Lyophilized Concentrate for Injection, for Intravenous Use

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

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**Warnings and Precautions:**

- **Malignancies (5.2)**
  - 10/2017

- **Ulcerative Colitis**: 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks. (2.3)

- **Pediatric Crohn’s Disease**: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.2)

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

- **Intravenous**: 10 mg/kg if they later lose their response. (2.1)

- **Pediatric Crohn’s Disease and Ulcerative Colitis**: most of whom were adolescent or young adult males. (5.2)

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**RECENT MAJOR CHANGES**

Warnings and Precautions: Malignancies (5.2) 10/2017

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**INDICATIONS AND USAGE**

REMICADE is a tumor necrosis factor (TNF) blocker indicated for:

- **Crohn’s Disease**: reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. (1.1)

- **Reducing signs and symptoms in patients with active disease**: (1.6)

- **Psoriatic Arthritis**: reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease. (1.8)

**DOSEAGE AND ADMINISTRATION**

**REMICADE** is administered by intravenous infusion over a period of not less than 2 hours.

- **Crohn’s Disease**: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. (2.1)

- **Pediatric Crohn’s Disease**: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.2)

- **Ulcerative Colitis**: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. (2.3)

**ADVERSE REACTIONS**

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

**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

**To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-888-FDA-1088 or www.fda.gov/medwatch.
FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

1 INDICATIONS AND USAGE
   1.1 Crohn's Disease
   1.2 Pediatric Crohn's Disease
   1.3 Ulcerative Colitis
   1.4 Pediatric Ulcerative Colitis
   1.5 Rheumatoid Arthritis
   1.6 Ankylosing Spondylitis
   1.7 Psoriatic Arthritis
   1.8 Plaque Psoriasis

2 DOSAGE AND ADMINISTRATION
   2.1 Crohn's Disease
   2.2 Pediatric Crohn's Disease
   2.3 Ulcerative Colitis
   2.4 Pediatric Ulcerative Colitis
   2.5 Rheumatoid Arthritis
   2.6 Ankylosing Spondylitis
   2.7 Psoriatic Arthritis
   2.8 Plaque Psoriasis
   2.9 Monitoring to Assess Safety
   2.10 Administration Instructions Regarding Infusion Reactions
   2.11 General Considerations and Instructions for Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
   5.1 Serious Infections
   5.2 Malignancies
   5.3 Hepatitis B Virus Reactivation
   5.4 Hepatotoxicity
   5.5 Patients with Heart Failure
   5.6 Hematologic Reactions
   5.7 Hypersensitivity
   5.8 Cardiovascular and Cerebrovascular Reactions During and After Infusion
   5.9 Neurologic Reactions
   5.10 Use with Anakinra
   5.11 Use with Abatacept
   5.12 Concurrent Administration with Other Biological Therapeutics
   5.13 Switching Between Biological Disease-Modifying Antirheumatic Drugs (DMARDs)
   5.14 Autoimmunity
   5.15 Live Vaccines/Therapeutic Infectious Agents

6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Postmarketing Experience

7 DRUG INTERACTIONS
   7.1 Use with Anakinra or Abatacept
   7.2 Use with Tocilizumab
   7.3 Use with Other Biological Therapeutics
   7.4 Methotrexate (MTX) and Other Concomitant Medications
   7.5 Immunosuppressants
   7.6 Cytochrome P450 Substrates
   7.7 Live Vaccines/Therapeutic Infectious Agents

8 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Nursing Mothers
   8.3 Pediatric Use
   8.4 Pediatric Use
   8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES
   14.1 Crohn's Disease
   14.2 Pediatric Crohn's Disease
   14.3 Ulcerative Colitis
   14.4 Pediatric Ulcerative Colitis
   14.5 Rheumatoid Arthritis
   14.6 Ankylosing Spondylitis
   14.7 Psoriatic Arthritis
   14.8 Plaque Psoriasis

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION
   *Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

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

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

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

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

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

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

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

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

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

1.2 Pediatric Crohn's Disease
REMICADE® (infliximab) is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Consideration may be given to adjusting the regimen of methotrexate. REMICADE should be given in combination with methotrexate. For patients who remain on an inadequate response to conventional therapy, then lose their response, consideration may be given to treatment with 10 mg/kg.

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

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

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

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

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

1.8 Plaque Psoriasis
REMICADE® (infliximab) is indicated for reducing signs and symptoms, and skin rashes. Anaphylaxis might occur at any time during REMICADE treatment. Approximately 20% of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo-treated patients.

2 DOSAGE AND ADMINISTRATION

2.1 Crohn's Disease
The recommended dose of REMICADE is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active Crohn's disease. For patients who respond and have regular follow-up visits with a physician [see Boxed Warning, Warnings and Precautions (5)].

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

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

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

2.5 Rheumatoid Arthritis
The recommended dose of REMICADE is 3 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks thereafter for the treatment of moderately to severely active rheumatoid arthritis. REMICADE should be given in combination with methotrexate. For patients who have an incomplete response, consideration may be given to adjusting the dose up to 10 mg/kg or treating as often as every 4 weeks bearing in mind that risk of serious infections is increased at higher doses [see Adverse Reactions (6.1)].

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

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

3 RECOMMENDATIONS REGARDING INFUSION REACTIONS
Adverse effects during administration of REMICADE have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes. Anaphylaxis might occur at any time during REMICADE treatment. Approximately 20% of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo-treated patients.
3 DOSAGE FORMS AND STRENGTHS

100 mg vial: 100 mg lyophilized infliximab in a 20 mL vial for injection, for intravenous use.

4 CONTRAINDICATIONS

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with REMICADE are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

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

Treatment with REMICADE should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Tuberculosis

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

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

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

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

Monitoring

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

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

Invasive Fungal Infections

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

5.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF-blocking agents (initiation of therapy <18 years of age), including REMICADE. Approximately half of these cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 3 years (range 1 to 94 months) after the first dose of TNF blocking therapy.

Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 10 years) vs 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn’s disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn’s disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Hepatosplenic T-cell Lymphoma (HSTCL)

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

Skin Cancer

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

Cervical Cancer

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

Other Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF-blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn’s disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma...
and NMCS) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up of 48.2 months for the REMICADE-treated patients, compared with 12.1 months 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 a clinical trial exploring the use of REMICADE in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in REMICADE-treated patients compared with control patients. All patients had a history of heavy smoking (see Adverse Reactions (6.1)). Prescribers should exercise caution when considering the use of REMICADE in patients with moderate to severe COPD.

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

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

5.4 Hepatotoxicity
Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported in postmarketing data in patients receiving REMICADE. Hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked 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. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE after progression to severe hepatic injury [see Adverse Reactions (6.1)].

5.5 Patients with Heart Failure
REMICADE has been associated with adverse outcomes in patients with heart failure, and should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of REMICADE in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality rates for REMICADE-treated patients, including REMICADE, and higher rates of cardiovasular 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 post-marketing reports of new onset heart failure, including heart failure in patients without carriers of 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 (4) and Adverse Reactions (6.1)].

5.6 Hematologic Reactions
Cases of leukaemia, 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 (i.e., fever, chills, malaise). Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities.

5.7 Hypersensitivity
REMICADE has been associated with hypersensitivity reactions that vary in their time of onset and required hospitalization in some cases. Most hypersensitivity reactions, which include anaphylaxis, urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial REMICADE therapy (i.e., as early as after the second dose), and when REMICADE therapy was re instituted following an extended period without REMICADE treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab, loss of detectable serum concentrations of infliximab, and possible loss of drug efficacy.

REMICADE should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction [see Adverse Reactions (6.1)].

In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, re-administration of REMICADE after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment [see Adverse Reactions (6.1)]. In general, the benefit-risk of re-administration of REMICADE after a period of no treatment, especially as a re-induction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where REMICADE maintenance therapy for psoriasis is interrupted, REMICADE should be reinitiated as a single dose followed by maintenance therapy.

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

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

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

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

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

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

5.14 Autoimmunity
Treatment with REMICADE may result in the formation of autoantibodies and in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued [see Adverse Reactions (6.1)].
6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

Adverse Reactions in Adults

The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with rheumatoid arthritis, 1304 patients with Crohn's disease, 202 with ankylosing spondylitis, 203 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. [For information on adverse reactions in pediatric patients see Adverse Reactions (6.1).] One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash).

Infusion-related Reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In Phase 3 clinical studies, 18% of REMICADE-treated patients experienced an infusion reaction compared to 5% of placebo-treated patients. Of the patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

Among all REMICADE infusions, 3% were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension, or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients. Approximately 3% of patients discontinued REMICADE because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. REMICADE infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 hour) was 7% in the 5 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group.

Patients who became positive for antibodies to infliximab were more likely (approximately two-to-three-fold) to have an infusion reaction than were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion reactions in infliximab-treated patients who had an infusion reaction during the induction period, 27% experienced an infusion reaction during the maintenance period. Of patients who did not have an infusion reaction during the induction period, 9% experienced an infusion reaction during the maintenance period.

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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-like symptoms, however, remain uncommon.

Malignancies

In controlled trials, more REMICADE-treated patients developed malignancies than placebo-treated patients [see Warnings and Precautions (5.2)].

In a randomized controlled trial comparing the use of REMICADE in patients with moderate to severe COPD who were either current smokers or ex-smokers, patients treated with REMICADE at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these REMICADE-treated patients, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.87 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.33 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 8.10). The majority of the malignancies developed in the lung or head and neck.

Patients with Heart Failure

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

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab in up to 13% of patients. An enzyme immunoassay (EIA) method was originally used to measure anti-infliximab antibodies in clinical studies of REMICADE. The EIA method is subject to interference by serum infliximab, possibly resulting in an overestimation of the rate of patient antibody formation. A separate, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method for detecting antibodies to infliximab was subsequently developed and validated. This method is 60-fold more sensitive than the original EIA. With the ECLIA method, all clinical samples can be classified as either positive or negative for antibodies to infliximab without the need for the inconclusive category.
The incidence of antibodies to infliximab was based on the original EIA method in all clinical studies of REMICADE except for the Phase 3 study in pediatric patients with ulcerative colitis where the incidence of antibodies to infliximab was detected using both the EIA and ECLIA methods (see Adverse Reactions, Pediatric Ulcerative Colitis (6.1)).

The incidence of antibodies to infliximab in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of REMICADE treatment. A higher incidence of antibodies to infliximab was observed in Crohn’s disease patients receiving REMICADE after drug-free intervals >16 weeks. In a study of pediatric arthritis in which 191 patients treated 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction (see Adverse Reactions (6.1)) than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn’s disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.

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

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

Hepatotoxicity

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

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

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

<table>
<thead>
<tr>
<th>Proportion of patients with elevated ALT</th>
<th>Placebo</th>
<th>REMICADE Placebo</th>
<th>REMICADE Placebo</th>
<th>REMICADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1 to &lt;3 x ULN</td>
<td>24%</td>
<td>34%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>≥3 x ULN</td>
<td>5%</td>
<td>0%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>≥5 x ULN</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

| Rheumatoid arthritisa                  | 24%     | 34%              | 3%               | 4%      |
| Crohn’s diseasea                       | 34%     | 39%              | 4%               | 5%      |
| Ulcerative colitisa                    | 12%     | 17%              | 1%               | 2%      |
| Ankylosing spondylitisa                | 15%     | 51%              | 0%               | 10%     |
| Psoriatic arthritisa                   | 16%     | 50%              | 0%               | 7%      |
| Plaque psoriasisa                      | 24%     | 49%              | <1%              | 8%      |

<table>
<thead>
<tr>
<th>Placebo</th>
<th>REMICADE Placebo</th>
<th>REMICADE Placebo</th>
<th>REMICADE</th>
</tr>
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<tbody>
<tr>
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<td>≥3 x ULN</td>
<td>5%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>≥5 x ULN</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
</tr>
</tbody>
</table>

- Placebo patients received methotrexate while REMICADE patients received both REMICADE and methotrexate. Median follow-up was 58 weeks.
- Placebo patients in the 2 Phase 3 trials in Crohn’s disease received an initial dose of 5 mg/kg REMICADE at study start and were on placebo in the maintenance phase. Patients who were randomized to the placebo maintenance group and then later crossed over to REMICADE are included in the REMICADE group in ALT analysis. Median follow-up was 54 weeks.

### Median follow-up

- Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for REMICADE.
- Median follow-up was 24 weeks for the placebo group and 102 weeks for the REMICADE group.
- Median follow-up was 39 weeks for the REMICADE group and 18 weeks for the placebo group.
- ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for REMICADE and 16 weeks for placebo.

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

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Placebo (n=350)</th>
<th>REMICADE (n=1129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weeks of follow-up</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>25%</td>
<td>32%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Coughing</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Skin and appendages disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Body as a whole-general disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Pain</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Resistance mechanism disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Moniliasis</td>
<td>3%</td>
<td>5%</td>
</tr>
</tbody>
</table>
The most common serious adverse reactions observed in clinical trials were infections [see Adverse Reactions (6.1)]. Other serious, medically relevant adverse reactions ≥0.2% or clinically significant adverse reactions by body system were as follows:

- **Body as a whole:** allergic reaction, edema
- **Blood and Lymphatic System:** anemia
- **Cardiovascular System:** hypertension
- **Gastrointestinal System:** constipation, intestinal obstruction
- **Central and Peripheral Nervous System:** dizziness
- **Heart Rate and Rhythm:** bradycardia
- **Liver and Biliary System:** hepatitis
- **Metabolic and Nutritional System:** dehydration
- **Neoplasms:** lymphoma
- **Respiratory System:** lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema
- **Skin and Appendages:** increased sweating
- **Vascular (ExtraCardiac):** thrombophlebitis
- **White Blood Cell:** leukopenia, lymphopenia

### Adverse Reactions in Pediatric Patients

**Pediatric Crohn’s Disease**

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

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

Infections were reported in 58% of randomized pediatric patients in Study Peds Crohn’s and in 50% of adult patients in Study Crohn’s I. In Study Peds Crohn’s, infections were reported more frequently for patients who received every 8-week infusions as opposed to every 12-week infusions (74% vs. 38%, respectively) while serious infections were reported for 3 patients in the every 8-week and 4 patients in the every 12-week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, 12 in the every 8-week and 1 in the every 12-week maintenance treatment group. Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group.

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

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

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 17% (10/60) of pediatric patients in the pediatric UC trial; 7% (4/60) had ALT elevations ≥3 x ULN, and 1% had elevations ≥5 x ULN. (Median follow-up was 53 weeks.)

### Pediatric Ulcerative Colitis

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

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

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

Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 22 (37%) required oral or parenteral antimicrobial treatment. The proportion of patients with infections in the pediatric UC trial was similar to that in the pediatric Crohn’s disease study (Study Peds Crohn’s) but higher than the proportion in the adults’ ulcerative colitis studies (Study UC I and Study UC II). The overall incidence of infections in the pediatric UC trial was 33/22 (59%) in the every 8-week maintenance treatment group. Upper respiratory tract infection (7/60 [12%]) and pharyngitis (5/60 [8%]) were the most frequently reported respiratory system infections. Serious infections were reported in 12% (7/60) of all treated patients. In the pediatric UC trial, 58 patients were evaluated for antibodies to infliximab using the EIA as well as the drug-tolerant ECLIA. With the EIA, 4 of 58 (7%) patients had antibodies to infliximab. With the ECLIA, 30 of 58 (52%) patients had antibodies to infliximab [see Adverse Reactions, Immunogenicity (6.1)]. The higher incidence of antibodies to infliximab by the ECLIA method was due to the 60-fold higher sensitivity compared to the EIA method. While EIA-positive patients generally had undetectable trough infliximab concentrations, ECLIA-positive patients could have detectable trough concentrations of infliximab because the ECLIA assay is more sensitive and drug-tolerant.

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

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

### 6.2 Postmarketing Experience

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

The following adverse reactions, some with fatal outcome, have been reported during post-approval use of REMICADE: neutropenia [see Warnings and Precautions (5.6)], agranulocytosis (including infants exposed in utero to infliximab), interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and rapidly progressive disease), idiopathic thrombocytopenic purpura, thombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barre syndrome), chronic inflammatory demyelinating polyradiculoneuropathy, motor neuropathy, new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neopathies (additional neurologic reactions have been also observed) [see Warnings and Precautions (5.8)], acute liver failure, jaundice, hepatitis, and cholestasis [see Warnings and Precautions (5.11)], malignancies, including melanoma, Merkel cell carcinoma, and cervical cancer [see Warnings and Precautions (5.2)] and vaccine breakthrough infection including bovine tuberculosis (disseminated BCG infection) following vaccination in an infant exposed in utero to infliximab [see Warnings and Precautions (5.15)].

**Infusion-related Reactions**

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

Cases of transient visual loss have been reported in association with REMICADE during or within 2 hours of infusion. Cerebrovascular accidents, myoccardial ischemia/infarction (some fatal), and arrhythmia occurring within 24 hours of the infusion have also been reported [see Warnings and Precautions (5.6)].

### Adverse Reactions in Pediatric Patients

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

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

7.1 Use with Anakinra or Abatacept

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

7.2 Use with Tocilizumab

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

7.3 Use with Other Biological Therapeutics

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

7.4 Methotrexate (MTX) and Other Concomitant Medications

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

7.5 Immunosuppressants

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

7.6 Cytochrome P450 Substances

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

7.7 Live Vaccines/Therapeutic Infectious Agents

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. It is not known whether REMICADE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. REMICADE should be given to a pregnant woman only if clearly needed. Because infliximab does not cross-react with TNFs 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 TNFs. 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.

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

Pediatric Crohn’s Disease

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

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

Pediatric Ulcerative Colitis

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

In the pediatric UC trial, approximately half of the patients were on concomitant immunomodulators (AZA, 6-MP, MTX) at study start. Due to the risk of HSTCL, a careful risk-benefit assessment should be made when REMICADE is used in combination with other immunosuppressants. The longer term (greater than 1 year) safety and effectiveness of REMICADE in pediatric ulcerative colitis patients have not been established in clinical trials.

Juvenile Rheumatoid Arthritis (JRA)

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

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

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

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

A total of 68% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks.

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The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was in patient and herpes zoster in patient.

8.5 Geriatric Use

In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received REMICADE, compared to younger patients—although the incidence of serious adverse reactions in patients aged 65 or older was higher in both REMICADE and control groups compared to younger patients. In Crohn’s disease, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis studies, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. There is a greater incidence of infections in the elderly population in general. The incidence of serious infections in REMICADE-treated patients 65 years and older was greater than in those under 65 years of age; therefore caution should be used in treating the elderly [see Adverse Reactions (8.1)].

10 OVERDOSE

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

11 DESCRIPTION

Infliximab, the active ingredient in REMICADE, is a chimeric IgG1κ monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNFα). It has a molecular weight of approximately 149.1 kilodaltons. Infliximab is produced by a recombinant cell line cultured in a mammalian continuous production and is purified by a series of steps that includes measures to inactivate and remove viruses. REMICADE is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-dose vial contains 100 mg infliximab, dibasic sodium phosphate, dihydrate (6.1 mg), monobasic sodium phosphate monohydrate (2.2 mg), polysorbate 80 (0.5 mg), and sucrose (500 mg). No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as interleukins (IL 1 and 6), enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leucocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synovioocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed in vitro or in vivo. Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship between these biological responses and the mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

In adults, single intravenous (IV) infusions of 3 mg/kg to 20 mg/kg showed a linear relationship between the dose administered and the maximum serum concentration. The volume of distribution at steady state was independent of dose and indicated that infliximab was distributed primarily within the vascular compartment. Pharmacokinetic results for single doses of 3 mg/kg to 10 mg/kg in rheumatoid arthritis, 5 mg/kg in Crohn’s disease, and 3 mg/kg to 5 mg/kg in plaque psoriasis indicate that the median terminal half-life of infliximab is 7.7 to 9.5 days. Following an initial dose of REMICADE, repeated infusions at 2 and 6 weeks resulted in predictable concentration-time profiles following each treatment. No systemic accumulation of infliximab occurred upon continued repeated treatment with 3 mg/kg or 10 mg/kg at 4- or 5-week intervals. Development of antibodies to infliximab increased infliximab clearance. At 8 weeks after a maintenance dose of 3 to 10 mg/kg of REMICADE, median infliximab serum concentrations ranged from approximately 0.5 to 6 mcg/mL; however, infliximab concentrations were not detectable (<0.1 mcg/mL) in patients who became positive for antibodies to infliximab. No major differences in clearance or volume of distribution were observed in patient subgroups defined by age, weight, or gender. It is not known if there are differences in clearance or volume of distribution in patients with marked impairment of hepatic or renal function.

Infliximab pharmacokinetic characteristics (including peak and trough concentrations and terminal half-life) were similar in pediatric (aged 6 to 17 years) and adult patients with rheumatoid disease or ulcerative colitis following the administration of 5 mg/kg of infliximab.

Population pharmacokinetic analysis showed that in children with juvenile rheumatoid arthritis (JRA) with a body weight of up to 35 kg receiving 6 mg/kg REMICADE and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3 mg/kg REMICADE, the steady state area under the concentration curve (AUCss) was similar to that observed in adults receiving 3 mg/kg of REMICADE.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The safety and efficacy of single and multiple doses of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn’s disease [Crohn’s Disease Activity Index (CDAI) ≥220 and ≤400] with an inadequate response to prior conventional therapies. Concomitant stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents were permitted and 92% of patients continued to receive at least one of these medications.

In the single-dose trial of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg REMICADE [p<0.001, two-sided, Fisher’s Exact test]. Additionally, 4% (1/25) of placebo patients and 46% (12/27) of patients receiving 5 mg/kg REMICADE achieved clinical remission (CDAI≤150) at Week 4.

In a multidose trial (ACCENT I [Study Crohn’s I]), 545 patients received 5 mg/kg at Week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 10 mg/kg at every 8 weeks. No patients in response at Week 2 were randomized and analyzed separately from those not in response at Week 2. Corticosteroid taper was permitted after Week 6.

At Week 2, 57% (311/545) of patients were in clinical response. At Week 30, a significantly greater proportion of these patients in the 5 mg/kg and 10 mg/kg maintenance groups achieved clinical remission compared to patients in the placebo maintenance group [Table 3].
Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg REMICADE maintenance groups were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 3).

### Table 3: Clinical remission and steroid withdrawal

<table>
<thead>
<tr>
<th></th>
<th>Placebo Maintenance</th>
<th>REMICADE Maintenance 10 mg/kg</th>
<th>REMICADE Maintenance 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 30</strong></td>
<td>25/102</td>
<td>41/104</td>
<td>48/105</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>25%</td>
<td>39%</td>
<td>46%</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.022</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Week 54</strong></td>
<td>6/54</td>
<td>14/56</td>
<td>18/53</td>
</tr>
<tr>
<td>Patients in remission able to discontinue corticosteroid use&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11%</td>
<td>25%</td>
<td>34%</td>
</tr>
<tr>
<td>P-value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.059</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> REMICADE at Week 0  
<sup>b</sup> REMICADE 5 mg/kg administered at Weeks 0, 2 and 6  
<sup>c</sup> P-values represent pairwise comparisons to placebo  
<sup>d</sup> Of those receiving corticosteroids at baseline

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

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

![Kaplan-Meier estimate](image)

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

Patients who achieved a response and subsequently lost response were eligible to receive REMICADE on an episodic basis at a dose that was 5 mg/kg higher than the dose to which they were randomized. The majority of such patients responded to the higher dose. Among patients who were not in response at Week 2, 59% (92/157) of REMICADE maintenance patients responded by Week 14 compared to 51% (59/117) of placebo maintenance patients. Among patients who did not respond by Week 14, additional therapy did not result in significantly more responses (see Dosage and Administration [2]).

**Fistulizing Crohn's Disease**

The safety and efficacy of REMICADE were assessed in 2 randomized, open-label studies (Study Peds Crohn's) in 112 pediatric patients aged 6 to 17 years old with moderately to severely active Crohn's disease and an inadequate response to conventional therapies. The median age was 13 years and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0 to 100). All patients were required to be on a stable dose of 6-MP, AZA, or MTX; 35% were also receiving corticosteroids at baseline.

All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given either every 8 weeks or every 12 weeks. At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥15 points and total PCDAI score of ≤30 points), and similar numbers developed abscesses (15% overall).

**14.2 Pediatric Crohn's Disease**

At both Week 30 and Week 54, the proportion of patients in clinical response was greater in the every 8-week treatment group than in the every 12-week treatment group (73% vs. 47% at Week 30, and 64% vs. 33% at Week 54). At both Week 30 and Week 54, the proportion of patients in clinical remission was also greater in the every 8-week treatment group than in the every 12-week treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54).
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Table 4: Response and remission in study peds Crohn's

<table>
<thead>
<tr>
<th>5 mg/kg REMICADE</th>
<th>Placebo</th>
<th>5 mg/kg REMICADE</th>
<th>10 mg/kg REMICADE</th>
<th>Placebo</th>
<th>10 mg/kg REMICADE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study UC I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients randomized</td>
<td>121</td>
<td>121</td>
<td>122</td>
<td>123</td>
<td>121</td>
</tr>
<tr>
<td>Clinical Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>37%</td>
<td>69%*</td>
<td>62%*</td>
<td>29%</td>
<td>65%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>38%</td>
<td>52%</td>
<td>51%**</td>
<td>26%</td>
<td>47%**</td>
</tr>
<tr>
<td>Week 54</td>
<td>20%</td>
<td>45%**</td>
<td>44%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sustained Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Clinical response at both Weeks 8 and 30)</td>
<td>23%</td>
<td>49%*</td>
<td>46%*</td>
<td>15%</td>
<td>41%*</td>
</tr>
<tr>
<td>(Clinical response at Weeks 8, 30, and 54)</td>
<td>14%</td>
<td>39%*</td>
<td>37%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>15%</td>
<td>39%*</td>
<td>32%**</td>
<td>6%</td>
<td>34%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>16%</td>
<td>24%**</td>
<td>37%</td>
<td>11%</td>
<td>26%**</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%</td>
<td>35%**</td>
<td>34%**</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

14.3 Ulcerative Colitis

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

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

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both REMICADE groups achieved clinical response, clinical remission and mucosal healing than in the placebo group. Each of these effects was maintained through the end of each trial (Week 54 in Study UC I, and Week 30 in Study UC II). In addition, a greater proportion of patients in REMICADE groups demonstrated sustained response and sustained remission than in the placebo groups (Table 5). Of patients on corticosteroids at baseline, greater proportions of patients in the REMICADE treatment groups were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups (22% in REMICADE treatment groups vs. 10% in placebo group in Study UC I, 22% in REMICADE treatment groups vs. 3% in placebo group in Study UC II). In Study UC I, this effect was maintained through Week 54 (21% in REMICADE treatment groups vs. 9% in placebo group). The REMICADE-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

Table 5: Response, remission and mucosal healing in ulcerative colitis studies

<table>
<thead>
<tr>
<th>Study UC I</th>
<th>Placebo</th>
<th>5 mg/kg REMICADE</th>
<th>10 mg/kg REMICADE</th>
<th>Placebo</th>
<th>10 mg/kg REMICADE</th>
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<tr>
<td>Patients randomized</td>
<td>121</td>
<td>121</td>
<td>122</td>
<td>123</td>
<td>121</td>
</tr>
<tr>
<td>Clinical Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>14%</td>
<td>39%**</td>
<td>37%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Week 30</td>
<td>16%</td>
<td>24%**</td>
<td>37%</td>
<td>11%</td>
<td>26%**</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%</td>
<td>35%**</td>
<td>34%**</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

**a** Defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings.)
**b** Defined as a Mayo score <2 points, no individual subscore >1.
**c** Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.
**d** Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

The improvement with REMICADE was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 6; Study UC II through Week 30 was similar).

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

<table>
<thead>
<tr>
<th>Study UC I</th>
<th>Placebo</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Week 8</td>
<td>35%</td>
<td>60%</td>
<td>58%</td>
</tr>
<tr>
<td>Week 30</td>
<td>35%</td>
<td>51%</td>
<td>53%</td>
</tr>
<tr>
<td>Week 54</td>
<td>31%</td>
<td>52%</td>
<td>51%</td>
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<tr>
<td>Rectal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>54%</td>
<td>40%</td>
<td>48%</td>
</tr>
<tr>
<td>Week 8</td>
<td>74%</td>
<td>86%</td>
<td>80%</td>
</tr>
<tr>
<td>Week 30</td>
<td>65%</td>
<td>74%</td>
<td>71%</td>
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<tr>
<td>Week 54</td>
<td>62%</td>
<td>69%</td>
<td>67%</td>
</tr>
<tr>
<td>Physician's Global Assessment</td>
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<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>4%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Week 8</td>
<td>44%</td>
<td>74%</td>
<td>64%</td>
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<tr>
<td>Week 30</td>
<td>36%</td>
<td>57%</td>
<td>55%</td>
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<tr>
<td>Week 54</td>
<td>26%</td>
<td>53%</td>
<td>53%</td>
</tr>
</tbody>
</table>
Endoscopy findings |       |         |         |
| Baseline   | 0%      | 0%      | 0%      |
| Week 8     | 34%     | 62%     | 59%     |
| Week 30    | 26%     | 51%     | 52%     |
| Week 54    | 21%     | 50%     | 51%     |

14.4 Pediatric Ulcerative Colitis

The safety and effectiveness of REMICADE for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients aged 6 years and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well-controlled studies of REMICADE in adults. Additional safety and pharmacokinetic data were collected in an open-label pediatric UC trial in 60 pediatric patients aged 6 through 17 years (median age 14.5 years) with moderately to severely active ulcerative colitis (Mayo score of 6 to 12, Endoscopic subscore ≥2) and an inadequate response to conventional therapies. At baseline, the median Mayo score was 8, 53% of patients were receiving immunomodulator therapy (6-MP/AZA/MTX), and 62% of patients were receiving corticosteroids (median dose 0.5 mg/kg/day in prednisone equivalents). Discontinuation of immunomodulators and corticosteroid taper were permitted after Week 0.
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All patients received induction dosing of 5 mg/kg REMICADE at Weeks 0, 2, and 6. Patients who did not respond to REMICADE at Week 8 received no further REMICADE and returned for safety follow-up. At Week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg REMICADE given either every 8 weeks through Week 46 or every 12 weeks through Week 42. Patients were allowed to change to a higher dose and/or more frequent administration schedule if they experienced loss of response.

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

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

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

Of the 60 patients treated, 44 were in clinical response at Week 8. Of 32 patients taking concomitant immunomodulators at baseline, 23 achieved clinical response at Week 8, compared to 21 of 28 of those not taking concomitant immunomodulators at baseline. At Week 8, 24 of 60 patients were in clinical remission as measured by the Mayo score and 17 of 51 patients were in remission as measured by the PUCAI score.

At Week 54, 8 of 21 patients in the every 8-week maintenance group and 4 of 22 patients in the every 12-week maintenance group achieved remission as measured by the PUCAI score.

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

14.5 Rheumatoid Arthritis

The safety and efficacy of REMICADE were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted. Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of REMICADE + MTX: 3 mg/kg or 10 mg/kg of REMICADE by IV infusion at Week 0, 2, and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX. Study RA II was a placebo-controlled study of 3 active treatment arms in 1004 MTX naive patients of 3 or fewer years’ duration active rheumatoid arthritis. Patients enrolled had a median age of 51 years with a median disease duration of 0.8 years, median swollen and tender joint count of 19 and 31 respectively, and ≥80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by Week 8) and either placebo, 3 mg/kg or 6 mg/kg REMICADE at Weeks 0, 2, and 6 and every 8 weeks thereafter.

Data on use of REMICADE without concurrent MTX are limited [see Adverse Reactions (6.1)].

Clinical Response

In Study RA I, all doses/schedules of REMICADE + MTX resulted in improvement in signs and symptoms as measured by the American College of Rheumatology response criteria (ACR 20) with a higher percentage of patients achieving an ACR 20, 50 and 70 compared to placebo + MTX (Table 7). This improvement was observed at Week 2 and maintained through Week 102. Greater effects on each component of the ACR 20 were observed in all patients treated with REMICADE + MTX compared to placebo + MTX (Table 8). More patients treated with REMICADE reached a major clinical response than placebo-treated patients (Table 7).

In Study RA II, after 54 weeks of treatment, both doses of REMICADE + MTX resulted in statistically significantly greater response in signs and symptoms compared to MTX alone as measured by the proportion of patients achieving ACR 20, 50 and 70 responses (Table 7). More patients treated with REMICADE reached a major clinical response than placebo-treated patients (Table 7).

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

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Placebo + MTX</th>
<th>REMICADE + MTX*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Tender Joints</td>
<td>24 16</td>
<td>32 8</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>19 13</td>
<td>20 7</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7 6.1</td>
<td>6.8 3.3</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td>6.5 5.2</td>
<td>6.2 2.1</td>
</tr>
<tr>
<td>Patient’s Global Assessment</td>
<td>6.2 6.2</td>
<td>6.3 3.2</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)</td>
<td>1.8 1.5</td>
<td>1.8 1.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.0 2.3</td>
<td>2.4 0.6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + MTX</th>
<th>REMICADE + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 54</td>
<td>(n=88)</td>
<td>(n=340)</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Phys’ Global</td>
<td>6.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Patient’s Global</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>

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

- All doses/schedules of REMICADE + MTX
- Visual Analog Scale (0=best, 10=worst)
- Health Assessment Questionnaire, measurement of 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities (0=best, 3=worst)

Radiographic Response

Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vDS-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet. In Study RA I, approximately 80% of patients had paired X-ray data at 54 weeks and approximately 70% at 102 weeks. The inhibition of progression of structural damage was observed at 54 weeks (Table 9) and maintained through 102 weeks. In Study RA II, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 (Table 9) in the REMICADE + MTX groups compared to MTX alone. Patients treated with REMICADE + MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute-phase reactants (ESR and CRP) were normal or elevated; patients with elevated baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vDS-S score of 4.2 units compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vDS-S score of 1.8 units compared to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had no progression (vDS-S score ≤0 unit) of structural damage compared to 45% of patients receiving MTX alone. In a subset of patients who began the study without erosions, REMICADE + MTX maintained an erosion-free state at 1 year in a greater proportion of patients than MTX alone, 79% (77/98) vs. 58% (23/40), respectively (P<0.01). Fewer patients in the REMICADE + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).
At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving REMICADE, compared to 9% and 4%, respectively, for patients receiving placebo. A low level of disease activity (defined as a value <20 [on a scale of 0-100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of REMICADE-treated patients vs. 1% in placebo-treated patients (P<0.001).

### Table 10: Components of ankylosing spondylitis disease activity

<table>
<thead>
<tr>
<th>Placebo</th>
<th>REMICADE 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24 Weeks</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>6.6</td>
</tr>
<tr>
<td>Pain</td>
<td>7.3</td>
</tr>
<tr>
<td>BASFI</td>
<td>5.8</td>
</tr>
<tr>
<td>Inflammation</td>
<td>6.9</td>
</tr>
</tbody>
</table>

### 14.6 Ankylosing Spondylitis

The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New York criteria for Ankylosing Spondylitis. Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of REMICADE 5 mg/kg or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18. At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in the REMICADE-treated group vs. 18% of patients in the placebo group (P<0.001). Improvement was observed at Week 2 and maintained through Week 24 (Figure 3 and Table 10).
**Clinical Response**

Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 56% of REMICADE-treated patients achieving ACR 20 at Week 14, compared with 11% of placebo-treated patients (P<0.001). The response was similar regardless of concomitant use of methotrexate. Improvement was observed as early as Week 2. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving REMICADE compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were observed in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

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

**Table 11: Components of ACR 20 and percentage of patients with 1 or more joints with dactylitis and percentage of patients with enthesopathy at baseline and Week 24**

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Placebo (n=100)</th>
<th>REMICADE 5 mg/kg (n=100)</th>
<th>Placebo (n=100)</th>
<th>REMICADE 5 mg/kg (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Tender Joints&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24</td>
<td>20</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>No. of Swollen Joints&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12</td>
<td>9</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Pain&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6.4</td>
<td>5.6</td>
<td>5.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Physician’s Global Assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.0</td>
<td>4.5</td>
<td>5.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Patient’s Global Assessment&lt;sup&gt;d&lt;/sup&gt;</td>
<td>6.1</td>
<td>5.0</td>
<td>5.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>CRP (mg/dL)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.2</td>
<td>0.9</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>% Patients with 1 or more digits with dactylitis</td>
<td>41</td>
<td>33</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>% Patients with enthesisopathy</td>
<td>35</td>
<td>36</td>
<td>42</td>
<td>22</td>
</tr>
</tbody>
</table>

<sup>a</sup>P<0.001 for percent change from baseline in all components of ACR 20 at Week 24, P<0.05 for % of patients with dactylitis, and P=0.004 for % of patients with enthesisopathy at Week 24

<sup>b</sup>Scale 0-68

<sup>c</sup>Scale 0-68

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

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

<sup>f</sup>Normal range 0-0.6 mg/dL

**Radiographic Response**

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints. The total modified vdH-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and feet. At Week 24, REMICADE-treated patients had less radiographic progression than placebo-treated patients (mean change of -0.7 vs. 0.82, P<0.001). REMICADE-treated patients also had less progression in their erosion scores (0.56 vs 0.51) and JSN scores (-0.14 vs 0.31). The patients in the REMICADE group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vdH-S score during this 12-month study (median change of 0 in both patients who initially received REMICADE or placebo). More patients in the placebo group (12%) had readily apparent radiographic progression compared with the REMICADE group (3%).

**Physical Function**

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

**14.8 Plaque Psoriasis**

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

Study I (EXPRESS) evaluated 378 patients who received placebo or REMICADE at a dose of 5 mg/kg at Weeks 0, 2, and 6 (induction therapy), followed by maintenance therapy every 8 weeks. At Week 24, the placebo group crossed over to REMICADE induction therapy (5 mg/kg), followed by maintenance therapy every 6 weeks. Patients originally randomized to REMICADE continued to receive REMICADE 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the static Physician Global Assessment (sPGA) score ranged from moderate (62% of patients) to marked (38%) to severe (2%). In addition, 75% of patients had a BSA >20%. Seventy-one percent of patients previously received systemic therapy, and 82% received phototherapy.

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

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

In Studies I, II, and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of “cleared” or “minimal” by the sPGA. The sPGA is a 6-category scale ranging from “0 = severe” to “5 = severe” indicating the physician’s overall assessment of the psoriasis severity focusing on erythema, scaling, and induration. Treatment success, defined as “cleared” or “minimal,” consisted of none or minimal fine scale over <5% of the plaque. In Study II, the proportion of patients who achieved a score of “clear” or “excellent” by the relative Physician’s Global Assessment (rPGA). The rPGA is a 6-category scale ranging from “6 = worse” to “1 = clear” that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as “clear” or “excellent,” consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>REMICADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>sPGA</td>
<td>3 (4%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>P<0.001 compared with placebo

<sup>b</sup>Patients with missing data at Week 10 were considered as nonresponders.

<sup>c</sup>Patients with missing data at Week 10 were imputed by last observation.
Efficacy and safety of REMICADE treatment beyond 50 weeks have not been evaluated in patients with plaque psoriasis.

15 REFERENCES


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


MEDICATION GUIDE
REMICADE® (Rem-eh-kaid)
(infliximab)
Lyophilized Concentrate for Injection, for Intravenous Use

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

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

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

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

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

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

See the section “What are the possible side effects of REMICADE?” below for more information.
**What is REMICADE?**

REMICADE is a prescription medicine that is approved for patients with:

- **Rheumatoid Arthritis** - adults with moderately to severely active rheumatoid arthritis, along with the medicine methotrexate.
- **Crohn’s Disease** - children 6 years and older and adults with Crohn’s disease who have not responded well to other medicines.
- **Ankylosing Spondylitis**
- **Psoriatic Arthritis**
- **Plaque Psoriasis** - adult patients with plaque psoriasis that is chronic (does not go away), severe, extensive, and/or disabling.
- **Ulcerative Colitis** - children 6 years and older and adults with moderately to severely active ulcerative colitis who have not responded well to other medicines.

REMICADE blocks the action of a protein in your body called tumor necrosis factor-alpha (TNF-alpha). TNF-alpha is made by your body's immune system. People with certain diseases have too much TNF-alpha that can cause the immune system to attack normal healthy parts of the body. REMICADE can block the damage caused by too much TNF-alpha.

**Who should not receive REMICADE?**

You should not receive REMICADE if you have:

- heart failure, unless your doctor has examined you and decided that you are able to receive REMICADE. Talk to your doctor about your heart failure.
- had an allergic reaction to REMICADE, or any of the other ingredients in REMICADE. See the end of this Medication Guide for a complete list of ingredients in REMICADE.

**What should I tell my doctor before starting treatment with REMICADE?**

Your doctor will assess your health before each treatment. Tell your doctor about all of your medical conditions, including if you:

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

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

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

What are the possible side effects of REMICADE?
REMICADE can cause serious side effects, including:

See “What is the most important information I should know about REMICADE?”

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

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

Treatment with REMICADE may need to be stopped if you get new or worse congestive heart failure.
What are the possible side effects of REMICADE? (continued)

Other Heart Problems
Some patients have experienced a heart attack (some of which led to death), low blood flow to the heart, or abnormal heart rhythm within 24 hours of beginning their infusion of REMICADE. Symptoms may include chest discomfort or pain, arm pain, stomach pain, shortness of breath, anxiety, lightheadedness, dizziness, fainting, sweating, nausea, vomiting, fluttering or pounding in your chest, and/or a fast or a slow heartbeat. Tell your doctor right away if you have any of these symptoms.

Liver Injury
Some patients receiving REMICADE have developed serious liver problems. Tell your doctor if you have:

- jaundice (skin and eyes turning yellow)
- dark brown-colored urine
- pain on the right side of your stomach area (right-sided abdominal pain)
- fever
- extreme tiredness (severe fatigue)

Blood Problems
In some patients receiving REMICADE, the body may not make enough of the blood cells that help fight infections or help stop bleeding. Tell your doctor if you:

- have a fever that does not go away
- bruise or bleed very easily
- look very pale

Nervous System Disorders
Some patients receiving REMICADE have developed problems with their nervous system. Tell your doctor if you have:

- changes in your vision
- numbness or tingling in any part of your body
- weakness in your arms or legs
- seizures

Some patients have experienced a stroke within approximately 24 hours of their infusion with REMICADE. Tell your doctor right away if you have symptoms of a stroke which may include: numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination or a sudden, severe headache.

Allergic Reactions
Some patients have had allergic reactions to REMICADE. Some of these reactions were severe. These reactions can happen while you are getting your REMICADE treatment or shortly afterward. Your doctor may need to stop or pause your treatment with REMICADE and may give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:

- hives (red, raised, itchy patches of skin)
- difficulty breathing
- chest pain
- high or low blood pressure
- fever
- chills

Some patients treated with REMICADE have had delayed allergic reactions. The delayed reactions occurred 3 to 12 days after receiving treatment with REMICADE. Tell your doctor right away if you have any of these signs of delayed allergic reaction to REMICADE:

- fever
- rash
- headache
- sore throat
- muscle or joint pain
- swelling of the face and hands
- difficulty swallowing

Lupus-like Syndrome
Some patients have developed symptoms that are like the symptoms of Lupus. If you develop any of the following symptoms, your doctor may decide to stop your treatment with REMICADE.

- chest discomfort or pain that does not go away
- shortness of breath
- joint pain
- rash on the cheeks or arms that gets worse in the sun
What are the possible side effects of REMICADE? (continued)

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

The most common side effects of REMICADE include:
- respiratory infections, such as sinus infections and sore throat
- headache

Infusion reactions can happen up to 2 hours after your infusion of REMICADE. Symptoms of infusion reactions may include:
- fever
- chills
- chest pain
- low blood pressure or high blood pressure

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

Tell your doctor about any side effect that bothers you or does not go away.
These are not all of the side effects with REMICADE. Ask your doctor or pharmacist for more information.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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

You can ask your doctor or pharmacist for information about REMICADE that is written for health professionals.
For more information go to www.remicade.com, or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in REMICADE?
The active ingredient is Infliximab.
The inactive ingredients in REMICADE include: dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, polysorbate 80, and sucrose. No preservatives are present.

Manufactured by: Janssen Biotech, Inc. Horsham, PA 19044 © 2013 Janssen Pharmaceutical Companies U.S. License No. 1864

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