**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**INFLECTRA (infliximab-dyyb) for Injection, for Intravenous Use**

Initial U.S. Approval: 2016

INFLECTRA (infliximab-dyyb) is biosimilar* to REMICADE (infliximab) for the indications listed. (1)

**WARNING: SERIOUS INFECTIONS AND MALIGNANCY**

See full prescribing information for complete boxed warning.

- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, invasive fungal infections (such as histoplasmosis) and infections due to other opportunistic pathogens. (5.1)
- Discontinue INFLECTRA if a patient develops a serious infection. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting INFLECTRA. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)
- Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor (TNF) blockers, including infliximab products. (5.2)
- Postmarketing cases of fatal hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers, including infliximab products. Almost all had received azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of cases were reported in patients with Crohn’s disease or ulcerative colitis, most of whom were adolescent or young adult males. (5.2)

**INDICATIONS AND USAGE**

**Crohn's Disease (1.1):**

- INFLECTRA is a tumor necrosis factor (TNF) blocker indicated for:
  - Pediatric Crohn's Disease (2.2)
  - (2.10)

**DOSAGE AND ADMINISTRATION**

**Plaque Psoriasis (1.7):**

Psoriatic Arthritis (1.6):  
- Ankylosing Spondylitis (1.5):

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

**Rheumatoid Arthritis (2.4):**  
- 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 (2.5):**  
- 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

**Psoriatic Arthritis (2.6) and Plaque Psoriasis (2.7):**  
- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

- Serious infections -- do not give INFLECTRA during an active infection. If an infection develops, monitor carefully and stop INFLECTRA if infection becomes serious. (5.1)
- Invasive fungal infections -- for patients who develop a systemic illness on INFLECTRA, 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 TNF blocker 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 (HBV) reactivation -- test for HBV infection before starting INFLECTRA. Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop INFLECTRA and begin anti-viral therapy. (5.3)
- Hepatoxicity -- rare severe hepatic reactions, some fatal or necessitating liver transplantation. Stop INFLECTRA in cases of jaundice and/or marked liver enzyme elevations. (5.4)
- Heart failure -- new onset or worsening symptoms may occur. (4, 5.5)
- Cytoopenias -- advise patients to seek immediate medical attention if signs and symptoms develop, and consider stopping INFLECTRA. (5.6)
- Hypersensitivity -- serious infusion reactions including anaphylaxis or serum sickness-like reactions may occur. (5.7)
- Demyelinating disease -- exacerbation or new onset may occur. (5.8)
- Lupus-like syndrome -- stop INFLECTRA if syndrome develops. (5.13)
- Live vaccines or therapeutic infectious agents -- should not be given with INFLECTRA. Bring pediatric patients up to date with all vaccinations prior to initiating INFLECTRA. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants exposed in utero to infliximab products (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 -- INFLECTRA 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.

* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

**REVISED: 08/2016**
INDICATIONS AND USAGE

1.1 Crohn’s Disease

INFLECTRA is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy. INFLECTRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician [see Boxed Warning, Warnings and Precautions (5)].

1.2 Pediatric Crohn’s Disease

INFLECTRA 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

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

1.4 Psoriatic Arthritis

INFLECTRA is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis and improving physical function in patients with moderately to severely active rheumatoid arthritis.

1.5 Ankylosing Spondylitis

INFLECTRA is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

1.6 Psoriatic Arthritis

INFLECTRA 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.

1.7 Plaque Psoriasis

INFLECTRA 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. INFLECTRA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician [see Boxed Warning, Warnings and Precautions (5)].

2 DOSAGE AND ADMINISTRATION

2.1 Crohn’s Disease

The recommended dose of INFLECTRA 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.

Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue INFLECTRA in these patients.

2.2 Pediatric Crohn’s Disease

The recommended dose of INFLECTRA 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 INFLECTRA 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 moderate to severely active ulcerative colitis.

2.4 Rheumatoid Arthritis

The recommended dose of INFLECTRA 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.

INFLECTRA 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)].

2.5 Ankylosing Spondylitis

The recommended dose of INFLECTRA 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 6 weeks thereafter for the treatment of active ankylosing spondylitis.

2.6 Psoriatic Arthritis

The recommended dose of INFLECTRA 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. INFLECTRA can be used with or without methotrexate.

2.7 Plaque Psoriasis

The recommended dose of INFLECTRA 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.

2.8 Monitoring to Assess Safety

Prior to initiating INFLECTRA and periodically during therapy, patients should be evaluated for active tuberculosis and tested for latent infection [see Warnings and Precautions (5.5)].

2.9 Administration Instructions Regarding Infusion Reactions

Adverse effects during administration of infliximab products have included flu-like symptoms, headache, dyspnea, hypotension, transient fever, chills, gastrointestinal symptoms, and skin rashes. Anaphylaxis might occur at any time during INFLECTRA infusion. Approximately 20% of patients in all clinical trials of infliximab experienced an infusion reaction compared with 10% of placebo-treated patients [see Adverse Reactions (6.1)]. Prior to infusion with INFLECTRA, 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, INFLECTRA should be discontinued.

During or following infusion, patients who have severe infusion-related hypersensitivity reactions should be discontinued from further INFLECTRA 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.

2.10 General Considerations and Instructions for Preparation and Administration

INFLECTRA 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 INFLECTRA solution required and the number of INFLECTRA vials needed. Each INFLECTRA vial contains 100 mg of the infliximab-dyyb antibody.

2. Reconstitute each INFLECTRA 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 reconstituted solution concentration is 10 mg/mL. 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 reconstituted INFLECTRA solution dose to 250 mL with sterile 0.9% Sodium Chloride Injection, USP, by withdrawing a volume equal to the volume of reconstituted INFLECTRA from the 0.9% Sodium Chloride Injection, USP, 250 mL bottle or bag. Do not dilute the reconstituted INFLECTRA solution with any other diluent. Slowly add the total volume of reconstituted INFLECTRA solution to the 250 mL infusion bottle or bag. Gently mix. The resulting infusion concentration should range between 0.4 mg/mL and 4 mg/mL.

4. The INFLECTRA 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 coadministration of INFLECTRA with other agents. INFLECTRA 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

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

4 CONTRAINDICATIONS

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

INFLECTRA should not be readministered to patients who have experienced a severe hypersensitivity reaction to infliximab products. Additionally, INFLECTRA should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with infliximab products 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, 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 INFLECTRA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with comorbid 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 infliximab products, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with infliximab products during treatment for latent tuberculosis.

Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating therapy with INFLECTRA. 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 INFLECTRA, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Anti-tuberculosis therapy should also be considered prior to initiation of INFLECTRA 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 INFLECTRA 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 INFLECTRA, 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 INFLECTRA.
INFLECTRA should be discontinued if a patient develops a serious infection or sepsis.

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

Invasive Fungal Infections

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

5.2 Malignancies

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF blocking agents (initiation of therapy ≤18 years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphoma. The other cases represented a variety of malignancies (exclusive of lymphoma) among 4019 infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among control patients). Of these, the most common malignancies were breast, colorectal, and skin cancer.

Reactions (6.1)

In a clinical trial exploring the use of infliximab in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, the majority of lung or head and neck origin, were reported in infliximab-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 INFLECTRA in patients with moderate to severe COPD.

Psoriasis patients should be monitored for NMSCs, particularly those patients who have had prior prolonged phototherapy treatment. In the maintenance portion of clinical trials for infliximab, NMSCs were more common in patients with previous phototherapy [see Adverse Reactions (6.1)]. The potential role of TNF blocking therapy in the development of malignancies is not known [see Adverse Reactions (6.1)]. Rates in clinical trials for infliximab 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 INFLECTRA treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving INFLECTRA.

For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the risk of treating patients who are carriers of HBV with anti-TNF therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, TNF blockers should be stopped and anti-viral therapy with appropriate supportive treatment provided. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, prescribers should exercise caution when considering resumption of TNF blocker therapy in this situation and monitor patients closely.

5.4 Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving infliximab products. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between 2 weeks to more than 1 year after initiation of infliximab; elevations in liver enzymes, including alkaline phosphatase and bilirubin, have been reported with liver injury of hepatitis nature in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develop, INFLECTRA should be discontinued, and a thorough investigation of the abnormality should be undertaken. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving infliximab products without progression to severe hepatic injury [see Adverse Reactions (6.1)].

5.5 Patients with Heart Failure

Infliximab products have been associated with adverse outcomes in patients with heart failure, and INFLECTRA should be used in patients with heart failure only after consideration of other treatment options. The results of a randomized study evaluating the use of infliximab in patients with heart failure (NYHA Functional Class III/IV) suggested higher mortality in patients who received 10 mg/kg infliximab, and higher rates of cardiovascular adverse events at doses of 5 mg/kg and 10 mg/kg. There have been post-marketing reports of worsening heart failure, with and without identifiable precipitating factors, in patients taking infliximab. There have also been rare postmarketing reports of new onset heart failure, including heart failure in patients without known pre-existing cardiovascular disease. Some of these patients have been under 50 years of age. If a decision is made to administer INFLECTRA to patients with heart failure, they should be closely monitored during therapy, and INFLECTRA should be discontinued if new or worsening symptoms of heart failure appear [see Contraindications (4) and Adverse Reactions (6.1)].

5.6 Hematologic Reactions

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving infliximab products. The causal relationship to infliximab therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with INFLECTRA 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 INFLECTRA.

Discontinuation of INFLECTRA therapy with infliximab products was reinstalled following an extended period without treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema.

Hematologic Reactions

5.7 Hypersensitivity

Infliximab products have 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 been observed during or within 2 hours of infusion. However, in some cases, serum sickness-like reactions have been observed in patients after initial therapy with infliximab products (i.e., as early as after the second dose), and when therapy was reinitiated, and in patients taking infliximab. The rate of malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.
and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab product, loss of detectable serum concentrations of infliximab products, and possible loss of drug efficacy. INFLECTRA should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be administered for immediate use in the event of a reaction [see Adverse Reactions (6.1)]. In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to no-treatment maintenance treatment [see Adverse Reactions (6.1)]. In general, the benefit-risk of readministration of INFLECTRA after a period of no-treatment, especially as a reinduction regimen given at weeks 0, 2 and 6, should be carefully considered. In the case where INFLECTRA maintenance therapy for psoriasis is interrupted, INFLECTRA should be reinitiated as a single dose followed by maintenance therapy.

5.8 Neurologic Reactions
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 associated with various neurologically-based disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of INFLECTRA in patients with these neurologic disorders and should consider discontinuation of INFLECTRA if these disorders develop.

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

5.10 Use with Abatacept
In 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 INFLECTRA 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 infliximab products with other biological therapeutics used to treat the same conditions as INFLECTRA. The concomitant use of INFLECTRA with these biologics is not recommended because of the possibility of an increased risk of infection [see Drug Interactions (7.3)].

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 infliximab products 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 INFLECTRA, 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 is contraindicated in clinical infections, including disseminated infections. The concurrent administration of live vaccines with INFLECTRA is not recommended. Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after in utero exposure to infliximab products. Infliximab products are known to cross the placenta and have been detected up to 6 months following birth. At least a six month waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to infliximab products. Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG, blader instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with INFLECTRA.

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not predict the rates observed in broader patient populations in clinical practice. Adverse reactions in adults

The data described herein reflect exposure to infliximab in 4,779 adult patients (1,304 patients with rheumatoid arthritis, 1,106 patients with Crohn's disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1,373 with plaque psoriasis, and 17 patients with other conditions), including 2,625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. For information on adverse reactions in pediatric patients see Adverse Reactions (6.1)]. One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash).

Infusion-related Reactions
An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In phase 3 clinical studies, 18% of patients treated with infliximab experienced an infusion reaction compared to 5% of placebo-treated patients. Of these 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 infusions with infliximab, 3% were accompanied by nonspecific symptoms such as fever, chills, weight loss, fatigue, or nausea, and 3% were accompanied by infusion reactions (primarily 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 treatment with infliximab because of infusion reactions, and all patients recovered with treatment and discontinuation of the infusion. Infusion reactions following 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 were those who were negative. Use of concomitant immunosuppressant agents appeared to reduce the frequency of both antibodies to infliximab and infusion reactions [see Adverse Reactions (6.1) and Drug Interactions (7.4)].

Infusion reactions following readministration
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 infliximab, 6.2% of cases with infusion reactions beyond the induction therapy arm experienced serious infusion reactions versus <1% (1/222) 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 swelling, and hypotension. In a Phase 3 trial, infusion discontinuation and/or discontinuation of the infusion therapy was more frequent in the 10 mg/kg infliximab group than in the 5 mg/kg and placebo groups (5.4% and 2.5% respectively).

Delayed Reactions/Reactions Following Readministration
In psoriasis studies, approximately 1% of patients treated with infliximab experienced a delayed hypedersensitivity 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 infliximab clinical studies, treated infections were reported in 36% of patients treated with infliximab (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 patients treated with infliximab, serious infections included pneumonia, cellulitis, abscess, skin ulceration, sepsis, and bacterial infection. In clinical trials, 7 opportunistic infections were reported; 2 cases each of coccidioidomycosis (1 case was fatal) and histoplasmosis (1 case was fatal), and 1 case each of pneumocystosis, Cryptococcus, cytomegalovirus, and aspergillosis. Tuberculosis was reported in 14 patients, 4 of whom experienced serious infusion reactions versus <1% (1/222) 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 swelling, and hypotension. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported postmarketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with infliximab and may reflect reactivation 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 receiving infliximab every 8 weeks and 3.7% of patients with methotrexate (MTX) developed serious infections as compared to 3.4% of placebo patients receiving MTX.

Of 924 patients receiving infliximab, 1.7% developed pneumonia and 0.4% developed tuberculosis, when compared to 0.3% and 0.0% in the placebo arm respectively. In a shorter (22-week) placebo-controlled study of 1082 RA patients randomized to receive placebo, 3 mg/kg or 10 mg/kg infusions with infliximab at 0, 2, and 6 weeks, followed by every 8 weeks with MTX, serious infections were more frequent in the 10 mg/kg infliximab group (5.6%) 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 new fistula-related abscess.

In clinical studies with infliximab in patients with ulcerative colitis, infections treated with antimicrobials were reported in 27% of patients treated with infliximab (average of 41 weeks of follow-up) and in 18% of placebo-treated patients (average 32 weeks of follow-up). The types of infections, including serious infections, reported in patients with 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 patients treated with infliximab in clinical trials who were antinuclear antibody (ANA) negative at baseline developed a positive ANA during the trial compared with approximately one-fifth of placebo-treated patients. Anti-dsDNA antibodies were not detected. Approximately one-fifth of patients treated with infliximab compared with 0% of placebo-treated patients. Reports of lupus and lupus-like syndromes, however, remain uncommon.
Malignancies
In controlled trials, more patients treated with infliximab developed malignancies than placebo-treated patients [see Warnings and Precautions (5.2)]. In a randomized controlled clinical trial exploring the use of infliximab in patients with moderate to severe COPD who were either current smokers or ex-smokers, 157 patients were treated with infliximab at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these patients treated with infliximab, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% confidence interval [CI] 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.83 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head and neck.

Patients with Heart Failure
In a randomized study evaluating infliximab in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤35%), 150 patients were randomized to receive treatment with 3 infusions of infliximab at 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were noted in patients treated with infliximab compared to placebo. At week 14, 8 patients in the 10 mg/kg infliximab group had died compared with 4 deaths each in the 5 mg/kg infliximab and the placebo groups. There were trends toward increased dyspnea, hypotension, angina, and dizziness in both the 10 mg/kg and 5 mg/kg infliximab treatment groups, versus placebo. Infliximab has not been studied in patients with mild heart failure (NYHA Class I/II) [see Contraindications (4) and Warnings and Precautions (5.5)].

Immunogenicity
Treatment with infliximab products 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 in patients given a 3-dose induction regimen followed by maintenance dosing was approximately 10% as assessed through 1 to 2 years of treatment with infliximab. A higher incidence of antibodies to infliximab was observed in Crohn's disease patients receiving infliximab 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 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-mercapto purine/azathioprine (6-MP/AZA) or MTX.

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

The data reflect the percentage of patients whose test results were positive for antibodies to infliximab in an ELISA assay, and 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 products 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 infliximab products [see Warnings and Precautions (5.5)]. Reactivation of HBV has occurred in patients receiving TNF blocking agents, including infliximab products, who are chronic carriers of this virus [see Warnings and Precautions (5.5)]. 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 infliximab than in controls (Table 1), both when infliximab 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 infliximab, or modification of concomitant medications.
Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn’s, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn’s, there were no serious infection reactions, and 2 patients had non-serious anaphylactoid reactions. In Study Peds Crohn’s, in which all patients received stable doses of 6-MP, AZA, or MTX, excluding inconclusive samples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample. Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 18% of pediatric patients in Crohn’s disease clinical trials; 4% had ALT elevations ≥3 x ULN, and 1% had elevations ≥5 x ULN. (Median follow-up was 53 weeks.)

6.2 Postmarketing Experience

Adverse reactions have been reported during post approval use of infliximab products in adult and pediatric patients. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions, some with fatal outcome, have been reported during postapproval use of infliximab products: neutropenia [see Warnings and Precautions (5.8)], interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, pericardial effusion, systemic and cutaneous vasculitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, peripheral demyelinating disorders (such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy), new onset and worsening psoriasis (all subtypes including pustular, primarily palmoplantar), transverse myelitis, and neutropathies (additional neurologic reactions have also been observed) [see Warnings and Precautions (5.8)], acute liver failure, jaundice, hepatitis, and cholestasis [see Warnings and Precautions (5.4)], serious infections [see Warnings and Precautions (5.1)] and malignancies, including melanoma and Merkel cell carcinoma [see Warnings and Precautions (5.2)] and vaccine breakthrough infection following vaccination in an infant exposed in utero to infliximab [see Warnings and Precautions (5.14)].

Infusion-related Reactions

In postmarketing experience, cases of anaphylactic reactions, including laryngeal/ pharyngeal edema and severe bronchospasm, and seizure have been associated with administration of infliximab products. Cases of myocardial ischemia/infarction and transient visual loss have also been rarely reported in association with infliximab products during or within 2 hours of infusion.

Adverse Reactions in Pediatric Patients

The following serious adverse reactions have been reported in the postmarketing experience in children: infections (some fatal) including opportunistic infections and tuberculosis, infusion reactions, and hypersensitivity reactions. Serious adverse reactions in the postmarketing experience with infliximab products in the pediatric population have also included malignancies, including HSTCL [see Boxed Warning and Warnings and Precautions (5.1)], transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.

7. DRUG INTERACTIONS

7.1 Use with Anakinra or Abatacept

An increased risk of serious infections was seen in clinical studies of other TNFα blocking agents used in combination with anakinra or abatacept, with no added clinical benefit. Because of the nature of the adverse reactions seen with these combinations with TNF blocker therapy, similar toxicities may also result from the combination of anakinra or abatacept with other TNFα blocking agents. Therefore, the combination of INFLECTRA 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 INFLECTRA, 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 INFLECTRA with other biological therapeutics used to treat the same conditions as INFLECTRA 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, 6-MP/aza and aminosalicylates. In psoriatic arthritis clinical trials, concomitant medications included MTX in approximately half of the patients as well as NSAIDs, folic acid and corticosteroids. Concomitant MTX use may decrease the incidence of anti-infliximab antibody production and increase infliximab concentrations.

7.5 Immunosuppressants

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

7.6 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, interleukin-1 (IL-1), IL-6, IL-10, IFN) during chronic inflammation. Therefore,
The safety and efficacy of infliximab products have been established in pediatric patients 6 to 17 years of age for induction and maintenance treatment of Crohn's disease. However, infliximab products have not been studied in children with Crohn's disease or conditions other than Crohn's disease. It is not known whether infliximab products are excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from infliximab products, women should not breast-feed their infants while taking INFLECTRA. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Nursing Mothers

It is not known whether infliximab products are excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from infliximab products, women should not breast-feed their infants while taking INFLECTRA. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.5 Geriatric Use

Infliximab-dyyb, the active ingredient in INFLECTRA, is a chimeric IgG1 monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNF-α). It has a molecular weight of approximately 149,130 daltons. Infliximab-dyyb 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.

INFLECTRA for injection is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab-dyyb, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg sodium diphosphate monohydrate, and 6.1 mg di-Sodium hydrogen phosphate dihydrate. No preservatives are present.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infliximab-dyyb, the active ingredient in INFLECTRA, is a chimeric IgG1 monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNF-α). It has a molecular weight of approximately 149,130 daltons. Infliximab-dyyb 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.

INFLECTRA for injection is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab-dyyb, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg sodium diphosphate monohydrate, and 6.1 mg di-Sodium hydrogen phosphate dihydrate. No preservatives are present.

12.2 Pharmacodynamics

Elevated concentrations of TNF-α 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 infliximab products results in decreases in the number of inflammatory cells into 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)], chemokine receptor expression in T cells and monocytes, and extracellular matrix deposition [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with infliximab products reduced infiltration of inflammatory cells and TNF-α production in inflamed intestinal mucosa and submucosal fat compared to placebo treatment. In psoriasis, treatment with infliximab products reduced expression of TNF-α in lesional skin.
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, infliximab products treatment may reduce the epidermal thickness and infiltration of inflammatory cells. The relationship between these pharmacodynamic activities and the mechanism(s) by which infliximab products exert their clinical effects is unknown.

12.3 Pharmacokinetics
In adults, single intravenous infusions of 3 mg/kg to 20 mg/kg of infliximab 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 infliximab, 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 infliximab, 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 following the administration of 5 mg/kg of infliximab. Population pharmacokinetic analysis showed that in children with JRA with body weight greater than 35 kg up to adult body weight receiving 3 mg/kg infliximab product, the steady state area under the concentration curve (AUCss) was similar to that observed in adults receiving 3 mg/kg of infliximab.

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 following the administration of 5 mg/kg of infliximab.

In a multidose trial (ACCENT I [Study Crohn’s I]), 545 patients received 5 mg/kg at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg of infliximab at Weeks 0, 2 and 6 and then every 8 weeks. Fistula response (absolute reduction in fistula counts from baseline) was seen in 68% (21/31) of patients in the infliximab group (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 of infliximab achieved clinical remission in medication or surgery for Crohn’s disease) was seen in 68% (21/31) of patients in the 5 mg/kg infliximab group (P=0.002) and 56% (18/32) of patients in the 10 mg/kg infliximab 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 patients treated with infliximab was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% patients treated with infliximab 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 5 mg/kg of infliximab at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg maintenance with infliximab at Week 14. Patients received maintenance doses at

### Table 3 Clinical remission and steroid withdrawal

<table>
<thead>
<tr>
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<th>Single 5-mg/kg Dose</th>
<th>Three-Dose Induction</th>
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<tbody>
<tr>
<td></td>
<td>Placebo Maintenance</td>
<td>Infliximab Maintenance 8 Wks</td>
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<tr>
<td></td>
<td>5 mg/kg</td>
<td>10 mg/kg</td>
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<tr>
<td>Week 30 Clinical remission</td>
<td>25/102</td>
<td>41/104</td>
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<td>P-value</td>
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<td>0.001</td>
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<tr>
<td>Patients in remission</td>
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<td>14/56</td>
</tr>
<tr>
<td>P-value</td>
<td>0.222</td>
<td>0.001</td>
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<tr>
<td>Patients in remission</td>
<td>11%</td>
<td>25%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.059</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Patients in infliximab 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 improvements from baseline were seen among the 5 mg/kg and 10 mg/kg groups treated with infliximab 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.

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

In a subset of 78 patients who had mucosal ulceration at baseline and who participated in an endoscopic substudy, 13 of 43 patients in infliximab maintenance group had endoscopic evidence of mucosal healing compared to 1 of 28 patients in the placebo group at Week 10. Of the patients treated with infliximab 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 infliximab 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 maintenance patients on infliximab 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)].

### Fostulating Crohn’s Disease

The safety and efficacy of infliximab 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-MP and/or AZA was permitted.

In the first trial, 94 patients received 3 doses of either placebo or infliximab 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 infliximab group (P=0.002) and 56% (18/32) of patients in the 10 mg/kg infliximab 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 patients treated with infliximab was 2 and 12 weeks, respectively. Closure of all fistulas was achieved in 52% patients treated with infliximab 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 5 mg/kg of infliximab at Weeks 0, 2 and 6. Patients were randomized to placebo or 5 mg/kg maintenance with infliximab at Week 14.
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 maintenance with infliximab had a longer time to loss of fistula response compared to the placebo maintenance group (Figure 2). At Week 54, 38% (33/87) of patients treated with infliximab had no draining fistulas compared with 22% (20/90) of placebo-treated patients (P=0.02). Compared to placebo maintenance, patients on maintenance treatment with infliximab had a trend toward fewer hospitalizations.

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

Patients who achieved a fistula response and subsequently lost response were eligible to receive maintenance therapy with infliximab 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 infliximab, and 57% (12/21) of maintenance patients on infliximab responded to 10 mg/kg.

Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of infliximab. 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 infliximab 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 ulcerative colitis (UC) (Mayo score5 6 to 12 [of possible range 0 to 12]; Endoscopy subscore ≥2) with an inadequate response to conventional oral therapies (Studies UC I and UC II). Concomitant treatment with stable doses of aminosalicylates, corticosteroids and/or immunomodulatory agents was permitted. Corticosteroid taper was permitted after Week 6. Patients were randomized at Week 0 to receive either placebo, 5 mg/kg infliximab or 10 mg/kg infliximab at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 46 in Study UC I, and at Weeks 0, 2, 6, and every 8 weeks thereafter through Week 22 in Study UC II. In Study UC II, patients were allowed to continue blinded therapy to Week 46 at the investigator’s discretion.

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

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both infliximab 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 infliximab 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 groups treated with infliximab were in clinical remission and able to discontinue corticosteroids at Week 30 compared with the patients in the placebo treatment groups (22% in infliximab treatment groups vs. 10% in placebo group in Study UC I; 23% in infliximab treatment groups vs. 12% in placebo group in Study UC II). Clinical response at Week 14 and then every 8 weeks through Week 46. Patients who were in clinical remission at Week 30 was 46% for the every 8-week maintenance group and 17% for the every 12-week maintenance group.

Table 4 Response and remission in Study Peds Crohn’s

<table>
<thead>
<tr>
<th></th>
<th>Every 6 Week Treatment Group</th>
<th>Every 12 Week Treatment Group</th>
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<tr>
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<td>Clinical Response</td>
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<tr>
<td>Week 30</td>
<td>73%*</td>
<td>47%</td>
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<tr>
<td>Week 54</td>
<td>64%*</td>
<td>37%</td>
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<td>Clinical Remission</td>
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<tr>
<td>Week 30</td>
<td>60%*</td>
<td>35%</td>
</tr>
<tr>
<td>Week 54</td>
<td>56%*</td>
<td>24%</td>
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</table>

a Defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician’s global assessment and endoscopy findings.)

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

<table>
<thead>
<tr>
<th>Study UC I</th>
<th>Placebo 5 mg/kg Infliximab 10 mg/kg Infliximab Placebo 5 mg/kg Infliximab 10 mg/kg Infliximab</th>
<th>Study UC II</th>
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<tr>
<td>Patients randomized</td>
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<tr>
<td>Clinical Response</td>
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<tr>
<td>Week 8</td>
<td>37%</td>
<td>69%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>30%</td>
<td>52%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>20%</td>
<td>45%*</td>
</tr>
<tr>
<td>Sustained Response</td>
<td>Clinical response at both Week 8 and 30 and Clinical response at both Week 30 and 54</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>23%</td>
<td>49%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>14%</td>
<td>39%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%</td>
<td>35%*</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>Clinical remission at both Week 8 and 30</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>15%</td>
<td>39%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>16%</td>
<td>34%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%</td>
<td>35%*</td>
</tr>
<tr>
<td>Sustained Remission</td>
<td>Clinical remission at both Week 8 and 30</td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>8%</td>
<td>23%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>7%</td>
<td>20%*</td>
</tr>
<tr>
<td>Mucosal Healing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>25%</td>
<td>50%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>34%</td>
<td>62%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>18%</td>
<td>45%*</td>
</tr>
</tbody>
</table>

* P<0.001, ** P<0.01

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 PCDAI score of ≤15 points and total score of ≤30 points.

c Defined as a PCDAI score of ≤10 points.

d P-value <0.05

e P-value <0.01

Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study drug due to lack of efficacy were considered not to be in clinical response, clinical remission or mucosal healing from the time of the event onward.
The improvement with infliximab was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 6; Study UC II through Week 30 was similar).

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

<table>
<thead>
<tr>
<th>Study UC I</th>
<th>Placebo (n=121)</th>
<th>5 mg/kg (n=121)</th>
<th>10 mg/kg (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17%</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Week 8</td>
<td>35%</td>
<td>60%</td>
<td>58%</td>
</tr>
<tr>
<td>Week 30</td>
<td>35%</td>
<td>51%</td>
<td>53%</td>
</tr>
<tr>
<td>Week 54</td>
<td>31%</td>
<td>52%</td>
<td>51%</td>
</tr>
<tr>
<td>Rectal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>54%</td>
<td>40%</td>
<td>48%</td>
</tr>
<tr>
<td>Week 8</td>
<td>74%</td>
<td>86%</td>
<td>80%</td>
</tr>
<tr>
<td>Week 30</td>
<td>65%</td>
<td>74%</td>
<td>71%</td>
</tr>
<tr>
<td>Week 54</td>
<td>62%</td>
<td>69%</td>
<td>67%</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Week 8</td>
<td>44%</td>
<td>74%</td>
<td>64%</td>
</tr>
<tr>
<td>Week 30</td>
<td>36%</td>
<td>57%</td>
<td>55%</td>
</tr>
<tr>
<td>Week 54</td>
<td>26%</td>
<td>53%</td>
<td>53%</td>
</tr>
<tr>
<td>Endoscopy findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Week 8</td>
<td>34%</td>
<td>62%</td>
<td>59%</td>
</tr>
<tr>
<td>Week 30</td>
<td>26%</td>
<td>51%</td>
<td>52%</td>
</tr>
<tr>
<td>Week 54</td>
<td>21%</td>
<td>50%</td>
<td>51%</td>
</tr>
</tbody>
</table>

### 14.4 Rheumatoid Arthritis

The safety and efficacy of infliximab were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted. Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of the infliximab + MTX: 3 mg/kg or 10 mg/kg infliximab by intravenous infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX. Study RA II was a placebo-controlled study of 3 active treatment arms in 1004 MTX naive patients of 3 or fewer years’ duration active rheumatoid arthritis. Patients enrolled had a median age of 51 years with a median disease duration of 0.6 years, median swollen and tender joint count of 19 and 31, respectively, and >80% of patients had baseline joint erosions. At randomization, all patients received MTX (optimized to 20 mg/wk by Week 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX).

#### Clinical Response

In Study RA I, all doses/schedules of infliximab + 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 infliximab + MTX compared to placebo + MTX (Table 8). More patients treated with infliximab reached a major clinical response than placebo-treated patients (Table 7).

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

### Table 7 ACR response (percent of patients) for infliximab

<table>
<thead>
<tr>
<th>Study RA I</th>
<th>Infliximab + MTX 3 mg/kg</th>
<th>Infliximab + MTX 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX (n=88)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=88)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=81)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=274)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=351)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
</tbody>
</table>

#### ACR 20

<table>
<thead>
<tr>
<th>Study RA I</th>
<th>Infliximab + MTX 3 mg/kg</th>
<th>Infliximab + MTX 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX (n=88)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=88)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=87)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=274)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=351)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
</tbody>
</table>

#### ACR 50

<table>
<thead>
<tr>
<th>Study RA I</th>
<th>Infliximab + MTX 3 mg/kg</th>
<th>Infliximab + MTX 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + MTX (n=88)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=88)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=87)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=274)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
<tr>
<td>Placebo + MTX (n=351)</td>
<td>q8 wks</td>
<td>q8 wks</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Baseline</th>
<th>Week 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Tender Joints</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td>6.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Patient’s Global Assessment</td>
<td>6.2</td>
<td>6.3</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>3.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

#### 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 (vH-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 infliximab + MTX groups compared to MTX alone. Patients treated with infliximab + 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 vH-S score of 4.2 units compared to patients treated with infliximab + MTX who demonstrated 0.5 units of progression; patients with normal baseline acute-phase reactants treated with MTX alone demonstrated a mean progression in vH-S score of 1.8 units compared to infliximab + MTX who demonstrated 0.2 units of progression. Of patients receiving infliximab + MTX, 59% had no progression (vH-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, infliximab + 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 infliximab + MTX groups (47%) developed erosions in uninvolved joints compared to MTX alone (59%).
At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving infliximab, compared to 9% and 4%, respectively, for patients receiving placebo (P < 0.001, infliximab vs. placebo). A low level of disease activity (defined as a value <20 [on a scale of 0 - 100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of patients treated with infliximab vs. 1% in placebo-treated patients (P < 0.001).

### Table 10 Components of ankylosing spondylitis disease activity

<table>
<thead>
<tr>
<th>Criteria (Mean)</th>
<th>Placebo</th>
<th>Infliximab 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24 Weeks</td>
<td>Baseline 24 Weeks</td>
</tr>
<tr>
<td>ASAS 20 response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Global Assessment</td>
<td>6.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Spinal pain*</td>
<td>7.3</td>
<td>6.5</td>
</tr>
<tr>
<td>BASFI²</td>
<td>5.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Inflammation²</td>
<td>6.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Acute Phase Reactants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median CRP (mg/dL)</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Spinal Mobility (cm, Mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Schober’s test*</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Chest expansion</td>
<td>3.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Tragus to wall³</td>
<td>17.3</td>
<td>17.4</td>
</tr>
<tr>
<td>Lateral spinal flexion³</td>
<td>10.6</td>
<td>11.0</td>
</tr>
</tbody>
</table>

a Measured on a VAS with 0 = “none” and 10 = “severe”

b Bath Ankylosing Spondylitis Functional Index (BASFI), average of 10 questions
c Inflammation, average of last 2 questions on the 6-question BASPDI
d CRP normal range 0–1.0 mg/dL

The median improvement from baseline in the general health-related quality-of-life questionnaire SF-36 physical component summary score at Week 24 was 10.2 for infliximab group vs. 0.8 for the placebo group (P < 0.001). There was no change in the SF-36 mental component summary score in either infliximab group or the placebo group.

Results of this study were similar to those seen in a multicenter double-blind, placebo-controlled study of 70 patients with ankylosing spondylitis. 14.6 Psoriatic Arthritis

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

### Clinical response

Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of patients treated with infliximab 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 infliximab 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 mutans and spondylitis with peripheral arthritis subtypes.

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

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

<table>
<thead>
<tr>
<th>Patients Randomized</th>
<th>Placebo (n=100)</th>
<th>Infliximab 5 mg/kg (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 24</td>
</tr>
<tr>
<td>Parameter (medians)</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>No. of Tender Joints</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>No. of Swollen Joints</td>
<td>6.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Pain</td>
<td>6.0</td>
<td>4.5</td>
</tr>
<tr>
<td>Physician’s Global Assessment</td>
<td>6.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Disability Index (HAQ-DI)</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>% Patients with 1 or more digits with dactylitis</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>% Patients with enthesopathy</td>
<td>35</td>
<td>36</td>
</tr>
</tbody>
</table>

Improvement in Psoriasis Area and Severity Index (PASI) in psoriatic arthritis patients with baseline body surface area (BSA) ≥3% (n=87 placebo, n=83 infliximab) was achieved at Week 14, regardless of concomitant methotrexate use, with 64% of patients treated with infliximab achieving at least 75% improvement from baseline vs. 2% of placebo-treated patients; improvement was observed in some patients as early as Week 2. At 6 months, the PASI 75 and PASI 90 responses were achieved by 60% and 39%, respectively, of patients receiving infliximab compared to 1% and 0%, respectively, of patients receiving placebo. The PASI response was generally maintained through Week 54. [See also Clinical Studies (14.9).]

Radiographic response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vHS-S) score, modified by the addition of hand DIP joints. The total modified vHS-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, patients treated with infliximab had less radiographic progression than placebo-treated patients (mean change of 0.70 vs. 0.82, P<0.001). Patients treated with infliximab also had less progression in their erosion scores (0.56 vs 0.51) and JSN scores (-0.14 vs 0.31). The patients in infliximab group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vHS-S score after 1 year of treatment (median change of 0 in both patients who initially received infliximab or placebo). More patients in the placebo group (12%) had readily apparent radiographic progression compared with infliximab group (3%).

Physical function

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

During the placebo-controlled portion of the trial (24 weeks), 54% of patients treated with infliximab achieved a clinically meaningful improvement in HAQ-DI (≥0.3 unit decrease) compared to 22% of placebo-treated patients. Patients treated with infliximab 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.

14.7 Plaque Psoriasis

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

Study I (EXPRESS) evaluated 378 patients who received placebo or infliximab 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 infliximab induction therapy (5 mg/kg), followed by maintenance therapy every 8 weeks. Patients originally randomized to infliximab continued to receive infliximab 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 (36%) to severe (2%). In addition, 75% of patients had a BSA ≥20%, Seventy-one percent of patients previously received systemic therapy, and 82% received phototherapy.

Study II (EXPRESS II) evaluated 835 patients who received placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6 (induction therapy). At Week 14, within each 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 infliximab 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 infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a PASI score of moderate or worse (greater than or equal to 3) or a change from Week 0 in PASI ≥14.7 (14.7) were randomized to either scheduled (every 8 weeks) or as needed (PRN) maintenance treatment through Week 46. Across all treatment groups, the median baseline PASI score was 0, and the baseline PASI score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA ≥20%. Of the enrolled patients, 114 (46%) received the Week 26 additional dose.

In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a score of “cleared” or “minimal” by the sPGA. The sPGA is a 6-category scale ranging from “5 = severe” to “0 = cleared” indicating the physician’s overall assessment of the psoriasis severity focusing on induration, erythema, and scaling. Treatment success, defined as “cleared” or “minimal,” consisted of none or minimal elevation in plaque, up to faint red coloration in erythema, and none or minimal fine scale over ≤50% of the plaque.

Study II also evaluated the proportion of patients who achieved a score of “clear” or “excellent” by the relative Physician’s Global Assessment (rPGA). The rPGA is a 6-category scale ranging from “0 = worst” to “1 = clear” that was assessed by the treating physician. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as “clear” or “excellent,” consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

Table 12 Psoriasis studies I, II, and III, Week 10 percentage of patients who achieved PASI75 and percentage who achieved treatment “success” with Physician’s Global Assessment

<table>
<thead>
<tr>
<th>PASI75</th>
<th>Placebo</th>
<th>3 mg/kg</th>
<th>5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>77</td>
<td>--</td>
<td>301</td>
</tr>
<tr>
<td>PASI75</td>
<td>2 (3%)</td>
<td>--</td>
<td>242 (80%)*</td>
</tr>
<tr>
<td>sPGA</td>
<td>3 (4%)</td>
<td>--</td>
<td>242 (80%)*</td>
</tr>
</tbody>
</table>

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 infliximab achieved a PASI 75 at Week 10 respectively, 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 infliximab 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 infliximab achieved a PASI 75 at Week 10 respectively, compared with 4% of patients 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 infliximab achieved a PASI 75 at Week 10 respectively, compared with 4% of patients 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 infliximab achieved a PASI 75 at Week 10 respectively, compared with 4% of patients on placebo.

Compared to placebo, treatment with infliximab 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.
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 infliximab 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.

Efficacy and safety of infliximab 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.
What is INFLECTRA?
INFLECTRA 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 - adults with moderately to severely active ulcerative colitis who have not responded well to other medicines.

INFLECTRA 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. INFLECTRA can block the damage caused by too much TNF-alpha.

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

Tell your doctor about all of your medical conditions, including if you:
• have an infection (see “What is INFLECTRA?”).
• 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 INFLECTRA.
• 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 INFLECTRA.
• 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 INFLECTRA.
• have or have had a condition that affects your nervous system such as multiple sclerosis, or Guillain-Barré syndrome, or if you experience any numbness or tingling, or if you have had a seizure.
• have recently received or are scheduled to receive a vaccine. Adults and children taking INFLECTRA should not receive live vaccines (for example, the Bacille Calmette-Guerin [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 INFLECTRA.
• are pregnant or planning to become pregnant. It is not known if INFLECTRA harms your unborn baby. INFLECTRA should be given to a pregnant woman only if clearly needed. Talk to your doctor about stopping INFLECTRA if you are pregnant or planning to become pregnant.

MEDICATION GUIDE
INFLECTRA™ (In-flec-tra) (infliximab-dyyb)

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

1. Risk of infection
INFLECTRA is a medicine that affects your immune system. INFLECTRA can lower the ability of your immune system to fight infections. Serious infections have happened in patients receiving INFLECTRA. 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 INFLECTRA.
• Your doctor should monitor you closely for signs and symptoms of TB during treatment with INFLECTRA.

Before starting INFLECTRA, tell your doctor if you:

• think you have an infection. You should not start taking INFLECTRA 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 INFLECTRA. 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 INFLECTRA.

After starting INFLECTRA, 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. INFLECTRA 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, such as INFLECTRA.
• For children and adults taking TNF blocker medicines, the chances of getting lymphoma or other cancers may increase.
• Some people receiving TNF-blockers 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 infliximab products, such as INFLECTRA 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 INFLECTRA, tell your doctor.
• Patients with COPD (a specific type of lung disease) may have an increased risk for getting cancer while being treated with INFLECTRA.
• 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 INFLECTRA?” below for more information.
Serious Infections

• Some patients, especially those 65 years and older have had serious infections while receiving infliximab products, such as INFLECTRA. 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 INFLECTRA your doctor will treat your infection and may need to stop your INFLECTRA treatment.

• Tell your doctor right away if you have any of the following signs of an infection while taking or after taking INFLECTRA:
  o a fever
  o feel very tired
  o have a cough
  o have flu-like symptoms
  o warm, red, or painful skin

• Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with INFLECTRA and during treatment with INFLECTRA.

• Even if your TB test is negative, your doctor should carefully monitor you for TB infections while you are taking INFLECTRA. Patients who had a negative TB skin test before receiving infliximab products 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 INFLECTRA. 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 INFLECTRA and occasionally while you are being treated. Tell your doctor if you have any of the following symptoms:
  o feel unwell
  o poor appetite
  o tiredness (fatigue)
  o 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 INFLECTRA. Your congestive heart failure may get worse while you are taking INFLECTRA. Be sure to tell your doctor of any new or worse symptoms including:
  o shortness of breath
  o swelling of ankles or feet
  o sudden weight gain

Treatment with INFLECTRA may need to be stopped if you get new or worse congestive heart failure.

Liver Injury

In rare cases, some patients taking infliximab products have developed serious liver problems. Tell your doctor if you have
  o jaundice (skin and eyes turning yellow)
  o dark brown-colored urine
  o pain on the right side of your stomach area (right-sided abdominal pain)
  o fever
  o extreme tiredness (severe fatigue)

Blood Problems

In some patients taking INFLECTRA, the body may not make enough of the blood cells that help fight infections or help stop bleeding. Tell your doctor if you
  o have a fever that does not go away
  o bruise or bleed very easily
  o look very pale

Nervous System Disorders

In rare cases, patients taking infliximab products have developed problems with their nervous system. Tell your doctor if you have
  o changes in your vision
  o weakness in your arms or legs
  o numbness or tingling in any part of your body
  o seizures
Allergic Reactions
Some patients have had allergic reactions to infliximab products. Some of these reactions were severe. These reactions can happen while you are getting your INFLECTRA treatment or shortly afterward. Your doctor may need to stop or pause your treatment with INFLECTRA and may give you medicines to treat the allergic reaction. Signs of an allergic reaction can include:
- hives (red, raised, itchy patches of skin)
- difficulty breathing
- chest pain
- high or low blood pressure
- fever
- chills

Some patients treated with infliximab products have had delayed allergic reactions. The delayed reactions occurred 3 to 12 days after receiving treatment with infliximab products. Tell your doctor right away if you have any of these signs of delayed allergic reaction to INFLECTRA:
- fever
- sore throat
- difficulty swallowing
- rash
- muscle or joint pain
- headache
- swelling of the face and hands

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 INFLECTRA:
- 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 infliximab products 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 INFLECTRA.

The most common side effects of infliximab products include:
- respiratory infections, such as sinus infections and sore throat
- headache
- coughing
- stomach pain

Infusion reactions can happen up to 2 hours after your infusion of INFLECTRA.

Symptoms of infusion reactions may include:
- fever
- chills
- chest pain
- low blood pressure or high blood pressure
- shortness of breath
- rash
- itching