REMICADE® (infliximab)

DOSAGE AND ADMINISTRATION

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

Crohn's Disease (2.1)
- 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.

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

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

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

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

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

Psoriatic Arthritis (2.7) and Plaque Psoriasis (2.8)
- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

DOSE FORMS AND STRENGTHS

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

CONTRAINDICATIONS
- REMICADE doses >5 mg/kg in moderate to severe heart failure. (4)
- Previous severe hypersensitivity reaction to REMICADE or known hypersensitivity to inactive components of REMICADE or to any murine proteins. (4)

WARNINGS AND PRECAUTIONS
- Serious infections – do not give REMICADE during an active infection. If an infection develops, monitor carefully and stop REMICADE if infection becomes serious. (5.1)
- Invasive fungal infections – for patients who develop a systemic illness on REMICADE, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic. (5.1)
- Malignancies – the incidence of malignancies including lymphoma was greater in REMICADE treated patients than in controls. Due to the risk of HSTCL carefully assess the risk/benefit especially if the patient has Crohn's disease or ulcerative colitis, is male, and is receiving azathioprine or 6-mercaptopurine treatment. (5.2)
- Hepatitis B virus reactivation – test for HBV infection before starting REMICADE. Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop REMICADE and begin anti-viral therapy. (5.3)
- Hepatotoxicity – rare severe hepatic reactions, some fatal or necessitating liver transplantation. Stop REMICADE in cases of jaundice and/or marked liver enzyme elevations. (5.4)
- Heart failure – new onset or worsening symptoms may occur. (4, 5.5)
- Cytopenias – advise patients to seek immediate medical attention if signs and symptoms develop, and consider stopping REMICADE. (5.6)
- Hypersensitivity – serious infusion reactions including anaphylaxis or serum sickness-like reactions may occur. (5.7)
- Demelinating disease – exacerbation or new onset may occur. (5.8)
- Lupus-like syndrome – stop REMICADE if syndrome develops. (5.13)
- Live vaccines or therapeutic infectious agents – should not be given with REMICADE. Bring pediatric patients up to date with all vaccinations prior to initiating REMICADE. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab. (5.14)

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
- Pediatric Use – REMICADE has not been studied in children with Crohn's disease or ulcerative colitis <6 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2015
**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 infection prior to initiating therapy.
- 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.

**MALIGNANCY**

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

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

**1 INDICATIONS AND USAGE**

**1.1 Crohn's Disease**

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

Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.

### 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 (see Boxed WARNINGS)**

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**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 Neurologic Reactions**

**5.9 Use with Anakinra**

**5.10 Use with Abatacept**

**5.11 Concurrent Administration with other Biological Therapeutics**

**5.12 Switching Between Biological Disease-Modifying Antirheumatic Drugs (DMARDs)**

**5.13 Autoimmunity**

**5.14 Live Vaccines/Therapeutic Infectious Agents**

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

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**7 DRUG INTERACTIONS**

**7.1 Use with Anakinra or Abatacept**

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**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**

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**8.1 Pregnancy**

**8.2 Nursing Mothers**

**8.3 Pediatric Use**

**8.4 Pediatric Use**

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**12.1 Mechanism of Action**

**12.2 Pharmacodynamics**

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**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**

**14.9 Psoriatic Arthritis**

**14.10 Psoriatic Arthritis**

**15 REFERENCES**

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

**17.1 Patient Counseling**

*Sections or subsections omitted from the full prescribing information are not listed.*
REMICADE® (infliximab)

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

1.3 Ulcerative Colitis
REMICADE is indicated for reducing signs and symptoms 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.

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

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

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

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

1.8 Plaque Psoriasis
REMICADE is indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate. REMICADE should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician [see Boxed Warnings, Warnings and Precautions (5)].

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 adults with moderately to severely active Crohn's disease or fistulizing Crohn's disease. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg.

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 active ankylosing spondylitis.

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

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

2.9 Monitoring to Assess Safety
Prior to initiating REMICADE and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection [see Warnings and Precautions (5.1)].

2.10 Administration Instructions Regarding Infusion Reactions
Adverse effects during administration of REMICADE have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rash. Anaphylaxis may occur at any time during REMICADE infusion. Approximately 20% of REMICADE-treated patients in all clinical trials experienced an infusion reaction compared with 10% of placebo-treated patients [see Adverse Reactions (6.1)]. Prior to infusion with REMICADE, premedication may be administered at the physician's discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids.

During infusion, mild to moderate infusion reactions may improve following slowing or suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients that do not tolerate the infusion following these interventions, REMICADE should be discontinued. During or following infusion, patients who have severe infusion-related reactions or reactions that require discontinuation from further REMICADE treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

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

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

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

3. Dilute the total volume of the reconstituted REMICADE solution to 250 mL with sterile 0.9% Sodium Chloride Injection, USP, by withdrawing a volume equal to the volume of reconstituted REMICADE from the 0.9% Sodium Chloride Injection, USP, to the glass wall of the vial. Gently mix. The resulting infusion concentration should range between 0.4 mg/mL and 4 mg/mL.

4. The REMICADE infusion should begin within 3 hours of reconstitution and dilution. The infusion must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS
REMICADE at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMICADE in patients with moderate to severe heart failure (New York Heart Association
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.

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

Active Infections

For patients who reside or travel in regions where mycobacteria 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 8 months (range 1 to 94 months) after the first dose of the TNF-blocking therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas

In the controlled portions of clinical trials of all the TNF-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of REMICADE clinical trials, 5 patients developed lymphomas among 5707 patients treated with REMICADE (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn’s disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn’s disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressants, 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 myeloid leukemia and Hodgkin’s lymphoma 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 occurred 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 these 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

Malignant 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.

Other Malignancies

In the controlled portions of clinical trials of some TNF-blocking agents including REMICADE, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF blockers compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis, Crohn’s disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 REMICADE-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among REMICADE-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for REMICADE-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast cancer 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 which were breast cancer 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 prolonged phototherapy treatment. In the maintenance portion of clinical trials for REMICADE, NMSCs were more common in patients receiving REMICADE in conjunction with methotrexate phototherapy [see Adverse Reactions (6.1)].

The potential role of TNF-blocking therapy in the development of malignancies is not known [see Adverse Reactions (6.1)]. Rates in clinical trials for REMICADE cannot be compared to rates in clinical trials of other TNF-blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering REMICADE treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving REMICADE.

5.14 Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to therapeutic infectious agents (e.g., BCG bladder instillation for the treatment of cancer) could result in clinical benefit. Therefore, the combination of REMICADE and abatacept is not recommended [see Adverse Reactions (6.1)].

5.12 Switching between Biological Disease-Modifying Antirheumatic Drugs (DMARDs)

Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

5.13 Autoimmunity

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

5.14 Live Vaccines/Therapeutic Infectious Agents

In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines in patients receiving REMICADE may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with REMICADE, treatment should be discontinued [see Adverse Reactions (6.1)].

5.8 Neurologic Reactions

REMICADE and other agents that inhibit TNF have been associated in rare cases with CNS manifestation 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. Premenopausal women should be advised to consider discontinuation of the use of REMICADE in patients with these neuromuscular disorders and should consider discontinuation of REMICADE if these disorders develop.

5.9 Use with Anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and other TNF-x-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 TNF-x-blocking agents. Therefore, the combination of REMICADE and anakinra is not recommended.

5.10 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)].

5.11 Concurrent Administration with other Biological Therapeutics

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

5.6 Hematologic Reactions

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

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 urticaria, dyspnea, and/or hypotension, have occurred during or within 2 hours of REMICADE infusion.
6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same drug, or to the rates observed in broad patient populations in clinical practice.

Adverse Reactions in Adults

The data described herein reflect exposure to REMICADE in 4779 adult patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn’s disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 3265 patients exposed for 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 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.

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

Patients who became positive for antibodies to infliximab were more likely (approximately two- to three-fold) to have an infusion reaction than those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions (see Adverse Reactions (6.1) and Drug Interactions (7.4)).

Infusion reactions following re-administration

In a clinical trial of patients with moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction regimen of REMICADE following disease flare, 4% (8/219) of patients in the maintenance therapy arm experienced an infusion reaction versus 1% (2/222) in the maintenance therapy arm. Patients enrolled in this trial did not receive any concomitant immunosuppressant therapy. In this study, the majority of serious infusion reactions occurred during the second infusion at Week 2. Symptoms included, but were not limited to, dyspnea, urticaria, facial edema, and hypotension. In all cases REMICADE treatment was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Reactions/Reactions Following Re-administration

In psoriasis studies, approximately 1% of REMICADE-treated patients experienced a possible delayed hypersensitivity reaction, generally reported as serum sickness or a combination of arthralgia and/or myalgia with fever and/or rash. These reactions generally occurred within 2 weeks after repeat infusion.

Infections

In REMICADE clinical studies, treated infections were reported in 36% of REMICADE-treated patients (average of 51 weeks of follow-up) and in 25% of placebo-treated patients (average of 37 weeks of follow-up). The infections most frequently reported were respiratory tract infections (including sinusitis, pharyngitis, and bronchitis) and urinary tract infections. Among REMICADE-treated patients, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystis, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported post-marketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with REMICADE and may reflect recrudescence of latent disease (see Warnings and Precautions (5.1)).

In the 1-year placebo-controlled studies RA I and RA II, 5.3% of patients with MTX had infections, compared to 3.4% of placebo patients. Of 924 patients receiving REMICADE, 1.7% developed pneumonia and 0.4% developed TB, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg REMICADE infusions at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg REMICADE group (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54-week Crohn’s II Study, 15% of patients with fistulizing Crohn’s disease developed a fistula-related abscess.

In REMICADE clinical studies in patients with ulcerative colitis, infections treated with antimicrobials were reported in 27% of REMICADE-treated patients (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average of 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with ulcerative colitis were similar to those reported in other clinical studies.

The onset of serious infections may be preceded by constitutional symptoms such as fever, chills, weight loss, and fatigue. The majority of serious infections, however, may also be preceded by signs or symptoms localized to the site of the infection.

Autoantibodies/Lupus-like Syndrome

Approximately half of REMICADE-treated patients in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during treatment with REMICADE. ANA was measured in serum at each visit with a Tissue Autoantibody Assay Kit using a 40X (or 10X) dilution. In this study, the majority of antibodies were detected using both the EIA and ECLIA methods.

Immunogenicity

Treatment with REMICADE can be associated with the development of antibodies to infliximab. An enzyme immunoassay (EIA) method was originally used to measure anti-infliximab antibodies in clinical studies of REMICADE. The EIA method is subject to interference by serum infliximab, possibly resulting in an underestimation of the rate of patient antibody formation. A separate, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method for detecting antibodies to infliximab was subsequently developed and validated. This method is 60-fold more sensitive than the original EIA. With the ECLIA method, all clinical samples can be classified as either positive or negative for antibodies to infliximab without the need for the inconclusive category.

The incidence of antibodies to infliximab was based on the original EIA method in all clinical studies of REMICADE except for the Phase 3 study in pediatric patients with ulcerative colitis where the incidence of antibodies to infliximab was detected using both the EIA and 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 with 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 psoriatic arthritis in which 191 patients received 5 mg/kg with or without MTX, antibodies to infliximab occurred in 15% of patients. The majority of antibody-positive patients had low titers. Patients who were antibody-positive were more likely to have higher rates of clearance, reduced efficacy and to experience an infusion reaction [see Adverse Reactions (6.1)] than were patients who were antibody negative. Antibody development was lower among rheumatoid arthritis and Crohn’s disease patients receiving immunosuppressant therapies such as 6-MP/AZA or MTX.
REMICADE® (infliximab)

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 (41.1% - 22.0%) 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 rarely in patients receiving REMICADE [see Warnings and Precautions (5.4)]. Reactivation of hepatitis B virus has occurred in patients receiving TNF-blocking agents, including REMICADE, who are chronic carriers of this virus [see Warnings and Precautions (5.3)].

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

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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>REMICADE 5 mg/kg</th>
<th>REMICADE 3 mg/kg</th>
<th>Median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>24%</td>
<td>34%</td>
<td>3%</td>
<td>58 weeks</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>34%</td>
<td>39%</td>
<td>4%</td>
<td>58 weeks</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>12%</td>
<td>17%</td>
<td>2%</td>
<td>58 weeks</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>15%</td>
<td>51%</td>
<td>0%</td>
<td>58 weeks</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>16%</td>
<td>50%</td>
<td>0%</td>
<td>58 weeks</td>
</tr>
<tr>
<td>Plaque psoriasis</td>
<td>24%</td>
<td>49%</td>
<td>&lt;1%</td>
<td>58 weeks</td>
</tr>
</tbody>
</table>

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

Study II, 1.0% and 1.3% of patients receiving REMICADE 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1 serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg REMICADE group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting REMICADE.

In the placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received REMICADE at any dose were diagnosed with at least one NMSC compared to 0 of 324 patients who received placebo.

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

**Other Adverse Reactions**

Safety data are available from 4779 REMICADE-treated adult patients, including 1304 with rheumatoid arthritis, 1106 with Crohn’s disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1732 with plaque psoriasis and 17 with other conditions. [For information on other adverse reactions in pediatric patients, see Adverse Reactions (6.1)]. Adverse reactions reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in REMICADE-treated rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn’s disease patients except for abdominal pain, which occurred in 28% of REMICADE-treated patients with Crohn’s disease. In the Crohn’s disease studies, there were insufficient numbers and duration of follow-up for patients who never received REMICADE to provide meaningful comparisons.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>REMICADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of follow-up (weeks)</td>
<td>59</td>
<td>66</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>5%</td>
<td>10%</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>Cough</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>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Rash</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>Body as a whole-general disorders</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Resistance mechanism disorders</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Fever</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Central and peripheral nervous system disorders</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Headache</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Cardiovascular disorders, general</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
<td>7%</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:** pancytopenia
- **Cardiovascular:** hypotension
- **Gastrointestinal:** constipation, intestinal obstruction
- **Central and Peripheral Nervous:** dizziness
- **Heart Rate and Rhythm:** bradycardia
- **Liver and Biliary:** hepatitis
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 (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract infection (5%).

Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn’s and in 50% of adult patients in Study Crohn’s l. In Study Peds Crohn’s, infections were reported more frequently for patients who received every 8-week infusion compared to every 8-week maintenance group. 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 inactive examples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in Crohn’s disease clinical trials; 4% had ALT elevations ≥3 x ULN, and 2% (1/60) had elevations ≥5 x ULN (median follow-up was 49 weeks).

Serum infliximab concentrations [see Adverse Reactions (6.1)].

Respiratory:

- cellulitis, sepsis, serum sickness, sarcoidosis

Red Blood Cell:

- anemia, hemolytic anemia

Vascular (Extracardiac):

- thrombophlebitis

Adverse Reactions in Pediatric Patients

**Pediatric Crohn’s Disease**

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Serious adverse reactions in the post-marketing experience with REMICADE in pediatric patients have also included malignancies, including melanoma and Merkel cell carcinoma [see Warnings and Precautions (5.14) and (6.1)], acute liver failure, jaundice, hepatic, and cholestasis [see Warnings and Precautions (5.4)], serious infections [see Warnings and Precautions (5.1)], malignancies, including melanoma and Merkel cell carcinoma [see Warnings and Precautions (5.2)], and tuberculosis (disseminated BCG infection) following vaccination in an infant exposed in utero to infliximab [see Warnings and Precautions (5.14)].

**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.

Infections were reported more frequently for patients who received every 8-week infusion than in 385 adult Crohn’s disease patients receiving a similar treatment regimen. Of the 112 patients 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 inactive examples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in Crohn’s disease clinical trials; 4% had ALT elevations ≥3 x ULN, and 2% (1/60) had elevations ≥5 x ULN (median follow-up was 52 weeks.)

Pediatric Ulcerative Colitis

Overall, the adverse reactions reported in the pediatric ulcerative colitis trial and adult ulcerative colitis (Study UC I and Study UC II) studies were generally consistent. In a pediatric UC trial, the most common adverse reactions were upper respiratory tract infection, pharyngitis, abdominal pain, fever, and headache. Infections were reported in 31 (52%) of 60 treated patients in the pediatric UC trial and 19 (37%) of 52 patients in the every 8-week and 4 patients in the every 12-week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8-week and 1 in the every 12-week maintenance treatment groups).

Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group. Herpes zoster was also higher in the younger age group (60% vs. 49%), for serious infections, the proportion was similar in the younger age group (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%).

**Post-marketing Experience**

Adverse Reactions in Pediatric Patients

The following adverse reactions have been reported in the post-marketing experience with REMICADE in the pediatric population have also included malignancies, including hematopoietic T-cell lymphomas [see Boxed Warnings 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-blockers agents used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNFα-blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra or abatacept is not recommended [see Warnings and Precautions (5.9) and (5.10)].

7.2 Use with Tocilizumab

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

7.3 Use with Other Biological Therapeutics

The combination of REMICADE with other biological therapeutics used to treat the same conditions as REMICADE is not recommended [see Warnings and Precautions (5.11)].

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 were nonsteroidal anti-inflammatory agents (NSAIDs), corticosteroids, and 6-MP/AZA. MTX and abatacept were used together in 11% of patients with psoriatic arthritis. The combination of REMICADE and anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNFα-blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNFα-blocking agents. Therefore, the combination of REMICADE and anakinra or abatacept is not recommended [see Warnings and Precautions (5.9) and (5.10)].

7.5 Immunosuppressors

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)].
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 of age were randomized to placebo or 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, 18, and 20, and then every 8 weeks through Week 44. Patients who completed the study continued to receive open-label treatment with REMICADE for up to 2 years in a companion extension study.

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

A total of 60 patients with JRA were treated with doses of 3 mg/kg and 57 patients were treated with doses of 6 mg/kg. The proportion of patients with infusion reactions who received 3 mg/kg REMICADE was 35% (21/60) over 52 weeks compared with 18% (10/57) in patients who received 6 mg/kg over 38 weeks. The most common infusion reactions reported were vomiting, fever, headache, and hypotension. In the 3 mg/kg REMICADE group, 4 patients had a serious infusion reaction and 3 patients reported a possible anaphylactic reaction (2 of which were among the serious infusion reactions). In the 6 mg/kg REMICADE group, 2 patients had a serious infusion reaction, 1 of whom had a possible anaphylactic reaction. Two of the 6 patients who experienced serious infusion reactions received REMICADE by rapid infusion (duration of less than 2 hours). Antibodies to infliximab developed in 38% (20/53) of patients who received 3 mg/kg REMICADE compared with 12% (6/49) of patients who received 6 mg/kg.

A total of 86% (41/60) of patients who received 3 mg/kg REMICADE in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg REMICADE in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

**8.5 Geriatric Use**

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

**10 OVERDOSAGE**

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

**11 DESCRIPTION**

Infliximab, the active ingredient in REMICADE, is a chimeric IgG1x1 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 by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

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Infliximab, the active ingredient in REMICADE, is a chimeric IgG1x1 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 by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

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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 receptor as TNFα. Infliximab inhibits the functional activity of TNFα in a wide variety of in vitro bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T-lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which REMICADE exerts its clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and 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 the areas of inflammation in involved areas of the joint as well as expression of molecules mediating cellular adhesion (E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)), chemoattraction (IL-8 and monocyte 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 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 lymphocytes from REMICADE-treated patients showed no significant decrease in number or in proliferative responses to in vitro mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with REMICADE resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, REMICADE treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which REMICADE exerts its clinical effects is unknown.

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 8-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 Crohn's disease or ulcerative colitis following the administration of 5 mg/kg 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 48% (13/27) 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 10 mg/kg every 8 weeks. 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 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>
<thead>
<tr>
<th>Table 3 Clinical remission and steroid withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single 5-mg/kg Dose*</td>
</tr>
<tr>
<td>Placebo Maintenance</td>
</tr>
<tr>
<td>5 mg/kg</td>
</tr>
<tr>
<td><strong>Week 30</strong></td>
</tr>
<tr>
<td>25/102</td>
</tr>
<tr>
<td><strong>Clinical remission</strong></td>
</tr>
<tr>
<td>25%</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
</tr>
<tr>
<td><strong>Week 54</strong></td>
</tr>
<tr>
<td>6/54</td>
</tr>
<tr>
<td><strong>Patients in remission able to discontinue corticosteroid use</strong></td>
</tr>
<tr>
<td>11%</td>
</tr>
<tr>
<td><strong>P-values</strong></td>
</tr>
</tbody>
</table>

* REMICADE at Week 0
* REMICADE 5 mg/kg administered at Weeks 0, 2 and 6
* P-values represent pairwise comparisons to placebo
* Of those receiving corticosteroids at baseline

Patients in the REMICADE maintenance groups (5 mg/kg and 10 mg/kg) had a longer 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.
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 26 patients in the placebo group at Week 10. Of the REMICADE-treated patients showing mucosal healing at Week 10, 9 of 12 patients also showed mucosal healing at Week 54.

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

**Fistulizing Crohn’s Disease**

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

In the first trial, 94 patients received 3 doses of either placebo or REMICADE at Weeks 0, 2 and 6. Fistula response (≥50% reduction in number of enterocutaneous fistulas draining upon gentle compression on at least 2 consecutive visits without an increase in medication or surgery for Crohn’s disease) was seen in 68% (21/31) of patients in the 5 mg/kg REMICADE group (P = 0.002) and 56% (16/29) of patients in the 10 mg/kg REMICADE group (P = 0.021) vs. 26% (8/31) of patients in the placebo arm. The median time to onset of response and median duration of response in REMICADE-treated patients was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% of REMICADE-treated patients compared with 13% of placebo-treated patients (P < 0.001).

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

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

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

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

**Figure 2** Life table estimates of the proportion of patients who had not lost fistula response through Week 54

Patients who achieved a fistula response and subsequently lost response were eligible to receive REMICADE maintenance therapy at a dose that was 5 mg/kg higher than the dose to which they were randomized. Of the placebo maintenance patients, 66% (25/38) responded to 5 mg/kg REMICADE, and 57% (12/21) of REMICADE maintenance patients responded to 10 mg/kg.

Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of REMICADE.

Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

**14.2 Pediatric Crohn’s Disease**

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

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 59% were in clinical remission (defined as PCDAI score of ≤10 points).

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

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), (Table 4).

For patients in Study Peds Crohn’s receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the every 8-week maintenance group and 33% for the every 12-week maintenance group. At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the every 8-week maintenance group and 17% for the every 12-week maintenance group.
**REMICADE® (infliximab)**

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

<table>
<thead>
<tr>
<th>Patients randomized</th>
<th>Clinical Response</th>
<th>Clinical Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/kg REMICADE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 8 Week</td>
<td>73%</td>
<td>60%</td>
</tr>
<tr>
<td>Treatment Group</td>
<td>47%</td>
<td>35%</td>
</tr>
<tr>
<td>Every 12 Week</td>
<td>64%</td>
<td>56%</td>
</tr>
<tr>
<td>Treatment Group</td>
<td>33%</td>
<td>24%</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 PCDAI score of ≤10 points.

**14.3 Ulcerative Colitis**

The safety and efficacy of REMICADE were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayo score ≥6 to 12 [of possible range 0 to 12], Endoscopy subscore ≥2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted.

**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; 23% in REMICADE treatment groups vs. 3% in placebo group in Study UC III). 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</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>121</td>
<td>121</td>
<td>122</td>
</tr>
<tr>
<td>Clinical Responsea</td>
<td>37%</td>
<td>69%**</td>
<td>62%*</td>
</tr>
<tr>
<td>Week 8</td>
<td>29%</td>
<td>65%*</td>
<td>69%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>26%</td>
<td>47%*</td>
<td>60%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>44%*</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical Remissionb</td>
<td>14%</td>
<td>39%*</td>
<td>37%*</td>
</tr>
<tr>
<td>Week 8</td>
<td>15%</td>
<td>39%*</td>
<td>37%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>16%</td>
<td>34%**</td>
<td>37%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%</td>
<td>35%**</td>
<td>34%*</td>
</tr>
<tr>
<td>Sustained Remissiond</td>
<td>23%</td>
<td>49%*</td>
<td>46%*</td>
</tr>
<tr>
<td>Clinical response at both Week 8 and 30</td>
<td>15%</td>
<td>41%*</td>
<td>53%*</td>
</tr>
<tr>
<td>Clinical remission at Weeks 8, 30, and 54</td>
<td>14%</td>
<td>39%*</td>
<td>37%*</td>
</tr>
<tr>
<td>Mucosal Healingc</td>
<td>34%</td>
<td>62%*</td>
<td>59%*</td>
</tr>
<tr>
<td>Week 8</td>
<td>31%</td>
<td>60%*</td>
<td>62%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>25%</td>
<td>48%*</td>
<td>46%**</td>
</tr>
<tr>
<td>Week 54</td>
<td>18%</td>
<td>45%*</td>
<td>47%*</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.

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

*c* 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.

*d* Defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

**The improvement with REMICADE was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 8; 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>Placebo</th>
<th>5 mg/kg</th>
<th>10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Week 8</td>
<td>35%</td>
<td>60%</td>
</tr>
<tr>
<td>Week 30</td>
<td>35%</td>
<td>51%</td>
</tr>
<tr>
<td>Week 54</td>
<td>31%</td>
<td>52%</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>54%</td>
<td>40%</td>
</tr>
<tr>
<td>Week 8</td>
<td>74%</td>
<td>86%</td>
</tr>
<tr>
<td>Week 30</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td>Week 54</td>
<td>62%</td>
<td>69%</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Week 8</td>
<td>44%</td>
<td>74%</td>
</tr>
<tr>
<td>Week 30</td>
<td>36%</td>
<td>57%</td>
</tr>
<tr>
<td>Week 54</td>
<td>26%</td>
<td>53%</td>
</tr>
<tr>
<td>Endoscopy findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Week 8</td>
<td>34%</td>
<td>62%</td>
</tr>
<tr>
<td>Week 30</td>
<td>26%</td>
<td>51%</td>
</tr>
<tr>
<td>Week 54</td>
<td>21%</td>
<td>50%</td>
</tr>
</tbody>
</table>
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 therapies, 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.

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 were returned for safety follow-up. At Week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg MORICADE 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)c, 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 an increase in frequency of REMICADE administration due to loss of response. Nine of the 23 patients who required a dose increase 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 >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 dosages/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 response (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</th>
<th>Study RA I</th>
<th>Study RA II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + MTX</td>
<td>REMICADE + MTX</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>(n=88)</td>
<td>8%</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>(n=86)</td>
<td>13%</td>
</tr>
<tr>
<td>10 mg/kg</td>
<td>(n=87)</td>
<td>18%</td>
</tr>
</tbody>
</table>

* Placebo = 0% 6% 10% 14% 18% 22% 26% 30% 34% 38% 42% 46% 50% 54% 58% 62% 66% 70% 74% 78% 82% 86% 90% 94% 98% 100%* 100%

* A major clinical response was defined as a 70% ACR response for 8 consecutive months (consecutive visits spanning at least 26 weeks) through week 102 for Study RA I and week 54 for Study RA II.

*P<0.001  *P<0.01  *P<0.05

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

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Placebo + MTX</th>
<th>REMICADE + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Tender Joints</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td>6.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Patient’s Global Assessment</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)c</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>

* All dosages/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 (vDH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.3

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

In Study RA II, >90% of patients had at least 2 evaluable X-rays. Inhibition of progression of structural damage was observed at Weeks 30 and 54 (Table 9) in the REMICADE + MTX groups compared to MTX alone. Patients treated with REMICADE + MTX demonstrated less progression of structural damage compared to MTX alone, whether baseline acute-phase reactants (ESR and CRP) were normal or elevated: patients with elevated baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vDH-S score of 4.2 units compared to patients treated with REMICADE + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute phase reactants treated with MTX alone demonstrated a mean progression in vDH-S score of 2.8 units compared to patients treated with REMICADE + MTX who demonstrated 0.3 units of progression.

### Table 9 Progression of Structural Damage (Week 54 vs Baseline)

<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</td>
<td>18</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td>6.5</td>
<td>5.2</td>
</tr>
<tr>
<td>Patient’s Global Assessment</td>
<td>6.2</td>
<td>6.2</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)c</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>
REMICADE® (infliximab)

1.8 units compared to REMICADE + MTX who demonstrated 0.2 units of progression. Of patients receiving REMICADE + MTX, 59% had no progression (vs H-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%).

Table 9 Radiographic change from baseline to Week 54

<table>
<thead>
<tr>
<th>Study RA I</th>
<th>Study RA II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX</td>
<td>Placebo + MTX</td>
</tr>
<tr>
<td>REMICADE + MTX</td>
<td>REMICADE + MTX</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>(n=64)</td>
<td>(n=71)</td>
</tr>
<tr>
<td>Total Score</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>79</td>
</tr>
<tr>
<td>Median</td>
<td>55</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.9</td>
</tr>
<tr>
<td>Median</td>
<td>4.0</td>
</tr>
<tr>
<td>Erosion Score</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44</td>
</tr>
<tr>
<td>Median</td>
<td>25</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>4.1</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
</tr>
<tr>
<td>JSN Score</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>36</td>
</tr>
<tr>
<td>Median</td>
<td>26</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.9</td>
</tr>
<tr>
<td>Median</td>
<td>1.5</td>
</tr>
</tbody>
</table>

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).

Table 10 Components of ankylosing spondylitis disease activity

<table>
<thead>
<tr>
<th>ASAS 20 response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria (Mean)</td>
</tr>
<tr>
<td>Patient Global Assessmenta</td>
</tr>
<tr>
<td>Spinal painb</td>
</tr>
<tr>
<td>BASFIb</td>
</tr>
<tr>
<td>Inflammationc</td>
</tr>
<tr>
<td>Acute Phase Reactants</td>
</tr>
<tr>
<td>Median CRP (mg/dL)</td>
</tr>
<tr>
<td>Spinal Mobility (cm, Mean)</td>
</tr>
<tr>
<td>Modified Schober’s testd</td>
</tr>
<tr>
<td>Chest expansione</td>
</tr>
<tr>
<td>Tragus to wallf</td>
</tr>
<tr>
<td>Spinal flexibilityg</td>
</tr>
</tbody>
</table>

1P<0.001 for each outcome against placebo.

Physical function response

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

In Study RA I, all doses/schedules of REMICADE + MTX showed significantly greater improvement from baseline in HAQ-DI and SF-36 physical component summary score averaged over time through Week 54 compared to placebo + MTX, and no worsening in the SF-36 mental component summary score. The median (interquartile range) improvement from baseline to Week 54 in HAQ-DI was 0.1 (-0.1, 0.5) for the placebo + MTX group and 0.4 (0.1, 0.9) for REMICADE + MTX (p<0.001). Both HAQ-DI and SF-36 effects were maintained through Week 102. Approximately 80% of patients in all doses/schedules of REMICADE + MTX remained in the trial through 102 weeks.

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

14.6 Ankylosing Spondylitis

The safety and efficacy of REMICADE were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 278 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.5 Patients had 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.
REMICADE® (infliximab)

improvement from baseline in both swollen and tender joint counts were switched to REMICADE induction (early escape). At Week 24, all placebo-treated patients crossed over to REMICADE induction. Dosing continued for all patients through Week 46.

Clinical response

Treatment with REMICADE resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% 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 seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondyloarthropathy with peripheral arthritis subtypes.

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

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

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Placebo</th>
<th>REMICADE 5 mg/kg</th>
<th>Placebo</th>
<th>REMICADE 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Tender Joints</td>
<td>24</td>
<td>20</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>4</td>
<td>9</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td>6.4</td>
<td>5.6</td>
<td>5.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td>6.0</td>
<td>4.5</td>
<td>5.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Patient’s Global Assessment</td>
<td>6.1</td>
<td>5.0</td>
<td>5.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>0.5</td>
</tr>
<tr>
<td>CRP (mg/dL)</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 enthesopathy</td>
<td>35</td>
<td>36</td>
<td>42</td>
<td>22</td>
</tr>
</tbody>
</table>

*P<0.001 for percent change from baseline in all components of ACR 20 at Week 24, P<0.05 for 5% of patients with dactylitis, and P=0.004 for 4% of patients with enthesopathy at Week 24

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 for 43% for REMICADE-treated patients vs 0% for placebo-treated patients).

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

14.8 Plaque Psoriasis

The safety and efficacy of REMICADE were assessed in 3 randomized, double-blind, placebo-controlled studies in patients 18 years of age and older with chronic, stable plaque psoriasis involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with pustular, guttate, 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 8 weeks. Patients originally randomized to REMICADE continued to receive REMICADE 5 mg/kg every 8 weeks through Week 46. Across all treatment groups, the median baseline PASI score was 21 and the baseline Static Physician Global Assessment (sPGA) score ranged from moderate (52% 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 825 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 psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or REMICADE at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline 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 PASI score of 90 (PASI 90) by the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving REMICADE compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54. [See also Clinical Studies (14.8)].

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 -0.70 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%).
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></th>
<th>Placebo</th>
<th>REMICADE 3 mg/kg</th>
<th>REMICADE 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis Study I</td>
<td>patients randomized(^a)</td>
<td>77</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>PASI 75</td>
<td>2 (3%)</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>sPGA</td>
<td>3 (4%)</td>
<td>---</td>
</tr>
<tr>
<td>Psoriasis Study II</td>
<td>patients randomized(^a)</td>
<td>208</td>
<td>313</td>
</tr>
<tr>
<td></td>
<td>PASI 75</td>
<td>4 (2%)</td>
<td>220 (70%)*</td>
</tr>
<tr>
<td></td>
<td>rPGA</td>
<td>2 (1%)</td>
<td>217 (89%)*</td>
</tr>
<tr>
<td>Psoriasis Study III</td>
<td>patients randomized(^a)</td>
<td>51</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>PASI 75</td>
<td>3 (6%)</td>
<td>71 (72%)*</td>
</tr>
<tr>
<td></td>
<td>sPGA</td>
<td>5 (10%)</td>
<td>71 (72%)*</td>
</tr>
</tbody>
</table>

\(^a\) P<0.001 compared with placebo
\(^b\) Patients with missing data at Week 10 were considered as nonresponders.
\(^c\) Patients with missing data at Week 10 were imputed by last observation.

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

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

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

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING
Each REMICADE 20 mL vial is individually packaged in a carton. REMICADE is supplied in an accumulator carton containing 10 vials.

NDC 57894-030-01 100 mg vial
Each single dose vial contains 100 mg of infliximab for final reconstitution volume of 10 mL.

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

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

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

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Medication Guide)

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

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

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

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MEDICATION GUIDE
REMICADE® (Rem-eh-kaid)
(infliximab)

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 taking 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 take 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 TNF-blocking agents.
- For children and adults taking 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 COPD (a specific type of lung disease) may have an increased risk for getting cancer while being treated with REMICADE.
- 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 (doesn't 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 take 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 take 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 (Chronic Obstructive Pulmonary Disease), a specific type of lung disease. Patients with COPD may have an increased risk of getting cancer while taking 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 recently received or are scheduled to receive a vaccine. Adults and children taking 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 planning 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 planning to become pregnant.
- are breast-feeding or planning to breast-feed. It is not known whether REMICADE passes into your breast milk. Talk to your doctor about the best way to feed your baby while taking REMICADE. You should not breast-feed while taking REMICADE.

If you have a baby and you were using 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 taking 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 non-prescription 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 taking or after taking REMICADE:
  - a fever
  - feel very tired
  - have a cough
- 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 taking 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
  - poor appetite
  - tiredness (fatigue)
  - fever, skin rash, or joint pain

**Heart Failure**

If you have a heart problem called congestive heart failure, your doctor should check you closely while you are taking REMICADE. Your congestive heart failure may get worse while you are taking 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)**

### Liver Injury
In rare cases, some patients taking 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 taking 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
In rare cases, patients taking 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

### 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)
- high or low blood pressure
- difficulty breathing
- fever
- chest pain
- 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
- muscle or joint pain
- swelling of the face and hands
- headache
- difficulty swallowing
- sore throat
- rash on the cheeks or arms that gets worse in the sun

### 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

### Psoriasis
Some people using 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
- coughing
- headache
- stomach pain
- shortness of breath
- fever
- rash
- chills
- itching
- chest pain
- low blood pressure or high blood pressure

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**REMICADE® (infliximab)***
What are the possible side effects of REMICADE? (continued)
Children who took REMICADE in studies for Crohn’s disease showed some differences in side effects compared with adults who took 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 took 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.

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.
This Medication Guide summarizes the most important information about REMICADE. You can ask your doctor or pharmacist for information about REMICADE that is written for health professionals.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
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.