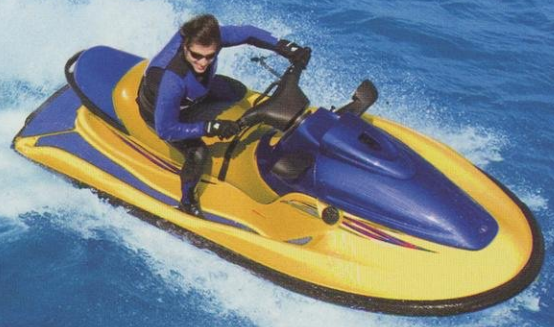
Remicade advertisement.

[s.l.]: [s.n.], 2003

In Crohn's therapy...

BREAK THE CYCLE OF FLARES



REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in 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 patients with fistulizing Crohn's disease.

Please see Important Safety Information contained in this advertisement.

Remicade®
INFLIXIMAB

The only anti–TNF-α therapy with experience in more than 634,000 patients across all uses[1*]

IMPORTANT SAFETY INFORMATION

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 administered to patients with hypersensitivity to murine proteins or other components of the product.

Risk of Infection

TUBERCULOSIS (TB) (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL. PATIENTS SHOULD BE EVALUATED FOR LATENT TB INFECTION WITH A SKIN TEST.[2] TREATMENT OF LATENT TB INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE. ACTIVE TB HAS DEVELOPED IN PATIENTS RECEIVING REMICADE WHO WERE TUBERCULIN SKIN TEST–NEGATIVE PRIOR TO RECEIVING REMICADE. MONITOR PATIENTS RECEIVING REMICADE FOR SIGNS AND SYMPTOMS OF ACTIVE TB, INCLUDING THOSE WHO ARE TUBERCULIN SKIN TEST–NEGATIVE.

Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their disease, could predispose them to infections. Cases of sepsis, pneumonia, histoplasmosis, coccidioidomycosis, listeriosis, and pneumocystosis have been reported. For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of REMICADE should be considered before initiation of therapy. REMICADE should not be given to patients with a clinically important, active infection. Use with caution in patients with a history of infection. Monitor patients for infection during or after treatment. Discontinue REMICADE if a patient develops a serious infection.

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. REMICADE has been associated with reactivation of hepatitis B. Chronic carriers of hepatitis B should be evaluated and monitored prior to and during treatment.

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 should not be administered to patients with hypersensitivity to murine proteins or other components of the product. 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, and optic neuritis, 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.

Malignancies

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 rheumatoid arthritis and Crohn's disease may be at higher risk for developing lymphoma. 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.

Please see brief summary of the full prescribing information starting on the adjacent page.

*As of February 2005.

References: 1. Data on file. Centocor, 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.

Remicade®
INFLIXIMAB

REMICADE® (infliximab) for IV Injection Brief Summary See package insert for full prescribing information.

WARNING
RISK OF INFECTIONS
TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH A REACTIVE TUBERCULIN SKIN TEST REDUCES THE RISK OF TB REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH REMICADE. HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS RECEIVING REMICADE WHO WERE TUBERCULIN SKIN TEST NEGATIVE PRIOR TO RECEIVING REMICADE. PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST[1]. TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING REMICADE FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

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 administered to patients with known hypersensitivity to any murine proteins or other component of the product. **WARNINGS: RISK OF INFECTIONS (See boxed WARNING) SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*). CASES OF TUBERCULOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE 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. Hepatotoxicity** Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e., surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with REMICADE. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see *ADVERSE REACTIONS, Hepatotoxicity*). **Patients with Heart Failure** REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear (see *CONTRAINDICATIONS* and *ADVERSE REACTIONS, Patients with Heart Failure*). **Hematologic Events** Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. **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 Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted 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 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, 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. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system 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 all the TNF-α-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis and Crohn's disease, 2 patients developed lymphoma among 1964 REMICADE-treated patients versus 0 among 483 control patients (median duration of follow-up 0.9 years). In the controlled and open-label portions of these clinical trials of REMICADE, 4 patients developed lymphomas (2 patients with rheumatoid arthritis and 2 patients with Crohn's disease) among 3469 patients (median duration of follow-up 1.0 years). In rheumatoid arthritis patients, this is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis and Crohn's disease, this is approximately 5-fold higher than expected in the general population. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Patients with Crohn's disease or rheumatoid arthritis, 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. The potential role of TNF-α-blocking therapy in the development of malignancies is not known (see *ADVERSE REACTIONS, Malignancies*). No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving REMICADE; thus additional caution should be exercised in considering REMICADE treatment of these patients. **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. **Information for Patients** Patients should be provided the REMICADE Patient Information Sheet and provided an opportunity to read it 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 reading of the Patient Information Sheet be discussed. **Drug Interactions** Concurrent administration of etanercept (another TNF-α-blocking agent) and anakinra (an interleukin-1 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 INFECTIONS*). 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, 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 nonsteroidal anti-inflammatory agents, folic acid and corticosteroids. Patients with Crohn's disease 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 Crohn's disease 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 Crohn's disease. 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 analogous 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, 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** Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease have not been established. **Geriatric Use** In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients aged 65 or older 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 Crohn's disease, 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. 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 2779 patients, including 1484 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most common reason 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 rheumatoid arthritis 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 Crohn's disease. **Infusion-related Reactions** *Acute 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. 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 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. *Reactions following readministration.* In a study where 37 of 41 patients with Crohn's disease 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 all clinical trials, six opportunistic infections were reported; two cases of coccidioidomycosis (one of which resulted in death) and one case each of histoplasmosis, pneumocystosis, nocardiosis, and cytomegalovirus. Tuberculosis was reported in thirteen patients, four of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF 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 Crohn's disease developed a new fistula-related abscess. In post-marketing experience, 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. **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** Among 3469 patients with moderately to severely active rheumatoid arthritis and Crohn's disease treated with REMICADE in clinical trials with a median of 1.0 years of follow-up, 4 patients developed lymphomas, for a rate of 0.08 cases per 100 patient-years of follow-up in patients with rheumatoid arthritis and 0.12 cases per 100 patient-years of follow up in the combined clinical trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold higher in the RA clinical trial population and 5-fold higher in the overall clinical trial population than expected in an age-, gender-, and race-matched general population based on the Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. An increased rate of lymphoma up to several fold has been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be further increased in patients with more severe disease activity. Other than lymphoma, 23 patients developed non-cutaneous malignancies, which was similar in number to what would be expected in the general population. Of these, the most common malignancies were breast, colorectal, and melanoma. (See *WARNINGS, Malignancies*.) 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 ≤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 one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. 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 rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. 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 has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive) (see *WARNINGS, Hepatotoxicity*). In clinical trials in RA, Crohn's disease, ankylosing spondylitis, and psoriatic arthritis 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. ALT elevations ≥5 times the upper limit of normal were observed in 1% of patients receiving REMICADE. In rheumatoid arthritis clinical trials, 34% of patients who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (≥ 2 but <3 times the upper limit of normal) elevations in ALT compared to 24% of patients treated with placebo + MTX. ALT elevations ≥ 3 times the upper limit of normal were observed in 3.9% of patients who received REMICADE + MTX compared with 3.2% of patients who received MTX alone (median follow up approximately 1 year). In Crohn's disease clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced mild to moderate elevations in ALT, compared to 34% of patients treated with placebo-maintenance. ALT elevations ≥ 3 times the upper limit of normal were observed in 5.0% of patients who received REMICADE-maintenance compared with 4.0% of patients who received placebo-maintenance. In an ankylosing spondylitis clinical trial in which patients were not receiving MTX, 40% of patients who received REMICADE experienced mild to moderate elevations in ALT compared to 13% of patients treated with placebo. ALT elevations ≥ 3 times the upper limit of normal were observed in 12 (6%) REMICADE-treated patients compared to none in placebo-treated patients. Similar rates of mild to moderate ALT elevations and elevations ≥ 3 times the upper limit of normal were observed in a psoriatic arthritis clinical trial. **Other Adverse Reactions** Safety data are available from 2779 REMICADE-treated patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, and 17 with other conditions. Adverse events reported in ≥ 5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. 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 ≥ 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* and *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. The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see *WARNINGS, Hematologic Events*), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*). 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. **OVERDOSAGE**: Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCE**: 1. 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.

REMICADE every 8 weeks*

- Induces and maintains clinical remission in patients with moderate-to-severe Crohn's disease who have had an inadequate response to conventional therapies
- Induces and maintains fistula closure

*After the first 3 doses at 0, 2, and 6 weeks.

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

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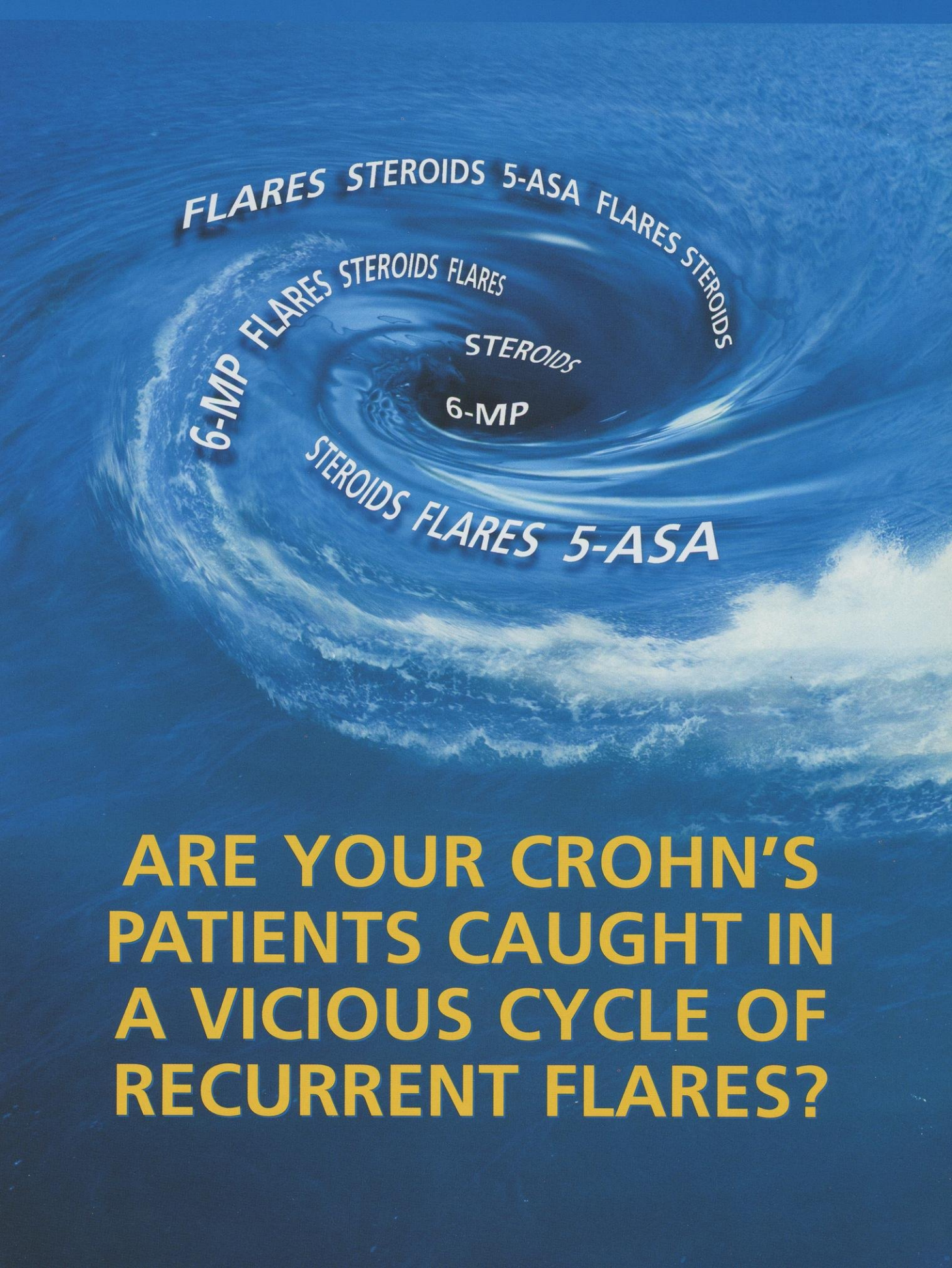

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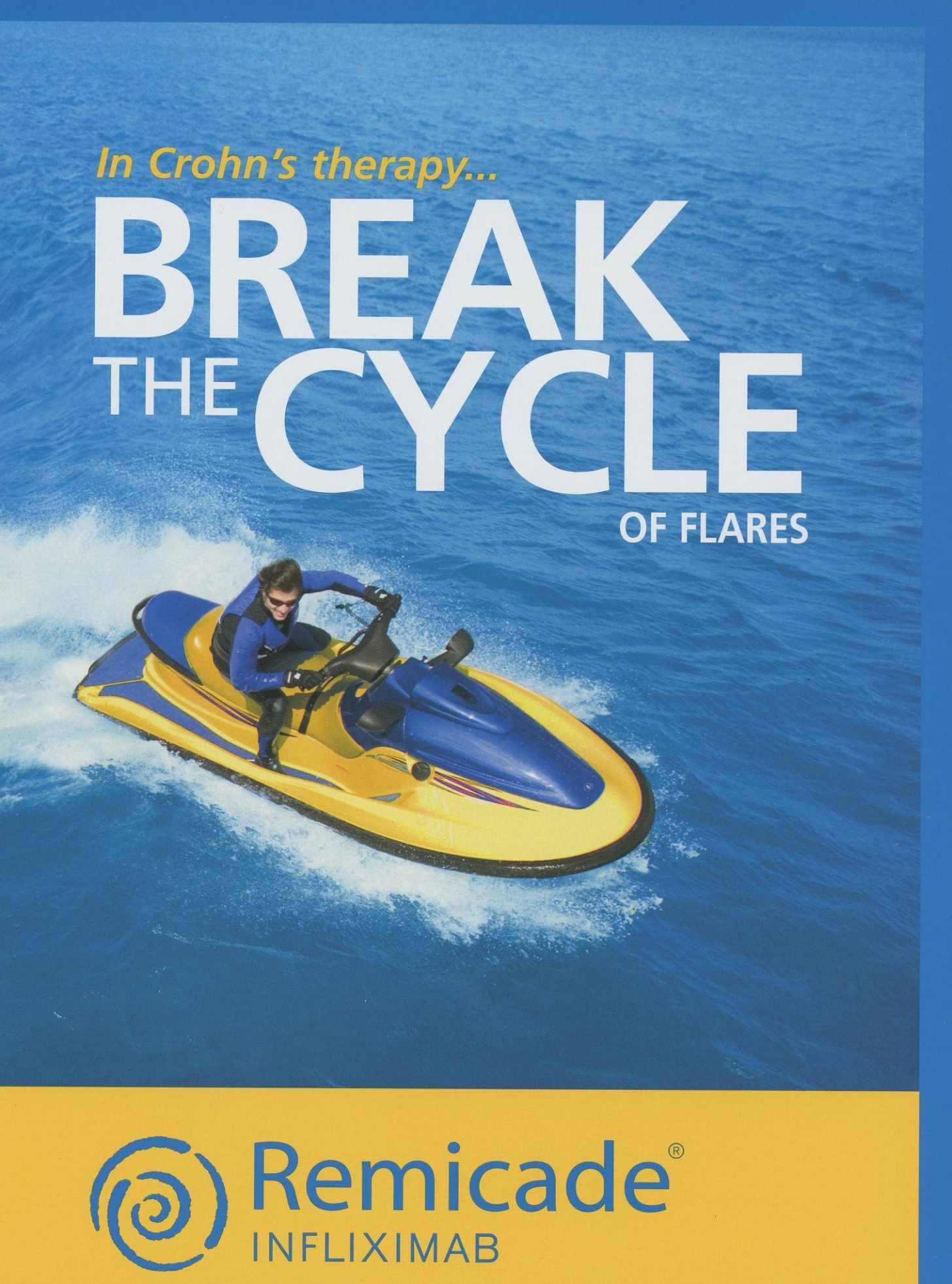

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IMPORTANT SAFETY INFORMATION

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.

TUBERCULOSIS (TB) (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL. PATIENTS SHOULD BE EVALUATED FOR LATENT TB INFECTION WITH A SKIN TEST.[2] TREATMENT OF LATENT TB INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their disease, could predispose them to infections. Cases of sepsis, pneumonia, histoplasmosis, coccidioidomycosis, listeriosis, and pneumocystosis have been reported. For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of REMICADE should be considered before initiation of therapy. REMICADE should not be given to patients with a clinically important, active infection. Use with caution in patients with a history of infection. Monitor patients for infection during or after treatment. Discontinue REMICADE if a patient develops a serious infection.

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. REMICADE has been associated with reactivation of hepatitis B. Chronic carriers of hepatitis B should be evaluated and monitored prior to and during treatment.

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.

REMICADE should not be administered to patients with hypersensitivity to murine proteins or other components of the product. 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.

TNF inhibitors, including REMICADE, have been associated with rare cases of new or exacerbated symptoms of demyelinating disorders including multiple sclerosis, and optic neuritis, 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.

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 rheumatoid arthritis and Crohn's disease may be at higher risk for developing lymphoma. 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. 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.

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WARNING
RISK OF INFECTIONS
TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

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 administered to patients with known hypersensitivity to any murine proteins or other component of the product. **WARNINGS: RISK OF INFECTIONS (See boxed WARNING) SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*). CASES OF HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, TUBERCULOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY. SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT USE OF ANAKINRA AND ANOTHER TNFα-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 TNFα-BLOCKING AGENTS. THEREFORE, THE COMBINATION OF REMICADE AND ANAKINRA IS NOT RECOMMENDED. Hepatotoxicity** Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e., surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with REMICADE. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see *ADVERSE REACTIONS, Hepatotoxicity*). **Patients with Heart Failure** REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear (see *CONTRAINDICATIONS* and *ADVERSE REACTIONS, Patients with Heart Failure*). **Hematologic Events** Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. **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 Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted 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 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, Infusion-related Reactions*). **Neurologic Events** Infliximab 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. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system 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 all the TNFα-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis and Crohn's disease, 1 patient developed lymphoma among 1389 REMICADE-treated patients versus 0 among 483 control patients (median duration of follow-up 1.1 years). In the controlled and open-label portions of these clinical trials of REMICADE, 3 patients developed lymphomas (1 patient with rheumatoid arthritis and 2 patients with Crohn's disease) among 2410 patients (median duration of follow-up 1.1 years). In rheumatoid arthritis patients, this is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis and Crohn's disease, this is approximately 6-fold higher than expected in the general population. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Patients with Crohn's disease or rheumatoid arthritis, 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. The potential role of TNFα-blocking therapy in the development of malignancies is not known (see *ADVERSE REACTIONS, Malignancies*). No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving REMICADE; thus additional caution should be exercised in considering REMICADE treatment of these patients. **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. **Information for Patients** Patients should be provided the REMICADE Patient Information Sheet and provided an opportunity to read it 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 reading of the Patient Information Sheet be discussed. **Drug Interactions** Concurrent administration of etanercept (another TNFα-blocking agent) and anakinra (an interleukin-1 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 TNFα-blocking agents (including REMICADE) used in combination with anakinra may also result in similar toxicities (see *WARNINGS, RISK OF INFECTIONS*). 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, folic acid, corticosteroids, and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA, and aminosalicylates. Patients with Crohn's disease 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 Crohn's disease 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 TNFα to evaluate tumorigenicity. cV1q is an analogous antibody that inhibits the function of TNFα 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 Crohn's disease. 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 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-TNF analogous 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 infliximab 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, 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** Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease have not been established. **Geriatric Use** In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients aged 65 or older compared to younger patients although the incidence of serious adverse events in patients aged 65 or older was higher in both infliximab and control groups compared to younger patients. In Crohn's disease and ankylosing spondylitis 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 2629 patients, including 1484 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most common reason 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 rheumatoid arthritis 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 Crohn's disease. **Infusion-related Reactions** *Acute 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. 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 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. *Reactions following readministration.* In a study where 37 of 41 patients with Crohn's disease 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 53 weeks of follow-up) and in 28% of placebo-treated patients (average of 47 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 all clinical trials, three opportunistic infections were reported; coccidioidomycosis (which resulted in death), nocardiosis, and cytomegalovirus. Tuberculosis was reported in six patients, one of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF INFECTIONS*). In the RA trials at 1 year, 5.3% of patients receiving infliximab and MTX every 8 weeks developed serious infections as compared to 3.4% of placebo patients receiving MTX. Of 924 patients receiving infliximab, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in placebo arm respectively. During the 54 weeks Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess. In post-marketing experience, 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. **Autoantibodies/Lupus-like Syndrome** Approximately half of infliximab-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 infliximab-treated patients compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon. **Malignancies** Among 2410 patients

with moderately to severely active rheumatoid arthritis and Crohn's disease treated with REMICADE in clinical trials with a median of 1.1 years of follow-up, 3 patients developed lymphomas, for a rate of 0.07 cases per 100 patient-years of follow-up in patients with rheumatoid arthritis and 0.12 cases per 100 patient-years of follow up in the combined clinical trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold higher in the RA clinical trial population and 6-fold higher in the overall clinical trial population than expected in an age-, gender-, and race-matched general population based on the Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. An increased rate of lymphoma up to several fold has been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be further increased in patients with more severe disease activity. Other than lymphoma, 13 patients developed malignancies, which was similar in number to what would be expected in the general population. Of these, the most common malignancies were breast, colorectal, and melanoma. (See *WARNINGS, Malignancies.*) 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 ≤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 one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. 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 rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. 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 has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive) (see *WARNINGS, Hepatotoxicity*). In clinical trials in RA, Crohn's disease and ankylosing spondylitis, 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. ALT elevations ≥5 times the upper limit of normal were observed in 1% of patients receiving REMICADE.In rheumatoid arthritis clinical trials, 34% of patients who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (≥2 but <3 times the upper limit of normal) elevations in ALT compared to 24% of patients treated with placebo + MTX. ALT elevations ≥3 times the upper limit of normal were observed in 3.9% of patients who received REMICADE + MTX compared with 3.2% of patients who received MTX alone (median follow up approximately 1 year). In Crohn's disease clinical trials (median follow up 54 weeks), 39% of patients receiving REMICADE-maintenance experienced mild to moderate elevations in ALT, compared to 34% of patients treated with placebo-maintenance. ALT elevations ≥3 times the upper limit of normal were observed in 5.0% of patients who received REMICADE-maintenance compared with 4.0% of patients who received placebo-maintenance. In an ankylosing spondylitis clinical trial in which patients were not receiving MTX, 40% of patients who received REMICADE experienced mild to moderate elevations in ALT compared to 13% of patients treated with placebo. ALT elevations ≥3 times the upper limit of normal were observed in 12 (6%) REMICADE-treated patients compared to none in placebo-treated patients. **Other Adverse Reactions** Safety data are available from 2629 REMICADE-treated patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 202 with ankylosing spondylitis and 17 with other conditions. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis 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. 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 ≥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 and 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. The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see *WARNINGS, Hematologic Events*), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*). 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. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCE: 1.** 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.

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In Crohn's therapy...

BREAK THE CYCLE OF FLARES

References: 1. Data on file, Centocor, 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.

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Based on ACT 1 and ACT 2 data[1,2*]

BREAK THE CYCLE OF FLARES

NOW APPROVED FOR Ulcerative Colitis

At 8 Weeks in ACT 1[1†]

Response

69% achieved clinical response

Remission

39% achieved clinical remission

Healing

62% achieved mucosal healing

At Week 8, placebo-infusion response, remission, and healing rates were 37%, 15%, and 34%, respectively ($P<0.001$ for all comparisons to the 5-mg/kg arm).

In both studies, greater percentages of patients in both REMICADE groups achieved a clinical response, a sustained clinical response (response at both Weeks 8 and 30), clinical remission, and other assessed clinical outcomes than in the placebo-infusion groups.[1]

REMICADE is indicated for reducing signs and symptoms, achieving 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.

Please see Important Safety Information contained in this advertisement.

*The safety and efficacy of REMICADE were assessed in ACT 1 (N=364) and ACT 2 (N=364) (ACT = A Colitis Trial), 2 randomized, double-blind, placebo-controlled, multicenter trials. These studies were conducted in patients with moderately-to-severely active ulcerative colitis who had an inadequate response or were intolerant to conventional therapy. Patients presented with a Mayo score between 6 and 12, and an endoscopy subscore of ≥2. Prior failed or intolerable therapies in ACT 1 included oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA). In ACT 2, patients had failed or were intolerant to these treatments and/or aminosalicylates (5-ASA) alone. In both studies, patients were randomized to the following treatment groups: REMICADE 5 mg/kg, REMICADE 10 mg/kg, or placebo infusion. In ACT 1, infusions were administered at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46. Patients in ACT 2 were infused at Weeks 0, 2, 6, 14, and 22. Final efficacy evaluations were completed 8 weeks following the last infusion. Concomitant treatment with stable doses of 5-ASA, corticosteroids, and/or immunomodulators was permitted throughout the study. Corticosteroid tapering was allowed beginning at Week 8. The primary efficacy endpoint was clinical response at Week 8 (decrease in Mayo score by ≥30% and ≥3 points, accompanied by a decrease in rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1). Remission was defined as a Mayo score ≤2 points with no individual subscore >1. Mucosal healing was defined as an endoscopy subscore of 0 or 1.

†In ACT 1, after 3 doses of REMICADE 5 mg/kg at 0, 2, and 6 weeks. The recommended dose of REMICADE is 5 mg/kg at 0, 2, and 6 weeks followed by 5 mg/kg every 8 weeks thereafter.

Remicade®
INFLIXIMAB

The only anti–TNF-α therapy with experience in more than 634,000 patients across all uses[2*]

IMPORTANT SAFETY INFORMATION

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 administered to patients with hypersensitivity to murine proteins or other components of the product.

Risk of Infection

TUBERCULOSIS (TB) (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL. PATIENTS SHOULD BE EVALUATED FOR LATENT TB INFECTION WITH A SKIN TEST.[3] TREATMENT OF LATENT TB INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE. ACTIVE TB HAS DEVELOPED IN PATIENTS RECEIVING REMICADE WHO WERE TUBERCULIN SKIN TEST–NEGATIVE PRIOR TO RECEIVING REMICADE. MONITOR PATIENTS RECEIVING REMICADE FOR SIGNS AND SYMPTOMS OF ACTIVE TB, INCLUDING THOSE WHO ARE TUBERCULIN SKIN TEST–NEGATIVE.

Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their disease, could predispose them to infections. Cases of sepsis, pneumonia, histoplasmosis, coccidioidomycosis, listeriosis, and pneumocystosis have been reported. For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of REMICADE should be considered before initiation of therapy. REMICADE should not be given to patients with a clinically important, active infection. Use with caution in patients with a history of infection. Monitor patients for infection during or after treatment. Discontinue REMICADE if a patient develops a serious infection.

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. REMICADE has been associated with reactivation of hepatitis B. Chronic carriers of hepatitis B should be evaluated and monitored prior to and during treatment.

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 should not be administered to patients with hypersensitivity to murine proteins or other components of the product. 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, and optic neuritis, 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.

Malignancies

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 rheumatoid arthritis and Crohn's disease 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.

Please see brief summary of the full prescribing information starting on the adjacent page.

*As of February 2005. Uses included rheumatoid arthritis, Crohn's disease, ankylosing spondylitis, psoriatic arthritis, and ulcerative colitis.

References: 1. REMICADE® (infliximab) Prescribing Information. Centocor, Inc. September 2005. **2.** Data on file. Centocor, Inc. **3.** 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.

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REMICADE® (infliximab) for IV Injection Brief Summary See package insert for full prescribing information.

WARNING
RISK OF INFECTIONS
TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE WARNINGS). ANTI-TUBERCULOSIS TREATMENT OF PATIENTS WITH A REACTIVE TUBERCULIN SKIN TEST REDUCES THE RISK OF TB REACTIVATION IN PATIENTS RECEIVING TREATMENT WITH REMICADE. HOWEVER, ACTIVE TUBERCULOSIS HAS DEVELOPED IN PATIENTS RECEIVING REMICADE WHO WERE TUBERCULIN SKIN TEST NEGATIVE PRIOR TO RECEIVING REMICADE. PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE. PHYSICIANS SHOULD MONITOR PATIENTS RECEIVING REMICADE FOR SIGNS AND SYMPTOMS OF ACTIVE TUBERCULOSIS, INCLUDING PATIENTS WHO ARE TUBERCULIN SKIN TEST NEGATIVE.

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 administered to patients with known hypersensitivity to any murine proteins or other component of the product. **WARNINGS: RISK OF INFECTIONS (See boxed *WARNING*) SERIOUS INFECTIONS, INCLUDING SEPSIS AND PNEUMONIA, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS. REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*). CASES OF TUBERCULOSIS, HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, OTHER BACTERIAL, MYCOBACTERIAL AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY. SERIOUS INFECTIONS WERE SEEN IN CLINICAL STUDIES WITH CONCURRENT USE OF ANAKINRA AND ANOTHER TNFα-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 TNFα-BLOCKING AGENTS. THEREFORE, THE COMBINATION OF REMICADE AND ANAKINRA IS NOT RECOMMENDED. Hepatotoxicity** Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e., surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with REMICADE. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see *ADVERSE REACTIONS, Hepatotoxicity*). **Patients with Heart Failure** REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg REMICADE, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking REMICADE. There have also been rare post-marketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer REMICADE to patients with heart failure, they should be closely monitored during therapy, and REMICADE should be discontinued if new or worsening symptoms of heart failure appear. (See *CONTRAINDICATIONS* and *ADVERSE REACTIONS, Patients with Heart Failure.*) **Hematologic Events** Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities. **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 Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted 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 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, 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. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system 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 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, and ulcerative colitis, 14 patients were diagnosed with malignancies among 2897 REMICADE-treated patients vs. 1 among 1262 control patients (at a rate of 0.65/100 patient-years among REMICADE-treated patients vs. a rate of 0.13/100 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, 4 patients developed lymphomas among 4292 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1265 control patients (median duration of follow-up 0.5 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 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis, 4 lymphomas were observed for a rate of 0.11 cases per 100 patient-years of follow-up, which is approximately 5-fold higher than expected in the general population. Patients with Crohn's disease or rheumatoid arthritis, 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 an exploratory clinical trial evaluating the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking (see *ADVERSE REACTIONS, Malignancies*). 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. **Information for Patients** Patients should be provided the REMICADE Patient Information Sheet and provided an opportunity to read it 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 reading of the Patient Information Sheet be discussed. **Drug Interactions** Concurrent administration of etanercept (another TNFα-blocking agent) and anakinra (an interleukin-1 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 TNFα-blocking agents (including REMICADE) used in combination with anakinra may also result in similar toxicities (see *WARNINGS, RISK OF INFECTIONS*). 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, 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 nonsteroidal anti-inflammatory agents, folic acid and corticosteroids. Patients with Crohn's disease 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 Crohn's disease 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 TNFα to evaluate tumorigenicity. cV1q is an analogous antibody that inhibits the function of TNFα 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 Crohn's disease. 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 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-TNF analogous 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, 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** Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease or ulcerative colitis have not been established. **Geriatric Use** In rheumatoid arthritis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients aged 65 or older 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 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. 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 3263 patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, 484 with ulcerative colitis and 17 patients with other conditions), including 1484 patients exposed beyond 30 weeks and 296 exposed beyond one year. The most common reason 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 rheumatoid arthritis 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 Crohn's disease. **Infusion-related Reactions** *Acute 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. 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 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. *Reactions following readministration.* In a study where 37 of 41 patients with Crohn's disease 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

(continued)

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 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 miliary 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 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 Crohn's disease developed a new fistula-related abscess. In REMICADE clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 19% of REMICADE-treated patients (average of 27 weeks of follow-up) and in 14% of placebo-treated patients (average 22 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies. In post-marketing experience, 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. **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 an exploratory randomized controlled clinical trial involving 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 rheumatoid arthritis and Crohn's disease. 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 ≤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 Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. 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 rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. 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 has occurred in patients receiving REMICADE who are chronic carriers of this virus (i.e., surface antigen positive) (see *WARNINGS, Hepatotoxicity*). In clinical trials in RA, Crohn's disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis 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 rheumatoid arthritis 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 ≥5 times ULN were observed in <1% of patients in both REMICADE + MTX and MTX alone groups. In Crohn's disease 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 ulcerative colitis clinical trials (median follow up 30 weeks), 15% 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 ankylosing spondylitis clinical trial (median follow up 24 weeks) 40% of patients receiving REMICADE experienced elevations in ALT at >1 to <3 times the ULN compared to 13% of patients treated with placebo. ALT elevations ≥3 times the ULN were observed in 6% 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 a psoriatic arthritis clinical trial (median follow up 24 weeks for REMICADE group and 18 weeks in placebo group) 42% 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 5% 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. **Other Adverse Reactions** Safety data are available from 3263 REMICADE-treated patients, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 150 with psoriatic arthritis, and 17 with other conditions. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease patients except for abdominal pain, which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. 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 ≥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 and 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. The following adverse events have been reported during post-approval use of REMICADE: neutropenia (see *WARNINGS, Hematologic Events*), interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*). 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. **OVERDOSAGE:** Single doses up to 20 mg/kg have been administered without any direct toxic effect. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately. **REFERENCE: 1.** 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.

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In moderate-to-severe Crohn's disease...

WHEN 5-ASAs FAIL,*

WHAT SHOULD YOU CONSIDER

*Conventional therapies include 5-ASAs, corticosteroids, and immunomodulators

IMPORTANT INFORMATION:

REMICADE is contraindicated in patients with moderate or 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.

TUBERCULOSIS (TB) (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL. PATIENTS SHOULD BE EVALUATED FOR LATENT TB INFECTION WITH A SKIN TEST.[1] TREATMENT OF LATENT TB INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their disease, could predispose them to infections. Cases of sepsis, histoplasmosis, coccidioidomycosis, listeriosis, and pneumocystosis have been reported. For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of REMICADE should be considered before initiation of therapy. REMICADE should not be given to patients with a clinically important, active infection. Use with caution in patients with a history of infection. Patients should be monitored for infection while on or after treatment with REMICADE. Discontinue REMICADE if a patient develops a serious infection.

REMICADE should not be administered to patients with hypersensitivity to murine proteins or other components of the product. 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.

TNF agents, including REMICADE, have been associated with rare cases of new or exacerbated symptoms of demyelinating disorders, including multiple sclerosis, optic neuritis, and seizure. Exercise caution when considering REMICADE in all patients with these disorders.

The only anti-TNF therapy with experience in more than 500,000 patients across all indications[2]

WHEN

† Results from ACCENT I, a 1-year, randomized, multicenter, double-blind trial of REMICADE in 545 patients with moderately-to-severely active Crohn's disease (baseline Crohn's Disease Activity Index [CDAI] ≥220 and ≤400). At baseline, median CDAI score was 295, and 90% of all patients were receiving stable doses of 1 or more concomitant therapies, including 5-ASA, corticosteroids, and 6-MP/AZA. All patients received an initial dose of REMICADE 5 mg/kg. Patients were then randomized based on clinical response at Week 2 to one of three treatment groups through Week 54: placebo at Weeks 2 and 6, and q 8 weeks thereafter (n=102); REMICADE 5 mg/kg at Weeks 2 and 6, and q 8 weeks thereafter (n=104); REMICADE 5 mg/kg at Weeks 2 and 6, followed by 10 mg/kg q 8 weeks thereafter (n=105). The coprimary endpoints of the study were the proportion of patients responding at Week 2 who were in remission at Week 30 and the time to loss of response through Week 54.

‡ Remission defined as CDAI <150, without crossover to another treatment due to treatment failure, treatment with medication or dosage change not allowed by protocol due to

5-ASAs FAIL,* CONSIDER REMICADE

*REMICADE is indicated in patients with moderately-to-severely active Crohn's disease who have had an inadequate response to conventional therapies which include 5-ASAs.

RESULTS FROM ACCENT I†...

- **Induction and maintenance of clinical remission‡**

ACCENT I ALSO SHOWED...

- **Mucosal healing achieved§**
- **Reduced or eliminated steroid use[2]**

In Fistulizing Crohn's Disease

RESULTS FROM ACCENT II...

- **Reduced surgeries and hospitalization[2]‖**

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in 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 patients with fistulizing Crohn's disease.

lack of efficacy or loss of response, or Crohn's disease-related surgeries. The CDAI score is a weighted sum of 8 different Crohn's disease-related measures: extraintestinal manifestations; abdominal mass; antidiarrheal drug use; body weight; hematocrit; number of liquid or soft stools; abdominal pain/cramps; and general well-being.

§ Based on a subset of 78 patients, who participated in ACCENT I, who had mucosal ulceration at baseline.

‖ Results from ACCENT II, a 1-year, randomized, double-blind trial of REMICADE in 296 patients with at least one draining, enterocutaneous fistula. At baseline, approximately 80% of patients were receiving stable doses of 1 or more concomitant Crohn's disease-related therapies. All patients received an initial 3-dose induction of REMICADE 5 mg/kg at Weeks 0, 2, and 6. Patients were then randomized based on clinical response at Week 14 to receive REMICADE 5 mg/kg q 8 weeks or placebo through Week 46. The primary endpoint of the study was time to loss of fistula response through Week 54 among patients responding at Week 14.

References: 1. 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. **2.** Data on file, Centocor, Inc.

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WARNING
RISK OF INFECTIONS
TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE *WARNINGS*). PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

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 administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS: RISK OF INFECTIONS (See boxed WARNING) SERIOUS INFECTIONS, INCLUDING SEPSIS, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*). CASES OF HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, TUBERCULOSIS, OTHER BACTERIAL, MYCOBACTERIAL, AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

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*).

Hypersensitivity REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. 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 Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted 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 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, Infusion-related Reactions*). **Neurologic Events** Infliximab 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. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders.

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*). **Malignancy** Patients with long duration of Crohn's disease or rheumatoid arthritis and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas (see *ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease*). The impact of treatment with REMICADE on these phenomena is unknown. **Vaccinations** No data are available on the response to vaccination 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. **Information for Patients** Patients should be provided the REMICADE Patient Information Sheet and provided an opportunity to read it 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 reading of the Patient Information Sheet be discussed. **Drug Interactions** 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, folic acid, corticosteroids, and/or narcotics. Concomitant Crohn's disease medications were antibiotics, antivirals, corticosteroids, 6-MP/AZA, and aminosalicylates. Patients with Crohn's disease 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 Crohn's disease 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 TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα 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 Crohn's disease. 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 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-TNF analogous 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 infliximab 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, 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** Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease have not been established. **Geriatric Use** In the ATTRACT study, no overall differences were observed in effectiveness or safety in 72 patients aged 65 or older compared to younger patients. In Crohn's disease 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 1678 patients, including 842 patients exposed beyond 30 weeks and 295 exposed beyond one year. The most common reason 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 rheumatoid arthritis 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 Crohn's disease. **Infusion-related Reactions** Acute 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. 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 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. *Reactions following readministration.* In a study where 37 of 41 patients with Crohn's disease 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 35% of REMICADE-treated patients (average of 53 weeks of follow-up) and in 26% of placebo-treated patients (average of 41 weeks of follow-up). When longer observation of patients on REMICADE was accounted for, the event rate was similar for both groups. The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis was observed with REMICADE compared with placebo in clinical studies. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. Three opportunistic infections were reported; coccidioidomycosis (which resulted in death), nocardiosis and cytomegalovirus. Tuberculosis was reported in two patients, one of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF INFECTIONS*). During the 54 week ACCENT II trial, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess. In post-marketing experience, 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. **Autoantibodies/Lupus-like Syndrome** Approximately 52% of 1261 infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately 19% of 129 placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of 1507 infliximab-treated patients compared with 0% of 162 placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon. **Malignancies/Lymphoproliferative Disease** In completed clinical studies of REMICADE for up to 102 weeks, 18 of 1678 patients developed 19 new or recurrent malignancies of various types, such as non-Hodgkin's B-cell lymphoma, breast, melanoma, squamous, rectal and basal cell. There are insufficient data to determine whether REMICADE contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied[2,3] (see *PRECAUTIONS, Malignancy*). **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 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 one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*). Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. 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. **Other Adverse Reactions** Safety data are available from 1678 REMICADE-treated patients, including 555 with rheumatoid arthritis, 1106 with Crohn's disease, and 17 with conditions other than rheumatoid arthritis or Crohn's disease. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis and Crohn's disease patients except for abdominal pain which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=81; average weeks of follow-up 73) and REMICADE-treated patients (n=430; average weeks of follow-up 82), respectively, are: *Gastrointestinal:* Abdominal pain: 12, 17; Nausea: 23, 24; Diarrhea: 19, 19; Dyspepsia: 9, 10. *Respiratory:* Upper respiratory tract infection: 35, 40; Pharyngitis: 12, 17; Sinusitis: 7, 20; Coughing: 9, 18; Rhinitis: 14, 14; Dyspnea: 2, 6; *Skin and appendage disorders:* Rash: 7, 18; Pruritis: 2, 9; *Body as a whole—general disorders:* Fatigue: 9, 13; Chest pain: 6, 7. *Resistance mechanism disorders:* Fever: 11, 13; Abcess: 5, 6; Moniliasis: 2, 8. *Central and peripheral nervous system disorders:* Headache: 21, 29; *Musculoskeletal system disorders:* Arthralgia: 7, 13; Back pain: 5, 13. *Psychiatric disorders:* Insomnia: 4, 6; Depression: 2, 8. *Urinary system disorders:* Urinary tract infection: 12, 14. *Cardiovascular disorders, general:* Hypertension 6, 10. 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 ≥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, 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. A greater proportion of patients enrolled into the ATTRACT study who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (≥2 but <3 times the upper limit of normal) elevations in AST or ALT (49% and 47%, respectively) compared to patients treated with placebo + MTX (27% and 35%, respectively). Six (1.8%) patients treated with REMICADE + MTX experienced more prolonged elevations in their ALT. The following adverse events have been reported during post-approval use of REMICADE: agranulocytosis, interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, vasculitis (primarily cutaneous), Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurologic events have also been observed, see *WARNINGS, Neurologic Events*). 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.

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

REFERENCES: 1. 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. 2. Bernstein C, Blanchard JF, Kliewer E, et al. Cancer risk in patients with inflammatory bowel disease. *Cancer* 2001;91:854–862. 3. Jones M, Symmons D, Finn J, et al. Does exposure to immunosuppressive therapy increase the 10 year malignancy and mortality risks in rheumatoid arthritis? A matched cohort study. *Br J Rheum* 1996;35:738–745.

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IN03475

In moderate-to-severe Crohn's disease...

WHEN 5-ASAs FAIL,*

WHAT SHOULD YOU CONSIDER

*Conventional therapies include 5-ASAs, corticosteroids, and immunomodulators

IMPORTANT INFORMATION:

REMICADE is contraindicated in patients with moderate or 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.

TUBERCULOSIS (TB) (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL. PATIENTS SHOULD BE EVALUATED FOR LATENT TB INFECTION WITH A SKIN TEST.[1] TREATMENT OF LATENT TB INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their disease, could predispose them to infections. Cases of sepsis, histoplasmosis, coccidioidomycosis, listeriosis, and pneumocystosis have been reported. For patients who have resided in regions where histoplasmosis or coccidioidomycosis is endemic, the benefits and risks of REMICADE should be considered before initiation of therapy. REMICADE should not be given to patients with a clinically important, active infection. Use with caution in patients with a history of infection. Patients should be monitored for infection while on or after treatment with REMICADE. Discontinue REMICADE if a patient develops a serious infection.

REMICADE should not be administered to patients with hypersensitivity to murine proteins or other components of the product. 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.

TNF agents, including REMICADE, have been associated with rare cases of new or exacerbated symptoms of demyelinating disorders, including multiple sclerosis, optic neuritis, and seizure. Exercise caution when considering REMICADE in all patients with these disorders.

The only anti-TNF therapy with experience in more than 500,000 patients across all indications[2]

WHEN

† Results from ACCENT I, a 1-year, randomized, multicenter, double-blind trial of REMICADE in 545 patients with moderately-to-severely active Crohn's disease (baseline Crohn's Disease Activity Index [CDAI] ≥220 and ≤400). At baseline, median CDAI score was 295, and 90% of all patients were receiving stable doses of 1 or more concomitant therapies, including 5-ASA, corticosteroids, and 6-MP/AZA. All patients received an initial dose of REMICADE 5 mg/kg. Patients were then randomized based on clinical response at Week 2 to one of three treatment groups through Week 54: placebo at Weeks 2 and 6, and q 8 weeks thereafter (n=102); REMICADE 5 mg/kg at Weeks 2 and 6, and q 8 weeks thereafter (n=104); REMICADE 5 mg/kg at Weeks 2 and 6, followed by 10 mg/kg q 8 weeks thereafter (n=105). The coprimary endpoints of the study were the proportion of patients responding at Week 2 who were in remission at Week 30 and the time to loss of response through Week 54.

‡ Remission defined as CDAI <150, without crossover to another treatment due to treatment failure, treatment with medication or dosage change not allowed by protocol due to

5-ASAs FAIL,* CONSIDER REMICADE

*REMICADE is indicated in patients with moderately-to-severely active Crohn's disease who have had an inadequate response to conventional therapies which include 5-ASAs.

RESULTS FROM ACCENT I†...

- **Induction and maintenance of clinical remission‡**

ACCENT I ALSO SHOWED...

- **Mucosal healing achieved§**
- **Reduced or eliminated steroid use[2]**

In Fistulizing Crohn's Disease

RESULTS FROM ACCENT II...

- **Reduced surgeries and hospitalization[2]‖**

REMICADE is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in 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 patients with fistulizing Crohn's disease.

lack of efficacy or loss of response, or Crohn's disease-related surgeries. The CDAI score is a weighted sum of 8 different Crohn's disease-related measures: extraintestinal manifestations; abdominal mass; antidiarrheal drug use; body weight; hematocrit; number of liquid or soft stools; abdominal pain/cramps; and general well-being.

§ Based on a subset of 78 patients, who participated in ACCENT I, who had mucosal ulceration at baseline.

‖ Results from ACCENT II, a 1-year, randomized, double-blind trial of REMICADE in 296 patients with at least one draining, enterocutaneous fistula. At baseline, approximately 80% of patients were receiving stable doses of 1 or more concomitant Crohn's disease-related therapies. All patients received an initial 3-dose induction of REMICADE 5 mg/kg at Weeks 0, 2, and 6. Patients were then randomized based on clinical response at Week 14 to receive REMICADE 5 mg/kg q 8 weeks or placebo through Week 46. The primary endpoint of the study was time to loss of fistula response through Week 54 among patients responding at Week 14.

References: 1. 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. **2.** Data on file, Centocor, Inc.

Remicade®

INFLIXIMAB

Please see brief summary of prescribing information on adjacent page.

REMICADE® (infliximab) for IV Injection Brief Summary See package insert for full prescribing information.

WARNING
RISK OF INFECTIONS
TUBERCULOSIS (FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION), INVASIVE FUNGAL INFECTIONS, AND OTHER OPPORTUNISTIC INFECTIONS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE *WARNINGS*). PATIENTS SHOULD BE EVALUATED FOR LATENT TUBERCULOSIS INFECTION WITH A TUBERCULIN SKIN TEST.[1] TREATMENT OF LATENT TUBERCULOSIS INFECTION SHOULD BE INITIATED PRIOR TO THERAPY WITH REMICADE.

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 administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS: RISK OF INFECTIONS (See boxed WARNING) SERIOUS INFECTIONS, INCLUDING SEPSIS, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS. SOME OF THESE INFECTIONS HAVE BEEN FATAL. MANY OF THE SERIOUS INFECTIONS IN PATIENTS TREATED WITH REMICADE HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR CROHN'S DISEASE OR RHEUMATOID ARTHRITIS, COULD PREDISPOSE THEM TO INFECTIONS. REMICADE SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT, ACTIVE INFECTION. CAUTION SHOULD BE EXERCISED WHEN CONSIDERING THE USE OF REMICADE IN PATIENTS WITH A CHRONIC INFECTION OR A HISTORY OF RECURRENT INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON OR AFTER TREATMENT WITH REMICADE. NEW INFECTIONS SHOULD BE CLOSELY MONITORED. IF A PATIENT DEVELOPS A SERIOUS INFECTION, REMICADE THERAPY SHOULD BE DISCONTINUED (see *ADVERSE REACTIONS, Infections*). CASES OF HISTOPLASMOSIS, COCCIDIOIDOMYCOSIS, LISTERIOSIS, PNEUMOCYSTOSIS, TUBERCULOSIS, OTHER BACTERIAL, MYCOBACTERIAL, AND FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS OR COCCIDIOIDOMYCOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

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*).

Hypersensitivity REMICADE has been associated with hypersensitivity reactions that vary in their time of onset. 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 Crohn's disease patients 3 to 12 days after REMICADE therapy was reinstituted 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 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, Infusion-related Reactions*). **Neurologic Events** Infliximab 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. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system demyelinating or seizure disorders.

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*). **Malignancy** Patients with long duration of Crohn's disease or rheumatoid arthritis and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas (see *ADVERSE REACTIONS, Malignancies/Lymphoproliferative Disease*). The impact of treatment with REMICADE on these phenomena is unknown. **Vaccinations** No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines in patients receiving anti-TNF therapy. 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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 Crohn's disease. 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 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-TNF analogous 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 infliximab 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, 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** Safety and effectiveness of REMICADE in patients with juvenile rheumatoid arthritis and in pediatric patients with Crohn's disease have not been established. **Geriatric Use** In the ATTRACT study, no overall differences were observed in effectiveness or safety in 72 patients aged 65 or older compared to younger patients. In Crohn's disease 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 1678 patients, including 842 patients exposed beyond 30 weeks and 295 exposed beyond one year. The most common reason 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 rheumatoid arthritis 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 Crohn's disease. **Infusion-related Reactions** Acute 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. 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 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. *Reactions following readministration.* In a study where 37 of 41 patients with Crohn's disease 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 35% of REMICADE-treated patients (average of 53 weeks of follow-up) and in 26% of placebo-treated patients (average of 41 weeks of follow-up). When longer observation of patients on REMICADE was accounted for, the event rate was similar for both groups. The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. No increased risk of serious infections or sepsis was observed with REMICADE compared with placebo in clinical studies. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. Three opportunistic infections were reported; coccidioidomycosis (which resulted in death), nocardiosis and cytomegalovirus. Tuberculosis was reported in two patients, one of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of the cases of tuberculosis occurred within the first two months after initiation of therapy with infliximab and may reflect recrudescence of latent disease (see *WARNINGS, RISK OF INFECTIONS*). During the 54 week ACCENT II trial, 15% of patients with fistulizing Crohn's disease developed a new fistula-related abscess. In post-marketing experience, 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. **Autoantibodies/Lupus-like Syndrome** Approximately 52% of 1261 infliximab-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately 19% of 129 placebo-treated patients. Anti-dsDNA antibodies were newly detected in approximately 17% of 1507 infliximab-treated patients compared with 0% of 162 placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon. **Malignancies/Lymphoproliferative Disease** In completed clinical studies of REMICADE for up to 102 weeks, 18 of 1678 patients developed 19 new or recurrent malignancies of various types, such as non-Hodgkin's B-cell lymphoma, breast, melanoma, squamous, rectal and basal cell. There are insufficient data to determine whether REMICADE contributed to the development of these malignancies. The observed rates and incidences were similar to those expected for the populations studied[2,3] (see *PRECAUTIONS, Malignancy*). **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 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 one to two years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving REMICADE after drug-free intervals >16 weeks. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*). Antibody development was lower among rheumatoid arthritis and Crohn's disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX. 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. **Other Adverse Reactions** Safety data are available from 1678 REMICADE-treated patients, including 555 with rheumatoid arthritis, 1106 with Crohn's disease, and 17 with conditions other than rheumatoid arthritis or Crohn's disease. Adverse events reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are listed below. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis and Crohn's disease patients except for abdominal pain which occurred in 26% of REMICADE-treated patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons. The percentages of adverse events for placebo-treated patients (n=81; average weeks of follow-up 73) and REMICADE-treated patients (n=430; average weeks of follow-up 82), respectively, are: *Gastrointestinal:* Abdominal pain: 12, 17; Nausea: 23, 24; Diarrhea: 19, 19; Dyspepsia: 9, 10. *Respiratory:* Upper respiratory tract infection: 35, 40; Pharyngitis: 12, 17; Sinusitis: 7, 20; Coughing: 9, 18; Rhinitis: 14, 14; Dyspnea: 2, 6; *Skin and appendage disorders:* Rash: 7, 18; Pruritis: 2, 9; *Body as a whole—general disorders:* Fatigue: 9, 13; Chest pain: 6, 7. *Resistance mechanism disorders:* Fever: 11, 13; Abcess: 5, 6; Moniliasis: 2, 8. *Central and peripheral nervous system disorders:* Headache: 21, 29; *Musculoskeletal system disorders:* Arthralgia: 7, 13; Back pain: 5, 13. *Psychiatric disorders:* Insomnia: 4, 6; Depression: 2, 8. *Urinary system disorders:* Urinary tract infection: 12, 14. *Cardiovascular disorders, general:* Hypertension 6, 10. 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 ≥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, 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. A greater proportion of patients enrolled into the ATTRACT study who received REMICADE + MTX experienced transient mild (<2 times the upper limit of normal) or moderate (≥2 but <3 times the upper limit of normal) elevations in AST or ALT (49% and 47%, respectively) compared to patients treated with placebo + MTX (27% and 35%, respectively). Six (1.8%) patients treated with REMICADE + MTX experienced more prolonged elevations in their ALT. The following adverse events have been reported during post-approval use of REMICADE: agranulocytosis, interstitial pneumonitis/fibrosis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, vasculitis (primarily cutaneous), Guillain-Barré syndrome, transverse myelitis, and neuropathies (additional neurological events have also been observed, see *WARNINGS, Neurologic Events*). 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.

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

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