitoring to Assess Safety
Prior to initiating REMICADE® and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection.

2.10 Administration Instructions Regarding Infusion Reactions
Adverse effects during administration of REMICADE® have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes. Anaphylaxis might occur at any time during REMICADE® infusion. Approximately 20% of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo patients.

2.11 General Considerations and Instructions for Preparation and Administration
REMICADE® is intended for use under the guidance and supervision of a physician. The reconstituted infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:

1. Calculate the dose, total volume of reconstituted REMICADE solution required and the number of REMICADE vials needed. Each REMICADE vial contains 100 mg of the infliximab antibody.
2. Reconstitute each REMICADE® vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle as follows: Remove the large flip-top from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the center of the rubber stopper and direct the stream of Sterile Water for Injection, USP, to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as infliximab is a protein. Do not use if the lyophilized cake has not fully dissolved or if opaque particles, discoloration, or other foreign particles are present.
3. Dilute the total volume of the reconstituted REMICADE solution dose to 250 mL with sterile 0.9% Sodium Chloride Injection, USP, by withdrawing a volume equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Do not dilute the reconstituted REMICADE solution with any other diluent. Slowly add the total volume of reconstituted REMICADE solution to the 250 mL infusion bottle or bag. Gently mix. The resulting infusion concentration should range between 0.4 mg/mL and 4 mg/mL.
4. The REMICADE infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.
5. No physical biochemical compatibility studies have been conducted to evaluate the co-administration of REMICADE® with other agents. REMICADE® should not be infused concomitantly in the same intravenous line with other agents.
6. Parenteral drug products should be inspected visually before and after reconstitution for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particulates are observed, the solution should not be used.
3 DOSE FORMS AND STRENGTHS
100 mg vial: 100 mg lyophilized infliximab in a 20 mL vial for injection, for intravenous use.

4 CONTRAINDICATIONS
REMICADE® at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association [NYHA] Functional Class III/IV), REMICADE treatment at 10 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure [see Warnings and Precautions (5.5) and Adverse Reactions (6.1)].

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

5 WARNINGS AND PRECAUTIONS
5.1 Serious Infections
Patients treated with REMICADE are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, salmonellosis and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:
- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis
Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving REMICADE, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with REMICADE during treatment for latent tuberculosis.

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

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

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

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

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

Invasive Fungal Infections
For patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

5.2 Malignancies
Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤18 years of age), including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 36 months (range 1 to 84 months) after the first dose of TNF-blocking therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas
In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years vs. 0 lymphomas in 1600 control patients [median duration of follow-up 0.4 years]). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn’s disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn’s disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Hepatosplenic T-cell Lymphoma (HSTCL)
Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers including REMICADE. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported REMICADE cases have involved patients with Crohn’s disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF-blockers or TNF-blockers in combination with other immunosuppressants. When treating patients, consideration of whether to use REMICADE alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with REMICADE monotherapy from the clinical trial data [see Warnings and Precautions (5.7) and Adverse Reactions (6.1)].

Skin Cancer
Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocker therapy, including REMICADE [see Adverse Reactions (6.2)]. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Cervical Cancer
A population-based retrospective cohort study using data from Swedish national health registries found a 2 to 3 fold increase in the incidence of invasive cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naive patients or the general population, particularly those over 60 years of age. A causal relationship between infliximab and cervical cancer cannot be excluded. Periodic screening should continue in women treated with REMICADE [see Adverse Reactions (6.2)].

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

In a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung cancer, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking [see Adverse Reactions (6.1)]. Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD.

Psoriasis patients should be monitored for nonmelanoma skin cancers (NMSCs), particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients with previous phototherapy [see Adverse Reactions (6.1)]. The potential role of TNF-blocking therapy in the development of malignancies is not known [see Adverse Reactions (6.1)]. Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE.

5.3 Hepatitis B Virus Reactivation
Use of TNF blockers, including REMICADE, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, the reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients should be tested for HBV infection before initiating TNF blocker therapy, including REMICADE. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

5.4 Hepatotoxicity
Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestaticia, have been reported in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatitis, occurring between 2 weeks to more than 1 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 elevation of hepatic aminotransferase levels (at least 5 times the upper limit of normal) develop, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. 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 (6.1)].

5.5 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 death in the second month than in patients who received placebo. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been 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 the age of 50. 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 (4) and Adverse Reactions (6.1)].

5.6 Hematologic Reactions
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 (including neutropenia, anemia, and/or thrombocytopenia) or any signs suggestive of sepsis during or within 24 hours of REMICADE infusion.

5.7 Hypersensitivity
REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include anaphylaxis, urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial REMICADE therapy (i.e., as early as after the second dose), and when REMICADE therapy was reinitiated following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy. REMICADE should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction [see Adverse Reactions (6.1)].

In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, re-administration of REMICADE after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment [see Adverse Reactions (6.1)]. In general, the benefit-risk of re-administration of REMICADE after a period of treatment, especially in re-induction regimens given at weeks 2–6, should be carefully considered. In the case where REMICADE maintenance therapy for psoriasis is interrupted, REMICADE should be reinstituted as a single dose followed by maintenance therapy.

5.8 Cardiovascular and Cerebrovascular Reactions During and After Infusion
Serious cardiovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, hypertension, and arrhythmias have been reported during and within 24 hours of initiation of REMICADE infusion. Cases of transient visual loss have been reported during or within 2 hours of infusion of REMICADE. REMICADE patients during infusion and if serious reaction occurs, discontinue infusion. Further management of reactions should be dictated by signs and symptoms [See Adverse Reactions (6.1)].

5.9 Neurologic Reactions
REMICADE and other agents that inhibit TNF have been associated with CNS manifestations of systemic vasculitis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMICADE in patients with these neurologic disorders and should consider discontinuation of REMICADE if these disorders develop.

5.10 Use with Anakinra
Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNFx-blocking agent, etanercept, with no clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNFx-blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended.

5.11 Use with Abatacept
In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Therefore, the combination of REMICADE and abatacept is not recommended [see Drug Interactions (7.1)].

5.12 Concurrent Administration with Other Biological Therapeutics
There is insufficient information regarding the concomitant use of REMICADE with other biological therapeutics used to treat the same conditions as REMICADE. The concomitant use of REMICADE with these biologics is not recommended because of the possibility of an increased risk of infection [see Drug Interactions (7.3)].

5.13 Switching Between Biological Disease-Modifying Antirheumatic Drugs (DMARDs)
Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

5.14 Autoimmunity
Treatment with REMICADE may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued [see Adverse Reactions (6.1)].
5.15 Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccine strains. Reactions can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with REMICADE is not recommended.

Fetal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after in utero exposure to infliximab. Infliximab is known to cross the placenta and has been detected up to 6 months following birth. At least 6 months waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to infliximab.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with REMICADE.

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Adults

The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with rheumatoid arthritis, 1373 patients with Crohn's disease, 202 with ankylosing spondylitis, 233 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 262 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. [For information on adverse reactions in pediatric patients see Adverse Reactions (6.1).] One of the most common reasons for discontinuation in adult treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash).

Infusion-related Reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In Phase 3 clinical studies, 18% of REMICADE-treated patients experienced an infusion reaction compared to 6.3% of placebo-treated patients. Of these infusion-related reactions, 15% were reported in patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients. Anaphylaxis, convulsions, erythematous rash, and hypotension. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infection reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In a randomized, controlled study evaluating REMICADE in moderate to severe heart failure (NYHA Class I/II) on remission-induced therapy, 1.5% of patients treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these REMICADE-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.87 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 0.03 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 8.10). The majority of the malignancies developed in the lung or head and neck.

Patients with Heart Failure

In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction <35%), 150 patients were randomized to receive treatment with 3 infusions of REMICADE 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidence of a new or worsening heart failure was observed in patients treated with REMICADE compared to placebo (13.3% vs. 3.3%, p = 0.004). The incidence of heart failure due to worsening heart failure were observed in patients receiving the 10 mg/kg REMICADE dose. At 1 year, 8 patients in the 10 mg/kg REMICADE group died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo group. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg REMICADE treatment groups, versus placebo. REMICADE has not been studied in patients with mild heart failure (NYHA Class I/II) [see Contraindications (4) and Precautions (5.5)].

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab and REMICADE. An enzyme immunoassay (EIA) method was originally used to measure anti-infliximab antibodies in clinical studies of REMICADE. The EIA method is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. A separate, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method for detecting antibodies to infliximab was subsequently developed and validated. This method is 60-fold more sensitive than the original EIA. With the ECLIA method, all clinical samples can be classified as either positive or negative for antibodies to infliximab without the need for the inconclusive category.
The incidence of antibodies to infliximab was based on the original EIA method in all clinical studies of REMICADE except for the Phase 3 study in pediatric patients with ulcerative colitis where the incidence of antibodies to infliximab was detected using both the EIA and ECIA methods (see Adverse Reactions, Pediatric Ulcerative Colitis (6.1)).

The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >18 weeks. In a study of psoriatic arthritis in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see Adverse Reactions (6.1)) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

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

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

Hepatotoxicity

Severe liver injury, including acute liver failure and autoimmune hepatitis, has been reported in patients receiving REMICADE (see Warnings and Precautions (5.4)). Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE, who are chronic carriers of this virus (see Warnings and Precautions (5.3)).

In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls (Table 1), both when REMICADE was given as monotherapy and when it was used in combination with other immunosuppressive agents. In general, patients who developed ALT and AST elevations were asymptomatic, and the abnormalities decreased or resolved with either continuation or discontinuation of REMICADE, or modification of concomitant medications.

Table 1: Proportion of patients with elevated ALT in clinical trials

<table>
<thead>
<tr>
<th>Proportion of patients with elevated ALT</th>
<th>Placebo REMICADE</th>
<th>Placebo REMICADE</th>
<th>Placebo REMICADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 x ULN</td>
<td>24%</td>
<td>34%</td>
<td>3%</td>
</tr>
<tr>
<td>&gt;3 x ULN</td>
<td>34%</td>
<td>39%</td>
<td>4%</td>
</tr>
<tr>
<td>&gt;5 x ULN</td>
<td>24%</td>
<td>49%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Rheumatoid arthritis

Crohn's disease

Ulcerative colitis

Ankylosing spondylitis

Psoriatic arthritis

Plaque psoriasis

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

b Placebo patients in the 2 Phase 3 trials in Crohn's disease received an initial dose of 5 mg/kg REMICADE at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT analysis. Median follow-up was 54 weeks.

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

d Median follow-up was 24 weeks for the placebo group and 102 weeks for the REMICADE group.

e Median follow-up was 39 weeks for the REMICADE group and 18 weeks for the placebo group.

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

Adverse Reactions in Psoriasis Studies

During the placebo-controlled portion across the 3 clinical trials up to Week 16, the incidence of patients who experienced at least 1 serious adverse reaction (SAE; defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 0.5% in the 3 mg/kg REMICADE group, 1.9% in the placebo group, and 1.6% in the 5 mg/kg REMICADE group. Among patients in the 2 Phase 3 studies, 12.4% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving REMICADE 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE.

One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg REMICADE. Serious infections included sepsis, and abscesses. In Study I, 2.1% of patients receiving REMICADE 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting REMICADE.

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

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

Other Adverse Reactions

Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions. [For information on other adverse reactions in pediatric patients, see Adverse Reactions (6.1)]. Adverse reactions reported in >5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis 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.

Table 2: Adverse reactions occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Average weeks of follow-up</th>
<th>Placebo</th>
<th>REMICADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>

Gastrointestinal

Nausea 20% 21%
Abdominal pain 8% 12%
Diarrhea 12% 12%
Dyspepsia 7% 10%

Respiratory

Upper respiratory tract infection 25% 32%
Sinusitis 8% 16%
Pharyngitis 8% 12%
Coughing 8% 12%
Bronchitis 9% 10%

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%
**Table 2: Adverse reactions occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis (continued)**

<table>
<thead>
<tr>
<th>Placebo (n=350)</th>
<th>REMICADE (n=1129)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central and peripheral nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Musculoskeletal system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Urinary system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Cardiovascular disorders, general</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
</tr>
</tbody>
</table>

The most common serious adverse reactions observed in clinical trials were infections [see Adverse Reactions (6.1)]. Other serious, medically relevant adverse reactions ≥0.2% or clinically significant adverse reactions by body system were as follows:

- **Body as a whole**: allergic reaction, edema
- **Blood and lymphatic**: pancytopenia
- **Cardiovascular**: hypotension
- **Gastrointestinal**: constipation, intestinal obstruction
- **Central and Peripheral Nervous System**: dizziness
- **Heart Rate and Rhythm**: bradycardia
- **Liver and Biliary**: hepatitis
- **Metabolic and Nutritional**: dehydration
- **Platelet, Bleeding and Clotting**: thrombocytopenia
- **Neoplasms**: lymphoma
- **Red Blood Cell**: anemia, hemolytic anemia
- **Resistance Mechanism Cellulitis**: sepsis, serum sickness, sarcoidosis
- **Respiratory**: lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema
- **Skin and Appendages**: increased sweating
- **Vascular (Extra Cardiac)**: thrombophlebitis
- **White Cell and Reticuloendothelial**: leukaemia, lymphadenopathy

**Adverse Reactions in Pediatric Patients**

**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 reactions 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%), leukaemia (8%), flushing (5%), viral infection (6%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

Infections were reported in 58% 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 than 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-week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group.

In Study Peds Crohn’s, 18% of randomized patients experienced 1 or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn’s, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions.

In Study Peds Crohn’s, in which all patients received stable doses of 6-MP, AZA, or MTX, excluding inconclusive samples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

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

**Pediatric Ulcerative Colitis**

Overall, the adverse reactions reported in the pediatric ulcerative colitis trial and adult ulcerative colitis (Study UC I and Study UC II) studies were generally consistent. In a pediatric UC trial, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache.

Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 22 (37%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in the pediatric UC trial was similar to that in the pediatric Crohn’ disease study (Study Peds Crohn’s) but higher than the proportion in the adults’ ulcerative colitis studies (Study UC I and Study UC II). The overall incidence of infections in the pediatric UC trial was 13/22 (59%) in the every 8-week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients. In the pediatric UC trial, 58 patients were evaluated for antibodies to infliximab using the EIA as well as the drug-tolerant ECLIA. With the EIA, 4 of 58 (7%) patients had antibodies to infliximab. With the ECLIA, 30 of 58 (52%) patients had antibodies to infliximab [see Adverse Reactions, Immunogenicity (6.1)]. The higher incidence of antibodies to infliximab by the ECLIA method was due to the 60-fold higher sensitivity compared to the EIA method. While EIA-positive patients generally had undetectable trough infliximab concentrations, ECLIA-positive patients could have detectable trough concentrations of infliximab because the ECLIA assay is more sensitive and drug-tolerant.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 17% (10/60) of pediatric patients in the pediatric UC trial; 7/60 (4%) had ALT elevations ≥3 x ULN, and 2% (1/60) had elevations ≥5 x ULN (median follow-up was 49 weeks). Overall, 8 of 60 (13%) treated patients experienced one or more infusion reactions, including 4 of 22 (18%) patients in the every 8-week maintenance treatment group. No serious infusion reactions were reported.

In the pediatric UC trial, 45 patients were in the 12 to 17 year age group and 15 in the 6 to 11 year age group. The numbers of patients in each subgroup are too small to make any definitive conclusions about the effect of age on any adverse events. There were higher proportions of patients with serious adverse events (40% vs. 18%) and discontinuation due to adverse events (40% vs. 16%) in the younger age group than in the older age group. While the proportion of patients with infections was also higher in the younger age group (60% vs. 49%), for serious infections, the proportions were similar in the two age groups (13% in the 6 to 11 year age group vs. 11% in the 12 to 17 year age group). Overall proportions of adverse reactions, including infusion reactions, were similar between the 6 to 11 and 12 to 17 year age groups (13%).

**6.2 Postmarketing Experience**

Adverse reactions have been identified during post approval use of REMICADE in adults and pediatric patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia [see Warnings and Precautions (5.6)], agranulocytosis (including infants exposed in utero to infliximab), interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neuromyopathies (additional neurologic reactions have also been observed) [see Warnings and Precautions (5.8)], acute liver failure, jaundice, hepatitis, and cholestasis [see Warnings and Precautions (5.9)], malignancies, including leukemia, melanoma, Merkel cell carcinoma, and cervical cancer [see Warnings and Precautions (5.11)], as well as cases of cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, pustular, primarily palmoplantar), transverse myelitis, and neuromyopathies (additional neurologic reactions have also been observed) [see Warnings and Precautions (5.11)]. Infusion-related reactions have been linked to REMICADE use in pediatric patients. Infusion-related reactions have been linked to REMICADE use in pediatric patients.

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

Cases of transient visual loss have been reported in association with REMICADE use during or within 2 hours of infusion. Cerebrovascular accidents, myocardial ischemia/infarction (some fatal), and arrhythmia occurring within 24 hours of infusion have also been reported [see Warnings and Precautions (5.10)]. Adverse Reactions in Pediatric Patients

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

Serious adverse reactions in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hematopoietic T-cell lymphomas [see boxed Warning and Warnings and Precautions (5.2)], transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.
REMICADE® (infliximab)

7 DRUG INTERACTIONS

7.1 Use with Anakinra or Abatacept
An increased risk of serious infections was seen in clinical studies of other TNF- 
blocker agents used in combination with anakinra or abatacept, with no added 
clinical benefit. Because the nature of the adverse reactions seen with these 
combinations with TNF-blocker therapy, similar toxicities may also result from 
the combination of anakinra or abatacept with other TNF-blocker agents. Therefore, 
the combination of REMICADE and anakinra or abatacept is not recommended [see Warnings and Precautions (5.10 and 5.11)].

7.2 Use with Tocilizumab
The use of tocilizumab in combination with biological DMARDs such as TNF 
antagonists, including REMICADE, should be avoided because of the possibility of 
increased immunosuppression and increased risk of infection.

7.3 Use with Other Biological Therapeutics
The combination of REMICADE with other biological therapeutics used to treat 
the same conditions as REMICADE is not recommended [see Warnings and Precautions (5.12)].

7.4 Methotrexate (MTX) and Other Concomitant Medications
Specific drug interaction studies, including interactions with MTX, have not been 
conducted. The majority of patients in rheumatoid arthritis or Crohn’s disease clinical 
studies received one or more concomitant medications. In rheumatoid arthritis, 
concomitant medications besides MTX were nonsteroidal anti-inflammatory 
agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn’s 
disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA and 
aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications 
included MTX in approximately half of the patients as well as NSAIDs, folic acid 
and corticosteroids. Concomitant MTX use may decrease the incidence of anti-
infliximab antibody production and increase infliximab concentrations.

7.5 Immunosuppressants
Patients with Crohn’s disease who received immunosuppressants tended to 
experience fewer infusion reactions compared to patients on no immunosup-
suppressants [see Adverse Reactions (6.1)]. Serum infliximab concentrations 
appeared to be unaffected by baseline use of medications for the treatment of 
Crohn’s disease including corticosteroids, antibiotics (metronidazole or 
ciprofloxacin) and aminosalicylates.

7.6 Cytochrome P450 Substrates
The formation of CYP450 enzymes may be suppressed by increased levels of 
cytokines (e.g., TNFα, IL-1, IL-6, IL-10, IFN) during chronic inflammation. Therefore, 
it is expected that for a molecule that antagonizes cytokine activity, such as 
infliximab, the formation of CYP450 enzymes could be normalized. Upon initiation 
or discontinuation of REMICADE in patients being treated with CYP450 substrates 
with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug 
congestion (e.g., cyclosporine or theophylline) is recommended and the 
individual dose of the drug product may be adjusted as needed.

7.7 Live Vaccines/Therapeutic Infectious Agents
It is recommended that live vaccines not be given concurrently with REMICADE. It 
is also recommended that live vaccines not be given to infants after in utero 
exposure to infliximab for at least 6 months following birth [see Warnings and Precautions (5.15)]. It is recommended that therapeutic infectious agents not be given concurrently, 
with REMICADE [see Warnings and Precautions (5.15)].

8 USE IN SPECIFIC POPULATIONS

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

As with other IgG antibodies, infliximab crosses the placenta. Infliximab has been 
detected in the serum of infants up to 6 months following birth. Consequently, these 
infants may be at increased risk of infection, including disseminated infection 
which can become fatal. At least a six month waiting period following birth is 
recommended before the administration of live vaccines (e.g., BCG vaccine or 
other live vaccines, such as the rotavirus vaccine) to these infants [see Warnings and Precautions (5.15)]. Cases of granulocytosis in infants exposed in utero have 
also been reported [see Adverse Reactions (6.2)].

8.2 Lactation
Infliximab is excreted in human milk. In one study, the maternal milk concentration 
was approximately 2% of corresponding serum concentrations observed in 
healthy volunteers following a 3 mg/kg dose. It is not known whether REMICADE, 
or any of its metabolites, are excreted in human milk. Because of the potential for 
adverse reactions in nursing infants from REMICADE, women should not breastfeed their infants while taking 
REMICADE. A decision should be made whether to discontinue nursing or to 
discontinue the drug, taking into account the importance of the drug to the mother.

8.3 Nursing Mothers
It is not known whether REMICADE is excreted in human milk or absorbed 
systemically after ingestion. Because many drugs and immunoglobulins are 
excreted in human milk, and to account for the potential for adverse reactions in 
nursing infants from REMICADE, women should not breastfeed their infants while taking 
REMICADE. A decision should be made whether to discontinue nursing or to 
discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and effectiveness of REMICADE have been established in pediatric 
patients 6 to 17 years of age for induction and maintenance treatment of Crohn’s 
disease or ulcerative colitis. However, REMICADE has not been studied in children 
with Crohn’s disease or ulcerative colitis <6 years of age.

Pediatric Crohn’s Disease
REMICADE is indicated for reducing signs and symptoms and inducing and 
maintaining clinical remission in pediatric patients with moderately to severely 
active Crohn’s disease who have had an inadequate response to conventional 
therapy [see Boxed Warning, Warnings and Precautions (5), Indications and 
Usage (1.2), Dosage and Administration (2.2), Clinical Studies (14.2) and 
Adverse Reactions (6.1)].

REMICADE has been studied only in combination with conventional immuno-
suppressive therapy in pediatric Crohn’s disease. The longer term (greater than 1 
year) safety and effectiveness of REMICADE in pediatric Crohn’s disease patients 
who have not been established in clinical trials.

Pediatric Ulcerative Colitis
The safety and effectiveness of REMICADE for reducing signs and symptoms and 
inducing and maintaining clinical remission in pediatric patients aged 6 years 
and older with moderately to severely active ulcerative colitis who have had an 
inadequate response to conventional therapy are supported by evidence from 
adequate and well-controlled studies of REMICADE in adults. Additional safety and 
pharmacokinetic data were collected in 60 pediatric patients aged 6 years and 
older [see Clinical Pharmacology (12.3), Dosage and Administration (2.4), 
Adverse Reactions (6.1), and Clinical Studies (14.4)]. The effectiveness of REMICADE in 
inducing and maintaining mucosal healing could not be established. Although 
41 patients had a Mayo endoscopy subscore of 0 or 1 at the Week 8 endoscopy, the 
induction phase was open-label and lacked a control group. Only 9 patients had an 
optional endoscopy at Week 54.

In the pediatric UC trial, approximately half of the patients were on concomitant 
immunomodulators (AZA, 6-MP, MTX) at study start. Due to the risk of HSTCL, a 
careful risk-benefit assessment should be made when REMICADE is used in 
treatment with other immunosuppressants.

Juvenile Rheumatoid Arthritis (JRA)
The safety and efficacy of REMICADE in patients with juvenile rheumatoid arthritis 
(JRA) were evaluated in a multicenter, randomized, placebo-controlled, double-
blind study for 14 weeks, followed by a double-blind, all-active treatment extension, 
for a maximum of 44 weeks. Patients with active JRA between the ages of 4 and 
17 years who had been treated with MTX for at least 3 months were enrolled. 
Concurrent use of folic acid, oral corticosteroids (<0.2 mg/kg/day of prednisone 
or equivalent), NSAIDs, and/or disease modifying antirheumatic drugs (DMARDs) 
was permitted.

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

The study failed to establish the efficacy of REMICADE in the treatment of JRA. Key 
observations in the study included a high placebo response rate and a higher rate 
of immunogenicity than what has been observed in adults. Additionally, a higher 
rate of clearance of infliximab was observed than had been observed in adults 
[see Clinical Pharmacology (12.3)].

A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients 
were treated with doses of 6 mg/kg. The proportion of patients with infusion 
reactions who received 3 mg/kg REMICADE was 35% (21/60) over 52 weeks 
compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The 
most common infusion reactions reported were vomiting, fever, headache, and 
hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious infusion 
reaction and 3 patients reported a possible anaphylactic reaction (2 of which 
were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 
2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic 
reaction. Two of the 6 patients who experienced serious infusion reactions 
received REMICADE by rapid infusion (duration of less than 2 hours). Antibodies 
to infliximab developed in 36% (20/53) of patients who received 3 mg/kg 
REMICADE compared with 12% (8/69) of patients who received 6 mg/kg.

A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination 
with MTX experienced an infection over 52 weeks compared with 65% (37/57) of 
patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks.
The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was in patient and herpes zoster in 1 patient.

8.5 Geriatric Use
In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received REMICADE, compared to younger patients—although the incidence of serious adverse reactions in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In Crohn’s disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. There is a greater incidence of infections in the elderly population in general. The incidence of serious infections in REMICADE-treated patients 65 years and older was greater than in those under 65 years of age; therefore caution should be used in treating the elderly [see Adverse Reactions (6.1)].

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

11 DESCRIPTION
Infliximab, the active ingredient in REMICADE, is a chimeric IgG1 monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNFα). It has a molecular weight of approximately 149.1 kilodaltons. Infliximab is produced by a recombinant cell line cultured in a continuous fermentation and is purified by a series of steps that includes measures to inactivate and remove viruses.

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

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

12.2 Pharmacodynamics
Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis, treatment with REMICADE reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion (E-selectin, intercellular adhesion molecule-1 [ICAM-1] and vascular cell adhesion molecule-1 [VCAM-1]), chemoattraction [IL-8 and monocyte chemoattractant protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn’s disease, treatment with REMICADE reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with REMICADE, patients with rheumatoid arthritis or Crohn’s disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to placebo. Peripheral blood lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to in vitro mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with REMICADE resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, REMICADE treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which REMICADE exerts its clinical effects is unknown.
Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg REMICADE maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 3).

### Table 3: Clinical remission and steroid withdrawal

<table>
<thead>
<tr>
<th></th>
<th>Placebo Maintenance</th>
<th>REMICADE Maintenance (q8 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 30</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>25/102</td>
<td>41/104</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>25%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Week 54</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients in remission able to discontinue corticosteroid use</td>
<td>6/54</td>
<td>14/56</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.022</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Notes:
- REMICADE at Week 0
- REMICADE 5 mg/kg administered at Weeks 0, 2 and 6
- REMICADE 10 mg/kg administered at Weeks 2 and 6
- P-values represent pairwise comparisons to placebo
- Of those receiving corticosteroids at baseline
- 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. Of the placebo maintenance group, 66% (25/38) responded to 5 mg/kg REMICADE, and 57% (12/21) of placebo 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).

#### 14.2 Pediatric Crohn’s Disease

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

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 [2]).

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.

For patients in Study Peds Crohn’s receiving corticosteroids at baseline.

In the second trial (ACCENT II [Study Crohn’s II]), patients who were enrolled had to have at least 1 draining enterocutaneous (perianal, abdominal) fistula. All patients received 5 mg/kg REMICADE at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg REMICADE maintenance at Week 14. Patients received maintenance doses at Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among patients who were in fistula response.

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

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

### Figure 2: Life table estimates of the proportion of patients who had not lost fistula 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 maintenance therapy 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 [2]).

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).
REMICADE® (infliximab)

Clinical Remission

Study UC I

- Week 30: 60% (52 of 121 patients)
- Week 54: 56% (64 of 116 patients)

Study UC II

- Week 30: 35% (51 of 147 patients)
- Week 54: 24% (35 of 147 patients)

Week 54

* Defined as a decrease from baseline in the PCDAI score of ≥15 points and total score of ≥30 points.
* Defined as a PCDAI score of ≤10 points.
* P-value <0.05
* P-value <0.01

14.3 Ulcerative Colitis

The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayo score 6 to 12 [of possible range 0 to 12]). Endoscopy subscore ≤2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroid taper was permitted after Week 8. Patients were randomized at week 0 to receive either placebo, 5 mg/kg REMICADE or 10 mg/kg REMICADE at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 in Study UC I, and at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 22 in Study UC II. In Study UC II, patients were allowed to continue blinded therapy to Week 46 at the investigator’s discretion.

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

The improvement with REMICADE was consistent across all Mayo subscores and endoscopic findings.

14.4 Pediatric Ulcerative Colitis

The safety and effectiveness of REMICADE for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of REMICADE in adults. Additional safety and pharmacokinetic data were collected in an open-label pediatric UC trial in 60 pediatric patients aged 6 through 17 years (median age 14.4 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12, Endoscopic subscore ≥2) and an inadequate response to conventional therapies. At baseline, the median Mayo score was 8, 53% of patients were receiving immunomodulator therapy (6-MP/AZA/MTX), and 62% of patients were receiving corticosteroids (median dose 0.5 mg/kg/day in prednisone equivalents). Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.

**Table 4: Response and remission in study peds Crohn’s**

<table>
<thead>
<tr>
<th>Study UC I</th>
<th>Study UC II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>5 mg/kg REMICADE</td>
<td>5 mg/kg REMICADE</td>
</tr>
<tr>
<td>10 mg/kg REMICADE</td>
<td>10 mg/kg REMICADE</td>
</tr>
<tr>
<td>Patients randomized</td>
<td>Patients randomized</td>
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<td>121</td>
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<td>121</td>
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<td>123</td>
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<tr>
<td>123</td>
<td>121</td>
</tr>
<tr>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Clinical Response</td>
<td>Clinical Response</td>
</tr>
<tr>
<td>Week 8</td>
<td>37%</td>
</tr>
<tr>
<td>Week 30</td>
<td>30%</td>
</tr>
<tr>
<td>Week 54</td>
<td>20%</td>
</tr>
<tr>
<td>Sustained Response</td>
<td>Sustained Response</td>
</tr>
<tr>
<td>Week 8</td>
<td>23%</td>
</tr>
<tr>
<td>Week 30</td>
<td>14%</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>Clinical Remission</td>
</tr>
<tr>
<td>Week 8</td>
<td>15%</td>
</tr>
<tr>
<td>Week 30</td>
<td>16%</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%</td>
</tr>
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</table>

**Table 5: Response, remission and mucosal healing in ulcerative colitis studies (continued)**

<table>
<thead>
<tr>
<th>Week 54 5 mg/kg REMICADE</th>
<th>Week 54 10 mg/kg REMICADE</th>
<th>Placebo 5 mg/kg REMICADE</th>
<th>Placebo 10 mg/kg REMICADE</th>
<th>Study UC I</th>
<th>Study UC II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained Remission</td>
<td>Sustained Remission</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8 **</td>
<td>8% **</td>
<td>22% **</td>
<td>26% **</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Week 30 **</td>
<td>7% **</td>
<td>20% **</td>
<td>20% **</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Week 54 **</td>
<td>7% **</td>
<td>20% **</td>
<td>20% **</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Mucosal Healing**

- Week 8: 34% (59%** 31% 60%* 62%* 6% 34%* 28%*)
- Week 30: 25% (50%* 49%* 30% 46%** 57%*)
- Week 54: 18% (45%* 47%* NA NA NA)

* P <0.001, ** P <0.01

**Table 6: Proportion of patients in Study UC I with Mayo subscores indicating inactive or mild disease through Week 54**

<table>
<thead>
<tr>
<th>Study UC I</th>
<th>Study UC II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>5 mg/kg REMICADE</td>
<td>5 mg/kg REMICADE</td>
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<tr>
<td>10 mg/kg REMICADE</td>
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<tr>
<td>Stool frequency</td>
<td>Stool frequency</td>
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<tr>
<td>Baseline</td>
<td>17%</td>
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<tr>
<td>Week 8</td>
<td>35%</td>
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<tr>
<td>Week 30</td>
<td>35%</td>
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<tr>
<td>Week 54</td>
<td>31%</td>
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<tr>
<td>Rectal bleeding</td>
<td>Rectal bleeding</td>
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<tr>
<td>Baseline</td>
<td>54%</td>
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<tr>
<td>Week 8</td>
<td>74%</td>
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<tr>
<td>Week 30</td>
<td>65%</td>
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<tr>
<td>Week 54</td>
<td>62%</td>
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<tr>
<td>Physician’s Global Assessment</td>
<td>Physician’s Global Assessment</td>
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<td>Baseline</td>
<td>4%</td>
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<td>Week 8</td>
<td>44%</td>
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<td>Week 30</td>
<td>36%</td>
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<td>Week 54</td>
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<td>Endoscopy findings</td>
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<td>Baseline</td>
<td>0%</td>
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<tr>
<td>Week 8</td>
<td>34%</td>
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<td>Week 30</td>
<td>26%</td>
</tr>
<tr>
<td>Week 54</td>
<td>21%</td>
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</tbody>
</table>

**Table 7: Response, remission and mucosal healing in ulcerative colitis studies**

<table>
<thead>
<tr>
<th>Study UC I</th>
<th>Study UC II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
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<tr>
<td>5 mg/kg REMICADE</td>
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<td>120</td>
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<tr>
<td>Clinical Response</td>
<td>Clinical Response</td>
</tr>
<tr>
<td>Week 8</td>
<td>37%</td>
</tr>
<tr>
<td>Week 30</td>
<td>30%</td>
</tr>
<tr>
<td>Week 54</td>
<td>20%</td>
</tr>
<tr>
<td>Sustained Response</td>
<td>Sustained Response</td>
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<td>Week 8</td>
<td>23%</td>
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<td>Week 30</td>
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<td>Clinical Remission</td>
<td>Clinical Remission</td>
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<td>Week 8</td>
<td>15%</td>
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<td>Week 30</td>
<td>16%</td>
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<tr>
<td>Week 54</td>
<td>17%</td>
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</table>
All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. Patients who did not respond to REMICADE at Week 8 received no further REMICADE and returned for safety follow-up. At Week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given either every 8 weeks through Week 46 or every 12 weeks through Week 42. Patients were allowed to change to a higher dose and/or more frequent administration schedule if they experienced loss of response.

Clinical response at Week 8 was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, including a decrease in the rectal bleeding subscore by ≥1 points or achievement of a rectal bleeding subscore of 0 or 1.

Clinical remission at Week 8 was measured by the Mayo score, defined as a Mayo score of ≤2 points with no individual subscore >1. Clinical remission was also assessed at Week 8 and Week 54 using the Pediatric Ulcerative Colitis Activity Index (PUCAI) score and was defined by a PUCAI score of <10 points.

Endoscopies were performed at baseline and at Week 8. A Mayo endoscopy subscore of 0 indicated normal or inactive disease and a subscore of 1 indicated mild disease (erythema, decreased vascular pattern, or mild friability).

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.

During maintenance phase, 23 of 45 randomized patients (9 in the every 8-week group and 14 in the every 12-week group) required an increase in their dose and/or increase in frequency of REMICADE administration due to loss of response. Nine of the 23 patients who required a change in dose had achieved remission at Week 54. Seven of those patients received the 10 mg/kg every 8-week dosing.

14.5 Rheumatoid Arthritis

The safety and efficacy of REMICADE were assessed in 2 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 (NSAIDs) 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 3 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 0.8 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, 3 mg/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 (6.1)].

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 7). 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 8). More patients treated with REMICADE reached a major clinical response than placebo-treated patients (Table 7).

REMICADE® (infliximab)

### Table 7: ACR response (percent of patients)

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Placebo + MTX</th>
<th>REMICADE + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=88)</td>
<td>(n=340)</td>
</tr>
<tr>
<td>No. of Tender Joints</td>
<td>24 16</td>
<td>32 8</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>19 13</td>
<td>20 7</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7 6.1</td>
<td>6.6 3.3</td>
</tr>
<tr>
<td>Physician’s Global Assessment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.5 5.2</td>
<td>6.2 2.1</td>
</tr>
<tr>
<td>Patient’s Global Assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.2 6.2</td>
<td>6.3 3.2</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8 1.5</td>
<td>1.8 1.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.0 2.3</td>
<td>2.4 0.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> All doses/schedules of REMICADE + MTX

<sup>b</sup> Visual Analog Scale (0=best, 10=worst)

<sup>c</sup> Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3-worst)

Radiographic Response

Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.<sup>3</sup>

In Study RA I, approximately 80% of patients had paired X-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 9) and maintained through 102 weeks.

In Study RA II, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 (Table 9) in the REMICADE + MTX groups compared to MTX alone. Patients treated with REMICADE + MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute-phase reactants (ESR and CRP) were normal or elevated; patients with elevated baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 4.2 units compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vdH-S score of 1.8 units compared to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had no progression (vdH-S score ≤0 unit) of structural damage compared to 45% of patients receiving MTX alone. In a subset of patients who began the study without erosions, REMICADE + MTX maintained an erosion-free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively (P<0.01). Fewer patients in the REMICADE + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).

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### Table 8: Components of ACR 20 at baseline and 54 weeks (Study RA I)

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Placebo + MTX</th>
<th>REMICADE + MTX*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=88)</td>
<td>(n=340)</td>
</tr>
<tr>
<td>No. of Tender Joints</td>
<td>24 16</td>
<td>32 8</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>19 13</td>
<td>20 7</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7 6.1</td>
<td>6.6 3.3</td>
</tr>
<tr>
<td>Physician’s Global Assessment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.5 5.2</td>
<td>6.2 2.1</td>
</tr>
<tr>
<td>Patient’s Global Assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.2 6.2</td>
<td>6.3 3.2</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8 1.5</td>
<td>1.8 1.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.0 2.3</td>
<td>2.4 0.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> All doses/schedules of REMICADE + MTX

<sup>b</sup> Visual Analog Scale (0=best, 10=worst)

<sup>c</sup> Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3-worst)
**Table 9: Radiographic change from baseline to Week 54**

<table>
<thead>
<tr>
<th></th>
<th>Study RA I</th>
<th>Study RA II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + MTX</td>
<td>REMICADE + MTX</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg q8 wks</td>
<td>10 mg/kg q8 wks</td>
</tr>
<tr>
<td></td>
<td>(n=64)</td>
<td>(n=71)</td>
</tr>
<tr>
<td></td>
<td>Placebo + MTX</td>
<td>REMICADE + MTX</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg q8 wks</td>
<td>6 mg/kg q8 wks</td>
</tr>
<tr>
<td></td>
<td>(n=77)</td>
<td>(n=282)</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>Mean: 79</td>
<td>Mean: 244</td>
</tr>
<tr>
<td></td>
<td>Median: 55</td>
<td>Median: 25</td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td>Mean: 6.9</td>
<td>Mean: 25</td>
</tr>
<tr>
<td></td>
<td>Median: 4.0</td>
<td>Median: 4.0</td>
</tr>
<tr>
<td><strong>Erosion Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>Mean: 44</td>
<td>Mean: 25</td>
</tr>
<tr>
<td></td>
<td>Median: 25</td>
<td>Median: 25</td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td>Mean: 4</td>
<td>Mean: 5</td>
</tr>
<tr>
<td></td>
<td>Median: 2</td>
<td>Median: 2</td>
</tr>
<tr>
<td><strong>JSN Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>Mean: 36</td>
<td>Mean: 44</td>
</tr>
<tr>
<td></td>
<td>Median: 26</td>
<td>Median: 25</td>
</tr>
<tr>
<td><strong>Change from baseline</strong></td>
<td>Mean: 2.9</td>
<td>Mean: 4</td>
</tr>
<tr>
<td></td>
<td>Median: 1.5</td>
<td>Median: 4</td>
</tr>
</tbody>
</table>

* P<0.001 for each outcome against placebo.

**Physical Function Response**

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

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

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

### 14.6 Ankylosing Spondylitis

The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New York criteria for Ankylosing Spondylitis.4 Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of DMARD or NSAID therapy (≥5 swollen joints and ≥5 tender joints) with 1 or more of the following subtypes: arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients also had plaque psoriasis with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (≥25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg REMICADE or placebo at Weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, placebo patients with ≥10% improvement from baseline in both swollen and tender joint counts were switched to REMICADE induction (early escape). At Week 24, all placebo-treated patients crossed over to REMICADE induction. Dosing continued for all patients through Week 46.

### 14.7 Psoriatic Arthritis

Safety and efficacy of REMICADE were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active psoriatic arthritis despite DMARD or NSAID therapy (<5 swollen joints and <5 tender joints) with 1 or more of the following subtypes: arthritis involving DIP joints (n=49), arthritis mutilans (n=3), asymmetric peripheral arthritis (n=40), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients also had plaque psoriasis with a qualifying target lesion ≥2 cm in diameter. Forty-six percent of patients continued on stable doses of methotrexate (<25 mg/week). During the 24-week double-blind phase, patients received either 5 mg/kg REMICADE or placebo at Weeks 0, 2, 6, 14, and 22 (100 patients in each group). At Week 16, placebo patients with ≥10% improvement from baseline in both swollen and tender joint counts were switched to REMICADE induction (early escape). At Week 24, all placebo-treated patients crossed over to REMICADE induction. Dosing continued for all patients through Week 46.
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Clinical Response

Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 56% of REMICADE-treated patients achieving ACR 20 at Week 10, compared to 11% of placebo-treated patients (P = 0.001). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as Week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving REMICADE compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Compared to placebo, treatment with REMICADE resulted in improvements in the components of the ACR response criteria, as well as in dactylitis and enthesopathy (Table 11). The clinical response was maintained through Week 54. Similar ACR responses were observed in an earlier randomized, placebo-controlled study of 104 psoriatic arthritis patients, and the responses were maintained through 98 weeks in an open-label extension phase.

Table 11: 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

<table>
<thead>
<tr>
<th>Patients Randomized</th>
<th>Placebo (n=100)</th>
<th>REMICADE 5 mg/kg (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter (median)</td>
<td>Baseline</td>
<td>Week 24</td>
</tr>
<tr>
<td>No. of Tender Jointsa</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>No. of Swollen Jointsa</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Painb</td>
<td>6.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Physician’s Global Assessmentd</td>
<td>6.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Patient’s Global Assessmentd</td>
<td>6.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)e</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>CRPe</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>% Patients with 1 or more digits with dactylitisa</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>% Patients with enthesopathy</td>
<td>35</td>
<td>36</td>
</tr>
</tbody>
</table>

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 0­68
c Scale 0­68
d Visual Analog Scale (0­best, 10­worst)
e Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0­best, 3­worst)

Improvement in Psoriasis Area and Severity Index (PASI) in psoriatic arthritis patients with baseline body surface area (BSA) ≥3% (n=87 placebo, n=83 REMICADE) was achieved at Week 14, regardless of concomitant methotrexate use, with 64% of REMICADE-treated patients achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed in some patients as early as Week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 33% and 22%, respectively, of patients receiving REMICADE compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54. (see Clinical Studies (14.8)).

Radiographic Response

Structural damage in both hands and feet was assessed radiographically by the HAQ Disability Index (HAQ-DI) and the SF-36 Health Survey. REMICADE-treated patients demonstrated significant improvement in physical function as assessed by HAQ-DI (median percent improvement in HAQ-DI score from baseline to Week 14 and 24 of 43% for REMICADE-treated patients vs 0% for placebo-treated patients).

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

14.8 Plaque Psoriasis

The safety and efficacy of REMICADE were assessed in 3 randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable plaque psoriasis involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after randomization.

Study I (EXPRESS) evaluated 378 patients who received placebo or REMICADE at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At Week 24, the placebo group crossed over to REMICADE induction therapy (5 mg/kg), followed by maintenance therapy every 6 weeks. Patients originally randomized to REMICADE continued to receive REMICADE 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (62% of patients) to marked (38%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received systemic therapy, and 92% received phototherapy.

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

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

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

Study II also evaluated the proportion of patients who achieved a score of “clear” or “excellent” by the relative Physician’s Global Assessment (rPGA). The rPGA is a 6-category scale ranging from “8 = worse” to “1 = clear” that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as “clear” or “excellent,” consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

Table 12: Psoriasis studies I, II, and III, Week 10 percentage of patients who achieved PASI 75 and percentage who achieved treatment “success” with Physician’s Global Assessment

<table>
<thead>
<tr>
<th>Placebo</th>
<th>REMICADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
<td>77 (%)</td>
</tr>
<tr>
<td>sPGA</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>PASI 75</td>
<td>77 (%)</td>
</tr>
<tr>
<td>sPGA</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>PASI 75</td>
<td>77 (%)</td>
</tr>
<tr>
<td>sPGA</td>
<td>7 (12%)</td>
</tr>
</tbody>
</table>

a P<0.001 compared with placebo

Patients with missing data at Week 10 were considered as nonresponders.

b Patients with missing data at Week 10 were imputed by last observation.
In Study I, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 85% of patients on 5 mg/kg REMICADE achieved a PASI 75 at Week 10 compared with 4% of patients on placebo.

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

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

The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through Week 50 as compared to patients who received the as-needed or PRN doses, and the best response was maintained with the 5 mg/kg every 8-week dose. These results are shown in Figure 4. At Week 46, when REMICADE serum concentrations were at trough level, in the every 8-week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8-week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum infliximab levels. This may be related in part to higher antibody rates (see Adverse Reactions (6.1)). In addition, in a subset of patients who had achieved a response at Week 10, maintenance of response appears to be greater in patients who received REMICADE every 8 weeks at the 5 mg/kg dose. Regardless of whether the maintenance doses are PRN or every 8 weeks, there is a decline in response in a subpopulation of patients in each group over time. The results of Study I through Week 50 in the 5 mg/kg every 8 weeks maintenance dose group were similar to the results from Study II.

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

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

15 REFERENCES

2. See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each REMICADE 20 mL vial is individually packaged in a carton. REMICADE is supplied in an accumulator carton containing 10 vials.

NDC 57894-030-01 100 mg vial

Each single dose vial contains 100 mg of infliximab for final reconstitution volume of 10 mL.

Storage and stability

Store unopened REMICADE vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not use REMICADE beyond the expiration date located on the carton and the vial. This product contains no preservative.

Unopened REMICADE vials may also be stored at temperatures up to a maximum of 30°C (86°F) for a single period of up to 6 months but not exceeding the original expiration date. The new expiration date must be written on the carton. Upon removal from refrigerated storage, REMICADE cannot be returned to refrigerated storage.

[For storage conditions of the reconstituted product, see Dosage and Administration (2.11)].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide). Patients or their caregivers should be advised of the potential benefits and risks of REMICADE. Physicians should instruct their patients to read the Medication Guide before starting REMICADE therapy and to reread it each time they receive an infusion. It is important that the patient’s overall health be assessed at each treatment visit and that any questions resulting from the patient's or their caregiver’s reading of the Medication Guide be discussed.

Immunosuppression

Inform patients that REMICADE may lower the ability of their immune system to fight infections. Instruct patients of the importance of contacting their doctors if they develop any symptoms of an infection, including tuberculosis and reactivation of hepatitis B virus infections. Patients should be counseled about the risk of lymphoma and other malignancies while receiving REMICADE.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as heart disease, neurological disease, or autoimmune disorders. Advise patients to report any symptoms of a cytopenia such as bruising, bleeding or persistent fever.

Manufactured by: Janssen Biotech Inc. Horsham, PA 19044

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

What is the most important information I should know about REMICADE?
REMICADE may cause serious side effects, including:

1. Risk of infection
REMICADE is a medicine that affects your immune system. REMICADE can lower the ability of your immune system to fight infections. Serious infections have happened in patients receiving REMICADE. These infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some patients have died from these infections.
   - Your doctor should test you for TB before starting REMICADE.
   - Your doctor should monitor you closely for signs and symptoms of TB during treatment with REMICADE.

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

After starting REMICADE, if you have an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your doctor right away. REMICADE can make you more likely to get infections or make any infection that you have worse.

2. Risk of Cancer
   - There have been cases of unusual cancers in children and teenage patients using tumor necrosis factor (TNF)-blocker medicines.
   - For children and adults receiving TNF-blocker medicines, including REMICADE, the chances of getting lymphoma or other cancers may increase.
   - Some people receiving TNF-blockers, including REMICADE, developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with a TNF-blocker and another medicine called azathioprine or 6-mercaptopurine.
   - People who have been treated for rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis for a long time may be more likely to develop lymphoma. This is especially true for people with very active disease.
   - Some people treated with REMICADE have developed certain kinds of skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with REMICADE, tell your doctor.
   - Patients with Chronic Obstructive Pulmonary Disease (COPD), a specific type of lung disease, may have an increased risk for getting cancer while being treated with REMICADE.
   - Some women being treated for rheumatoid arthritis with REMICADE have developed cervical cancer. For women receiving REMICADE, including those over 60 years of age, your doctor may recommend that you continue to be regularly screened for cervical cancer.
   - Tell your doctor if you have ever had any type of cancer. Discuss with your doctor any need to adjust medicines you may be taking.

See the section “What are the possible side effects of REMICADE?” below for more information.
What is REMICADE?
REMICADE is a prescription medicine that is approved for patients with:
• Rheumatoid Arthritis - adults with moderately to severely active rheumatoid arthritis, along with the medicine methotrexate.
• Crohn’s Disease - children 6 years and older and adults with Crohn’s disease who have not responded well to other medicines.
• Ankylosing Spondylitis
• Psoriatic Arthritis
• Plaque Psoriasis - adult patients with plaque psoriasis that is chronic (does not go away), severe, extensive, and/or disabling.
• Ulcerative Colitis - children 6 years and older and adults with moderately to severely active ulcerative colitis who have not responded well to other medicines.
REMICADE blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is made by your body's immune system. People with certain diseases have too much TNF-alpha that can cause the immune system to attack normal healthy parts of the body. REMICADE can block the damage caused by too much TNF-alpha.

Who should not receive REMICADE?
You should not receive REMICADE if you have:
• heart failure, unless your doctor has examined you and decided that you are able to receive REMICADE. Talk to your doctor about your heart failure.
• had an allergic reaction to REMICADE, or any of the other ingredients in REMICADE. See the end of this Medication Guide for a complete list of ingredients in REMICADE.

What should I tell my doctor before starting treatment with REMICADE?
Your doctor will assess your health before each treatment. Tell your doctor about all of your medical conditions, including if you:
• have an infection (see “What is the most important information I should know about REMICADE?”).
• have other liver problems including liver failure.
• have heart failure or other heart conditions. If you have heart failure, it may get worse while you receive REMICADE.
• have or have had any type of cancer.
• have had phototherapy (treatment with ultraviolet light or sunlight along with a medicine to make your skin sensitive to light) for psoriasis. You may have a higher chance of getting skin cancer while receiving REMICADE.
• have COPD, a specific type of lung disease. Patients with COPD may have an increased risk of getting cancer while receiving REMICADE.
• have or have had a condition that affects your nervous system such as:
  ° multiple sclerosis, or Guillain-Barré syndrome, or
  ° if you experience any numbness or tingling, or
  ° if you have had a seizure.
• have recently received or are scheduled to receive a vaccine. Adults and children receiving REMICADE should not receive live vaccines (for example, the Bacille Calmette-Guérin [BCG] vaccine) or treatment with a weakened bacteria (such as BCG for bladder cancer). Children should have all of their vaccines brought up to date before starting treatment with REMICADE.
• are pregnant or plan to become pregnant. It is not known if REMICADE harms your unborn baby. REMICADE should be given to a pregnant woman only if clearly needed. Talk to your doctor about stopping REMICADE if you are pregnant or plan to become pregnant.
• are breastfeeding or plan to breastfeed. It is not known whether REMICADE passes into your breast milk. Talk to your doctor about the best way to feed your baby while receiving REMICADE. You should not breastfeed while receiving REMICADE.

If you have a baby and you were receiving REMICADE during your pregnancy, it is important to tell your baby's doctor and other health care professionals about your REMICADE use so they can decide when your baby should receive any vaccine. Certain vaccinations can cause infections.
If you received REMICADE while you were pregnant, your baby may be at higher risk for getting an infection. If your baby receives a live vaccine within 6 months after birth, your baby may develop infections with serious complications that can lead to death. This includes live vaccines such as the BCG, rotavirus, or any other live vaccines. For other types of vaccines, talk with your doctor.
How should I receive REMICADE?
• You will be given REMICADE through a needle placed in a vein (IV or intravenous infusion) in your arm.
• Your doctor may decide to give you medicine before starting the REMICADE infusion to prevent or lessen side effects.
• Only a healthcare professional should prepare the medicine and administer it to you.
• REMICADE will be given to you over a period of about 2 hours.
• If you have side effects from REMICADE, the infusion may need to be adjusted or stopped. In addition, your healthcare professional may decide to treat your symptoms.
• A healthcare professional will monitor you during the REMICADE infusion and for a period of time afterward for side effects. Your doctor may do certain tests while you are receiving REMICADE to monitor you for side effects and to see how well you respond to the treatment.
• Your doctor will determine the right dose of REMICADE for you and how often you should receive it. Make sure to discuss with your doctor when you will receive infusions and to come in for all your infusions and follow-up appointments.

What should I avoid while receiving REMICADE?
Do not take REMICADE together with medications such as KINERET (anakinra), ORENCIA (abatacept), ACTEMRA (tocilizumab), or other medicines called biologics that are used to treat the same conditions as REMICADE.
Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. These include any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis.
Know the medicines you take. Keep a list of your medicines and show them to your doctor and pharmacist when you get a new medicine.

What are the possible side effects of REMICADE?
REMICADE can cause serious side effects, including:
See “What is the most important information I should know about REMICADE?”

Serious Infections
• Some patients, especially those 65 years and older have had serious infections while receiving REMICADE. These serious infections include TB and infections caused by viruses, fungi, or bacteria that have spread throughout the body. Some patients die from these infections. If you get an infection while receiving treatment with REMICADE your doctor will treat your infection and may need to stop your REMICADE treatment.
• Tell your doctor right away if you have any of the following signs of an infection while receiving or after receiving REMICADE:
  • a fever
  • feel very tired
  • have a cough
  • have flu-like symptoms
  • warm, red, or painful skin
• Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with REMICADE and during treatment with REMICADE.
• Even if your TB test is negative, your doctor should carefully monitor you for TB infections while you are receiving REMICADE. Patients who have had a negative TB skin test before receiving REMICADE have developed active TB.
• If you are a chronic carrier of the hepatitis B virus, the virus can become active while you are being treated with REMICADE. In some cases, patients have died as a result of hepatitis B virus being reactivated. Your doctor should do a blood test for hepatitis B virus before you start treatment with REMICADE and occasionally while you are being treated. Tell your doctor if you have any of the following symptoms:
  • feel unwell
  • poor appetite
  • tiredness (fatigue)
  • fever, skin rash, or joint pain

Heart Failure
If you have a heart problem called congestive heart failure, your doctor should check you closely while you are receiving REMICADE. Your congestive heart failure may get worse while you are receiving REMICADE. Be sure to tell your doctor of any new or worse symptoms including:
• shortness of breath
• swelling of ankles or feet
• sudden weight gain

Treatment with REMICADE may need to be stopped if you get new or worse congestive heart failure.
<table>
<thead>
<tr>
<th>What are the possible side effects of REMICADE? (continued)</th>
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<tbody>
<tr>
<td><strong>Other Heart Problems</strong></td>
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<tr>
<td>Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of beginning their infusion of REMICADE. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.</td>
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<tr>
<th><strong>Liver Injury</strong></th>
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<tr>
<td>Some patients receiving REMICADE have developed serious liver problems. Tell your doctor if you have:</td>
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<td>• jaundice (skin and eyes turning yellow)</td>
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<td>• dark brown-colored urine</td>
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<td>• pain on the right side of your stomach area (right-sided abdominal pain)</td>
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<td>• fever</td>
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<td>• extreme tiredness (severe fatigue)</td>
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<th><strong>Blood Problems</strong></th>
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<tr>
<td>In some patients receiving REMICADE, the body may not make enough of the blood cells that help fight infections or help stop bleeding. Tell your doctor if you:</td>
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<tr>
<td>• have a fever that does not go away</td>
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<tr>
<td>• bruise or bleed very easily</td>
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<td>• look very pale</td>
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<tr>
<th><strong>Nervous System Disorders</strong></th>
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<tr>
<td>Some patients receiving REMICADE have developed problems with their nervous system. Tell your doctor if you have:</td>
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<tr>
<td>• changes in your vision</td>
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<tr>
<td>• numbness or tingling in any part of your body</td>
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<tr>
<td>• weakness in your arms or legs</td>
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<tr>
<td>• seizures</td>
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| **Some patients have experienced a stroke within approximately 24 hours of their infusion with REMICADE. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.** |

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<thead>
<tr>
<th><strong>Allergic Reactions</strong></th>
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<tbody>
<tr>
<td>Some patients have had allergic reactions to REMICADE. Some of these reactions were severe. These reactions can happen while you are getting your REMICADE treatment or shortly afterward. Your doctor may need to stop or pause your treatment with REMICADE and may give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:</td>
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<tr>
<td>• hives (red, raised, itchy patches of skin)</td>
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<td>• difficulty breathing</td>
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<td>• chest pain</td>
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<tr>
<td>• high or low blood pressure</td>
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<tr>
<td>• fever</td>
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<tr>
<td>• chills</td>
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| **Some patients treated with REMICADE have had delayed allergic reactions. The delayed reactions occurred 3 to 12 days after receiving treatment with REMICADE. Tell your doctor right away if you have any of these signs of delayed allergic reaction to REMICADE:** |
| • fever |
| • rash |
| • headache |
| • sore throat |
| • muscle or joint pain |
| • swelling of the face and hands |
| • difficulty swallowing |

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<tr>
<th><strong>Lupus-like Syndrome</strong></th>
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<tr>
<td>Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any of the following symptoms, your doctor may decide to stop your treatment with REMICADE.</td>
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<tr>
<td>• chest discomfort or pain that does not go away</td>
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<tr>
<td>• shortness of breath</td>
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<tr>
<td>• joint pain</td>
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<tr>
<td>• rash on the cheeks or arms that gets worse in the sun</td>
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</table>
What are the possible side effects of REMICADE? (continued)

Psoriasis
Some people receiving REMICADE had new psoriasis or worsening of psoriasis they already had. Tell your doctor if you develop red scaly patches or raised bumps on the skin that are filled with pus. Your doctor may decide to stop your treatment with REMICADE.

The most common side effects of REMICADE include:

- respiratory infections, such as sinus infections and sore throat
- headache

Infusion reactions can happen up to 2 hours after your infusion of REMICADE. Symptoms of infusion reactions may include:

- fever
- chills
- chest pain
- low blood pressure or high blood pressure
- shortness of breath
- rash
- itching

Children who received REMICADE in studies for Crohn’s disease showed some differences in side effects compared with adults who received REMICADE for Crohn’s disease. The side effects that happened more in children were: anemia (low red blood cells), leukopenia (low white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils, the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions of the breathing tract. Among patients who received REMICADE for ulcerative colitis in clinical studies, more children had infections as compared with adults.

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

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

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

General information about REMICADE

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use REMICADE for a condition for which it was not prescribed. Do not give REMICADE to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your doctor or pharmacist for information about REMICADE that is written for health professionals.

For more information go to www.remicade.com, or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in REMICADE?

The active ingredient is Infliximab.

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

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