



Break the Cycle™ of flares with REMICADE®

REMICADE® is the **Only** Biologic Approved
in Crohn's Disease and Ulcerative Colitis (UC)

Proven Efficacy

- **Proven** clinical response
- **Proven** long-term remission
- **Proven** to eliminate steroids
- **Proven** mucosal healing in UC
- **Proven** fistula closure in Crohn's

Unmatched Experience

- **More than one million patients** treated worldwide across all uses^{1*}
- **Over 400,000 IBD patients** treated worldwide^{1†}
- **Over 16 years of safety data** collected in 37 clinical trials¹

Please see Important Safety Information contained in this advertisement.

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

REMICADE® is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric 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.

*As of August 2008. Uses include rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, and plaque psoriasis.
See full indication statements in Full Prescribing Information.

†As of August 2008. Uses include Crohn's disease and ulcerative colitis.



IMPORTANT SAFETY INFORMATION FOR REMICADE®

RISK OF INFECTIONS

Patients treated with REMICADE® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue REMICADE® if a patient develops a serious infection or sepsis.

Reported infections include:

- Active tuberculosis (TB), including reactivation of latent TB. Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before REMICADE® use and during therapy.^{2,3} Treatment for latent infection should be initiated prior to REMICADE® use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, and pneumocystosis. Patients may present with disseminated, rather than localized, disease. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens.

The risks and benefits of treatment with REMICADE® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with REMICADE®, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MALIGNANCIES

HEPATOSPLENIC T-CELL LYMPHOMAS

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

In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population. However, patients with Crohn's disease, rheumatoid arthritis, or plaque psoriasis may be at higher risk for developing lymphoma. In clinical trials of some TNF inhibitors, including REMICADE®, more cases of other malignancies were observed compared with controls. The rate of these malignancies among REMICADE®-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected. As the potential role of TNF inhibitors in the development of malignancies is not known, caution should be exercised when considering treatment of patients with a current or a past history of malignancy or other risk factors such as chronic obstructive pulmonary disease (COPD).

CONTRAINDICATIONS

REMICADE® is contraindicated in patients with moderate to severe (NYHA Class III/IV) congestive heart failure (CHF) at doses greater than 5 mg/kg. Higher mortality rates at the 10 mg/kg dose and higher rates of cardiovascular events at the 5 mg/kg dose have been observed in these patients. REMICADE® should be used with caution and only after consideration of other treatment options. Patients should be monitored closely. Discontinue REMICADE® if new or worsening CHF symptoms appear. REMICADE® should not be (re)administered to patients who have experienced a severe hypersensitivity reaction or to patients with hypersensitivity to murine proteins or other components of the product.

HEPATITIS B REACTIVATION

TNF inhibitors, including REMICADE®, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating REMICADE®. Exercise caution when prescribing REMICADE® for patients identified as carriers of HBV and monitor closely for active HBV infection during and following termination of therapy with REMICADE®. Discontinue REMICADE® in patients who develop HBV reactivation and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of REMICADE® and monitor patients closely.

HEPATOTOXICITY

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in patients receiving REMICADE® postmarketing. Some cases were fatal or required liver transplant. Aminotransferase elevations were not noted prior to discovery of liver injury in many cases. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥ 5 times the upper limit of normal) develop, REMICADE® should be discontinued, and a thorough investigation of the abnormality should be undertaken.

HEMATOLOGIC EVENTS

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some fatal, have been reported. The causal relationship to REMICADE® therapy remains unclear. Exercise caution in patients who have ongoing or a history of significant hematologic abnormalities. Advise patients to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection. Consider discontinuation of REMICADE® in patients who develop significant hematologic abnormalities.

HYPERSENSITIVITY

REMICADE® has been associated with hypersensitivity reactions that differ in their time of onset. Acute urticaria, dyspnea, and hypotension have occurred in association with REMICADE® infusions. Serious infusion reactions including anaphylaxis were infrequent. Medications for the treatment of hypersensitivity reactions should be available.

NEUROLOGIC EVENTS

TNF inhibitors, including REMICADE®, have been associated with rare cases of new or exacerbated symptoms of demyelinating disorders including multiple sclerosis, optic neuritis, and Guillain-Barré syndrome, seizure, and CNS manifestations of systemic vasculitis. Exercise caution when considering REMICADE® in all patients with these disorders. Consider discontinuation for significant CNS adverse reactions.

Please see Brief Summary of Full Prescribing Information accompanying this advertisement.

References: 1. Data on file. Centocor Ortho Biotech Inc. 2. American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med.* 2000;161:S221-S247. 3. See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients.

REMICADE® (infliximab) for IV Injection Brief Summary See package insert for Full Prescribing Information.

WARNINGS

RISK OF SERIOUS INFECTIONS

Patients treated with REMICADE are at increased risk for developing serious infections that may lead to hospitalization or death (see WARNINGS and ADVERSE REACTIONS). 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.^{1,2} 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.
- Bacterial, viral and other infections due to opportunistic pathogens.

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.

HEPATOSPLENIC T-CELL LYMPHOMAS

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

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 ADVERSE REACTIONS, Patients with Heart Failure). 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. **WARNINGS: RISK OF SERIOUS INFECTIONS (See Boxed WARNINGS)** Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving TNF-blocking agents. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported. Patients have frequently presented with disseminated rather than localized disease, and are often taking concomitant immunosuppressants such as methotrexate or corticosteroids with REMICADE. Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. 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; • 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. 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. 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.³ 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. 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. 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. Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF- α -blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF- α -blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended. **HEPATOSPLENIC T-CELL LYMPHOMAS (See Boxed WARNINGS)** Rare postmarketing cases of hepatosplenic T-cell lymphomas have been reported in adolescent and young adult patients with Crohn's disease treated with REMICADE. All of these reports have occurred in patients on concomitant treatment with azathioprine or 6-mercaptopurine. The clinical course of this disease is very aggressive with a fatal outcome in most patients within 2 years of diagnosis.⁴ The causal relationship of hepatosplenic T-cell lymphoma to REMICADE therapy remains unclear. **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, HBV 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 at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers, including REMICADE, for patients identified as carriers of HBV. 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 controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely. **Hepatotoxicity** Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver

transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥ 5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS, Hepatotoxicity). **Patients with Heart Failure** REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear. (See CONTRAINDICATIONS and ADVERSE REACTIONS, Patients with Heart Failure.) **Hematologic Events** Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. **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 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 reinstated 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 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 (see also CONTRAINDICATIONS). 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, Infusion-related Reactions). **Neurologic Events** REMICADE and other agents that inhibit TNF have been associated in rare cases with optic neuritis, seizure and new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and CNS manifestation of systemic vasculitis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of demyelinating or seizure disorders. Discontinuation of REMICADE should be considered in patients who develop significant CNS adverse reactions. **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 these TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis (RA), Crohn's disease (CD), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC), and plaque psoriasis (PsO), 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. Of these, the most 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 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 RA patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for RA, CD, PsA, AS, UC, and PsO, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately 4-fold higher than expected in the general population. Patients with CD, RA or PsO, 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. 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 or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking (see ADVERSE REACTIONS, Malignancies). 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, Adverse Reactions in Psoriasis Studies). The potential role of TNF-blocking therapy in the development of malignancies is not known (see ADVERSE REACTIONS, Malignancies). 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. **PRECAUTIONS: Autoimmunity** Treatment with REMICADE may result in the formation of autoantibodies and, rarely, 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, Autoantibodies/Lupus-like Syndrome). **Vaccinations** No data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. It is recommended that live vaccines not be given concurrently. It is recommended that all pediatric CD 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. **Information for Patients: Patients developing signs and symptoms of infection should seek medical evaluation immediately.** Patients or their caregivers should be provided the REMICADE Medication Guide and provided an opportunity to read and ask questions prior to each treatment infusion session. Because caution should be exercised in administering REMICADE to patients with clinically important active infections, it is important that the patient's overall health be assessed at each treatment visit and any questions resulting from the patient's or caregiver's reading of the Medication Guide be discussed. **Drug Interactions** Concurrent administration of etanercept (another TNF- α -blocking agent) and anakinra (an interleukin-1 receptor antagonist) has been associated with an increased risk of serious infections, and increased risk of neutropenia and no additional benefit compared to these medicinal products alone. Other TNF- α -blocking agents (including REMICADE) used in combination with anakinra may also result in similar toxicities (see WARNINGS, RISK OF SERIOUS INFECTIONS). Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in RA or CD clinical studies received one or more concomitant medications. In RA concomitant medications besides MTX were nonsteroidal anti-inflammatory agents, folic acid, corticosteroids, and/or narcotics. Concomitant CD medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA, and aminosalicylates. In PsA clinical trials, concomitant medications included MTX in approximately half of the patients as well as nonsteroidal anti-inflammatory agents, folic acid and corticosteroids. Patients with CD who received immunosuppressants tended to experience fewer infusion reactions compared to patients on no immunosuppressants (see ADVERSE REACTIONS, Immunogenicity and Infusion-related Reactions). Serum infliximab concentrations appeared to be unaffected by baseline use of medications for the treatment of CD including corticosteroids, antibiotics (metronidazole or ciprofloxacin) and aminosalicylates. **Carcinogenesis, Mutagenesis and Impairment of Fertility** A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNF- α to evaluate tumorigenicity. cV1q is an analogous antibody that inhibits the function of TNF- α in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg, or 40 mg/kg cV1q given weekly for

6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for CD. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. The significance of these findings for human risk is unknown. It is not known whether infliximab can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study. **Pregnancy Category B** Since infliximab does not cross-react with TNF α 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 TNF α . Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analog antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies. 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. **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 because of the potential for adverse reactions in nursing infants from REMICADE, women should not breast-feed 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. **Pediatric Use** REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active CD who have had an inadequate response to conventional therapy (see **Boxed WARNINGS, WARNINGS, INDICATIONS AND USAGE, PRECAUTIONS, Vaccinations, DOSAGE AND ADMINISTRATION, CLINICAL STUDIES, Active Crohn's Disease in Pediatric Patients and ADVERSE REACTIONS, Adverse Reactions in Pediatric Crohn's Disease**). REMICADE has not been studied in children with CD <6 years of age. The longer term (greater than one year) safety and effectiveness of REMICADE in pediatric CD patients have not been established in clinical trials. Safety and effectiveness of REMICADE in pediatric patients with UC and PsO have not been established. 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 DMARDs was permitted. Doses of 3 mg/kg REMICADE or placebo were administered intravenously at Weeks 0, 2, and 6. Patients randomized to placebo crossed-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, Pharmacokinetics**). 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, one 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 38% (20/53) of patients who received 3 mg/kg REMICADE compared with 12% (6/49) 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 pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient. **Geriatric Use** In RA and PsO clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with RA and 75 patients with PsO, aged 65 or older who received REMICADE, compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In CD, UC, AS, and PSA studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly (see **ADVERSE REACTIONS, Infections**). **ADVERSE REACTIONS:** The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with RA, 1106 patients with CD, 202 with AS, 293 with PSA, 484 with UC, 1373 with PsO, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond one year. (For information on adverse reactions in pediatric patients see **ADVERSE REACTIONS, Adverse Reactions in Pediatric Crohn's Disease**.) One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g. dyspnea, flushing, headache and rash). Adverse events have been reported in a higher proportion of RA patients receiving the 10 mg/kg dose than the 3 mg/kg dose, however, no differences were observed in the frequency of adverse events between the 5 mg/kg dose and 10 mg/kg dose in patients with CD. **Infusion-related Reactions** Infusion reactions: An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 to 2 hours after an infusion. Approximately 20% of REMICADE-treated patients in all clinical studies experienced an infusion reaction compared to approximately 10% of placebo-treated patients. 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 and included 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 infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 to 2 hours) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group. Patients who became positive for antibodies to infliximab were more likely (approximately 2- to 3-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions (see **ADVERSE REACTIONS, Immunogenicity and PRECAUTIONS, Drug Interactions**). In post-marketing experience, cases of anaphylactic-like reactions, including laryngeal/pharyngeal edema and severe bronchospasm, and seizure have been associated with REMICADE administration. **Delayed Reactions/Reactions following readministration. Plaque Psoriasis** In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within two weeks after repeat infusion. **Crohn's disease** In a study where 37 of 41 patients with CD were retreated with infliximab following a 2 to 4 year period without infliximab treatment, 10 patients experienced adverse events manifesting 3 to 12 days following infusion of which 6 were considered serious. Signs and symptoms included myalgia and/or arthralgia with fever and/or rash, with some patients also experiencing pruritus, facial, hand or lip edema, dysphagia, urticaria, sore throat, and headache. Patients experiencing these adverse events had not experienced infusion-related adverse events associated with their initial infliximab therapy. These adverse events occurred in 39% (9/23) of patients who had received liquid formulation which is no longer in use and 7% (1/14) of patients who received lyophilized formulation. The clinical data are not adequate to determine if occurrence of these reactions is due to differences in formulation. Patients' signs and symptoms improved substantially or resolved with treatment in all cases. There are insufficient data on the incidence of these events after drug-free intervals of 1 to 2 years. These events have

been observed only infrequently in clinical studies and post-marketing surveillance with retreatment intervals up to 1 year. **Infections** In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to military tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE and may reflect recrudescence of latent disease (see **WARNINGS, RISK OF SERIOUS INFECTIONS**). In the 1 year placebo-controlled studies RA I and RA II, 5.3% of patients receiving REMICADE every 8 weeks with MTX developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54 weeks Crohn's II Study, 15% of patients with fistulizing CD developed a new fistula-related abscess. In REMICADE clinical studies in patients with UC, infections treated with antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with UC were similar to those reported in other clinical studies. In post-marketing experience in the various indications, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving REMICADE alone or in combination with immunosuppressive agents. The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection. **Autoantibodies/Lupus-like Syndrome** Approximately half of REMICADE-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately one-fifth of REMICADE-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon. **Malignancies** In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients (see **WARNINGS, Malignancies**). In a randomized controlled clinical trial exploring the use of REMICADE in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with REMICADE at doses similar to those used in RA and CD. Nine of these REMICADE-treated patients developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51-14.56). There was one reported malignancy among 77 control patients for a rate of 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04-9.10). The majority of the malignancies developed in the lung or head and neck. Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use. **Patients with Heart Failure** In a randomized study evaluating REMICADE in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction $\leq 35\%$), 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 incidences of mortality and hospitalization 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 had died compared with 4 deaths each in the 5 mg/kg REMICADE and the placebo groups. There were trends towards 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 and WARNINGS, Patients with Heart Failure**). **Immunogenicity** Treatment with REMICADE can be associated with the development of antibodies to infliximab. 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 CD patients receiving REMICADE after drug free intervals >16 weeks. In a study of PSA, where 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, Infusion-related Reactions**) than were patients who were antibody negative. Antibody development was lower among RA and CD 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 infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for one 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 diseases 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 ELISA assay, and 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 rarely in patients receiving REMICADE (see **WARNINGS, Hepatotoxicity**). Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE who are chronic carriers of this virus (see **WARNINGS, Hepatitis B Virus Reactivation**). In clinical trials in RA, CD, UC, AS, PsO and PSA, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving REMICADE than in controls, 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. In RA clinical trials (median follow-up 58 weeks), 34% of patients who received REMICADE + MTX experienced elevations in ALT at >1 to <3 times the upper limit of normal (ULN) compared to 24% of patients treated with placebo + MTX. ALT elevations ≥ 3 times ULN were observed in 4% of patients who received REMICADE + MTX compared with 3% of patients who received MTX alone. ALT elevations ≥ 3 times ULN were observed in <1% of patients in both REMICADE + MTX and MTX alone groups. In CD clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced elevations in ALT at >1 to <3 times the ULN compared to 34% of patients treated with placebo-maintenance. ALT elevations ≥ 3 times the ULN were observed in 5% of patients who received REMICADE-maintenance compared with 4% of patients who received placebo-maintenance. ALT elevations ≥ 5 times ULN were observed in 2% of patients who received REMICADE-maintenance compared to none in patients treated with placebo-maintenance. In UC clinical trials (median follow up 30 weeks). Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for REMICADE. 17% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 12% of patients treated with placebo. ALT elevations ≥ 3 times the ULN were observed in 2% of patients who received REMICADE compared with 1% of patients who received placebo. ALT elevations ≥ 5 times ULN were observed in <1% of patients in both REMICADE and placebo groups. In an AS clinical trial (median follow up 24 weeks for placebo group and 102 weeks for REMICADE group) 51% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 15% of patients treated with placebo. ALT elevations ≥ 3 times the ULN were observed in 10% of patients who received

REMICADE compared to none in patients who received placebo. ALT elevations ≥ 5 times ULN were observed in 4% of patients who received REMICADE compared to none in patients treated with placebo. In a PsA clinical trial (median follow up 39 weeks for REMICADE group and 18 weeks in placebo group) 50% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 16% of patients treated with placebo. ALT elevations ≥ 3 times the ULN were observed in 7% of patients who received REMICADE compared to none in patients who received placebo. ALT elevations ≥ 5 times ULN were observed in 2% of patients who received REMICADE compared to none in patients treated with placebo. In PsO clinical trials, (ALT values are obtained in 2 phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo). 49% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 24% of patients treated with placebo. ALT $\geq 3 \times$ ULN were observed in 8% of patients who received REMICADE compared to $<1\%$ who received placebo. ALT elevations $\geq 5 \times$ ULN were observed in 3% of patients who received REMICADE compared to none in patients treated with placebo.

Adverse Reactions in Pediatric Crohn's Disease There were some differences in the adverse reactions observed in the pediatric patients receiving REMICADE compared to those observed in adults with CD. The following adverse events were reported more commonly in 103 randomized pediatric CD patients administered 5 mg/kg REMICADE through 54 weeks than in 385 adult CD patients receiving a similar treatment regimen: anemia (11%), blood in stool (10%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%). Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8 week as opposed to every 12 week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8 week and 4 patients in the every 12 week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8 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 one 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. Antibodies to REMICADE developed in 3% of pediatric patients in Study Peds Crohn's. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in CD clinical trials; 4% had ALT elevations $\geq 3 \times$ ULN, and 1% had elevations $\geq 5 \times$ ULN. (Median follow-up was 53 weeks.)

Adverse Reactions in Psoriasis Studies During the placebo-controlled portion across the three clinical trials up to Week 16, the proportion of patients who experienced at least 1 SAE (defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 1.7% in the 3 mg/kg REMICADE group, 3.2% in the placebo group, and 3.9% 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 one 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 one 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, 2.7% 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 infections (requiring hospitalization) were abscesses (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 placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received REMICADE at any dose were diagnosed with at least one NMSC 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 RA, 1106 with CD, 484 with UC, 202 with AS, 293 with PsA, 1373 with PsO and 17 with other conditions. (For information on other adverse reactions in pediatric patients, see *ADVERSE REACTIONS, Adverse Reactions in Pediatric Crohn's Disease*.) Adverse events reported in $\geq 5\%$ of all patients with RA receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated RA, AS, PsA, PsO and CD patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with CD. In the CD studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=350; average weeks of follow-up 59) and REMICADE-treated patients (n=1129; average weeks of follow-up 66), respectively, are: *Gastrointestinal*: Nausea: 20, 21; Abdominal pain: 8, 12; Diarrhea: 12, 12; Dyspepsia: 7, 10; *Respiratory*: Upper respiratory tract infection: 25, 32; Sinusitis: 8, 14; Pharyngitis: 8, 12; Coughing: 8, 12; Bronchitis: 9, 10; Rhinitis: 5, 8; *Skin and appendages disorders*: Rash: 5, 10; Pruritis: 2, 7; *Body as a whole—general disorders*: Fatigue: 7, 9; Pain: 7, 8; *Resistance mechanism disorders*: Fever: 4, 7; Moniliasis: 3, 5; *Central and peripheral nervous system disorders*: Headache: 14, 18; *Musculoskeletal system disorders*: Back pain: 5, 8; Arthralgia: 7, 8; *Urinary system disorders*: Urinary tract infection: 6, 8; *Cardiovascular disorders, general*: Hypertension: 5, 7. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. The most common serious adverse events observed in clinical trials were infections (see *ADVERSE REACTIONS, Infections*). Other serious, medically relevant adverse events $\geq 0.2\%$ or clinically significant adverse events by body system were as follows: *Body as a whole*: allergic reaction, diaphragmatic hernia, edema, surgical/procedural sequela; *Blood*: pancytopenia; *Cardiovascular*: circulatory failure, hypotension, syncope; *Gastrointestinal*: constipation, gastrointestinal hemorrhage, ileus, intestinal obstruction, intestinal perforation, intestinal stenosis, pancreatitis, peritonitis, proctalgia; *Central & Peripheral Nervous*: meningitis, neuritis, peripheral neuropathy, dizziness; *Heart Rate and Rhythm*: arrhythmia, bradycardia, cardiac arrest, tachycardia; *Liver and Biliary*: biliary pain, cholecystitis, cholelithiasis, hepatitis; *Metabolic and Nutritional*: dehydration; *Musculoskeletal*: intervertebral disk herniation, tendon disorder; *Myo-, Endo-, Pericardial, and Coronary Valve*: myocardial infarction; *Platelet, Bleeding, and Clotting*: thrombocytopenia; *Neoplasms*: basal cell, breast, lymphoma; *Psychiatric*: confusion, suicide attempt; *Red Blood Cell*: anemia, hemolytic anemia; *Reproductive*: menstrual irregularity; *Resistance Mechanism*: cellulitis, sepsis, serum sickness; *Respiratory*: adult respiratory distress syndrome, lower respiratory tract infection (including pneumonia), pleural effusion, pleurisy, pulmonary edema, respiratory insufficiency; *Skin and Appendages*: increased sweating, ulceration; *Urinary*: renal calculus, renal failure; *Vascular (Extracardiac)*: brain infarction, pulmonary embolism, thrombophlebitis; *White Cell and Reticuloendothelial*: leukopenia, lymphadenopathy.

Post-marketing Adverse Events The following adverse events, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia (see *WARNINGS, Hematologic Events*), interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare 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), psoriasis (including new onset and pustular, primarily palmar/plantar), transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*) and acute liver failure, jaundice, hepatitis, and cholestasis (see *WARNINGS, Hepatotoxicity*). Because these events 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 REMICADE exposure. The following serious adverse events 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 events in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hepatosplenic T-cell lymphomas (see *Boxed WARNINGS and WARNINGS*), transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies. **OVERDOSAGE**: 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. **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-treated patients (see *ADVERSE REACTIONS, Infusion-related Reactions*). Prior to infusion with REMICADE, premedication may be administered at the physician's discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids. During infusion, mild to moderate infusion reactions may improve following slowing or suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients that do not tolerate the infusion following these interventions, REMICADE should be discontinued. During or following infusion, patients that have severe infusion-related hypersensitivity reactions should be discontinued from further REMICADE treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

REFERENCES: 1. *Am J Respir Crit Care Med*. 2000;161:S221-S247. 2. See latest Centers for Disease Control guidelines and recommendations for tuberculosis testing in immunocompromised patients. 3. Gardam MA, Keystone EC, Menzies R, et al. Antitumor necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis*. 2003;3:148-155. 4. Belhadj K, Reyes F, Farcet JP, et al. Hepatosplenic $\gamma\delta$ T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients. *Blood*. 2003;102(13):4261-4269.

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