CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125544Orig1s000

<u>LABELING</u>

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----------

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

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

Pediatric Crohn's Disease (1.2):
- reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Ulcerative Colitis (1.3):
- reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis (1.4) in combination with methotrexate:
- reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active disease.

Ankylosing Spondylitis (1.5):
- reducing signs and symptoms in patients with active disease.

Psoriatic Arthritis (1.6):
- reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function.

Plaque Psoriasis (1.7):
- 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.

----------DOSAGE AND ADMINISTRATION----------

INFLECTRA is administered by intravenous infusion over a period of not less than 2 hours. (2.10)

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

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

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

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.

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 100 mg of lyophilized infliximab-dyyb in a 20 mL vial for intravenous infusion. (3)

----------CONTRAINDICATION----------

- 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)

----------WARNING 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)
- Hepatotoxicity – 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)
- Cytopenias – 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)

To report SUSPECTED ADVERSE REACTIONS, contact CELLTRION, Inc. at 1-800-383-7504 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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----------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)

----------DRUG INTERACTIONS----------

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

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.

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS and MALIGNANCY

SERIOUS INFECTIONS

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

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

Reported infections include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before INFLECTRA use and during therapy.[1,2] Treatment for latent infection should be initiated prior to INFLECTRA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.**

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

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

MALIGNANCY

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

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell

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lymphoma, have been reported in patients treated with TNF blockers including infliximab products. These cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males.

1 INDICATIONS AND USAGE

1.1 Crohn's Disease

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 is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

1.2 Pediatric Crohn's Disease

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 inadequate response to conventional therapy.

1.4 Rheumatoid Arthritis

INFLECTRA, in combination with methotrexate, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

1.5 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.

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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 adult patients with moderately 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.

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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 (5.1)*].

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

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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 the 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.

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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, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with 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.

<u>Tuberculosis</u>

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

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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 INFLECTRA and periodically during therapy. Treatment of latent tuberculosis infection prior to therapy with TNF blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating 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

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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, including rare malignancies that are usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported postmarketing and are derived from a variety of sources, including registries and spontaneous postmarketing reports.

Lymphomas

In the controlled portions of clinical trials of all the TNF blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. In the controlled and open-label portions of infliximab clinical trials, 5 patients developed lymphomas among 5707 patients treated with infliximab (median duration of follow-up 1.0 years) vs. 0 lymphomas in 1600 control patients (median duration of follow-up 0.4 years). In rheumatoid arthritis patients, 2 lymphomas were observed for a rate of 0.08 cases per 100 patient-years of follow-up, which is approximately three-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 5 lymphomas were observed for a rate of 0.10 cases per 100 patient-years of follow-up, which is approximately four-fold higher than expected in the general population. Patients with Crohn's disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies**,** may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF blocking therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Hepatosplenic T-cell Lymphoma (HSTCL)

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have been reported in patients treated with TNF blockers, including infliximab products. These

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cases have had a very aggressive disease course and have been fatal. Almost all patients had received treatment with the immunosuppressants azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF blockers or TNF blockers in combination with these other immunosuppressants. When treating patients, consideration of whether to use INFLECTRA alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine should take into account a possibility that there is a higher risk of HSTCL with combination therapy versus an observed increased risk of immunogenicity and hypersensitivity reactions with infliximab product monotherapy from the clinical trial data from studies with infliximab [see *Warnings and Precautions (5.7)* and *Adverse Reactions (6.1)*].

Skin Cancer

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

Other Malignancies

In the controlled portions of clinical trials of some TNF blocking agents, including infliximab products, more malignancies (excluding lymphoma and nonmelanoma skin cancer [NMSC]) have been observed in patients receiving those TNF blockers compared with control patients. During the controlled portions of trials with infliximab, in patients with moderately to severely active rheumatoid arthritis, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and plaque psoriasis, 14 patients were diagnosed with malignancies (excluding lymphoma and NMSC) among 4019 infliximab-treated patients vs. 1 among 1597 control patients (at a rate of 0.52/100 patient-years among infliximab-treated patients vs. a rate of 0.11/100 patient-years among control patients), with median duration of follow-up 0.5 years for infliximab-treated patients and 0.4 years for control patients. Of these, the most common malignancies were breast, colorectal, and melanoma. The rate of malignancies among infliximab-treated patients was similar to that expected in the general population whereas the rate in control patients was lower than expected.

In a clinical trial exploring the use of 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.

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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.

5.3 Hepatitis B Virus Reactivation

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

5.4 Hepatotoxicity

Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported 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 hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with

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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 should be considered in patients who develop significant hematologic abnormalities.

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 occurred 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 with infliximab products was reinstituted following an extended period without

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treatment. Symptoms associated with these reactions include fever, rash, headache, sore throat, myalgias, polyarthralgias, hand and facial edema and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab 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 available for immediate use in the event of a reaction [see *Adverse Reactions (6.1)*].

In rheumatoid arthritis, Crohn's disease and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to regular maintenance treatment [see *Adverse Reactions (6.1)*]. In general, the benefit-risk of 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 and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of 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 TNFα blocking agents. Therefore, the combination of INFLECTRA and anakinra is not recommended.

5.10 Use with Abatacept

In clinical studies, concurrent administration of TNF blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF blocking agents alone, without increased clinical benefit. Therefore, the combination of

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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 could result 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 bladder 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.

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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 4779 adult patients (1304 patients with rheumatoid arthritis, 1106 patients with Crohn's disease, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 484 with ulcerative colitis, 1373 with plaque psoriasis, and 17 patients with other conditions), including 2625 patients exposed beyond 30 weeks and 374 exposed beyond 1 year. [For information on adverse reactions in pediatric patients see *Adverse Reactions (6.1)*]. One of the most common reasons for discontinuation of treatment was infusion-related reactions (e.g., dyspnea, flushing, headache and rash).

Infusion-related Reactions

An infusion reaction was defined in clinical trials as any adverse event occurring during an infusion or within 1 hour after an infusion. In phase 3 clinical studies, 18% of 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 or chills, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and <1% were accompanied by pruritus, urticaria, or the combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Serious infusion reactions occurred in <1% of patients and included anaphylaxis, convulsions, erythematous rash and hypotension. Approximately 3% of patients discontinued treatment with infliximab because of infusion reactions, and all patients recovered with treatment and/or discontinuation of the infusion. Infliximab infusions beyond the initial infusion were not associated with a higher incidence of reactions. The infusion reaction rates remained stable in psoriasis through 1 year in psoriasis Study I. In psoriasis Study II, the rates were variable over time and somewhat higher following the final infusion than after the initial infusion. Across the 3 psoriasis studies, the percent of total infusions resulting in infusion reactions (i.e., an adverse event occurring within 1 hour) was 7% in the 3 mg/kg group, 4% in the 5 mg/kg group, and 1% in the placebo group.

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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 following disease flare, 4% (8/219) of patients in the re-treatment 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 edema, and hypotension. In all cases, treatment with infliximab was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Delayed Reactions/Reactions Following Readministration

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

Infections

In 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, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom died due to miliary tuberculosis. Other cases of tuberculosis, including disseminated tuberculosis, also have been reported postmarketing. Most of these cases of tuberculosis occurred within the first 2 months after initiation of therapy with infliximab and may reflect recrudescence of latent disease [see *Warnings and Precautions (5.1)*]. In the 1-year placebo-controlled studies RA I and RA II, 5.3% of patients receiving infliximab every 8 weeks with methotrexate (MTX) developed serious infections as compared to 3.4% of placebo patients

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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 (5.3%) than the 3 mg/kg or placebo groups (1.7% in both). During the 54-week Crohn's II Study, 15% of patients with fistulizing Crohn's disease developed a 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 newly detected in 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 1.63 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head and neck.

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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 observed in patients receiving the 10 mg/kg infliximab dose. At 1 year, 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-mercaptopurine /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

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induction. Despite the increase in antibody formation, the infusion reaction rates in Studies I and II in patients treated with 5 mg/kg induction followed by every 8 week maintenance for 1 year and in Study III in patients treated with 5 mg/kg induction (14.1% - 23.0%) and serious infusion reaction rates (<1%) were similar to those observed in other study populations. The clinical significance of apparent increased immunogenicity on efficacy and infusion reactions in psoriasis patients as compared to patients with other diseases treated with 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 (5.4)*]. 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 (5.3)*].

In clinical trials in rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, and psoriatic arthritis, elevations of aminotransferases were observed (ALT more common than AST) in a greater proportion of patients receiving 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.

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Table 1 Proportion of patients with elevated ALT in clinical trials

	Proportion of patients with elevated ALT					
	>1 to 3 x ULN		≥3 x ULN		≥5 x ULN	
	Placebo	**Infliximab**	**Placebo**	**Infliximab**	**Placebo**	**Infliximab**
Rheumatoid arthritis[a]	24%	34%	3%	4%	<1%	<1%
Crohn's disease[b]	34%	39%	4%	5%	0%	2%
Ulcerative colitis[c]	12%	17%	1%	2%	<1%	<1%
Ankylosing spondylitis[d]	15%	51%	0%	10%	0%	4%
Psoriatic arthritis[e]	16%	50%	0%	7%	0%	2%
Plaque psoriasis[f]	24%	49%	<1%	8%	0%	3%

a Placebo patients received methotrexate while patients treated with infliximab received both infliximab and methotrexate. Median follow-up was 58 weeks.

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

c Median follow-up was 30 weeks. Specifically, the median duration of follow-up was 30 weeks for placebo and 31 weeks for infliximab.

d Median follow-up was 24 weeks for the placebo group and 102 weeks for infliximab group.

e Median follow-up was 39 weeks for infliximab group and 18 weeks for the placebo group.

f ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 50 weeks for infliximab and 16 weeks for placebo.

Adverse Reactions in Psoriasis Studies

During the placebo-controlled portion across the 3 clinical trials up to week 16, the proportion of patients who experienced at least 1 serious adverse reaction (SAE; defined as resulting in death, life threatening, requires hospitalization, or persistent or significant disability/incapacity) was 0.5% in the 3 mg/kg infliximab group, 1.9% in the placebo group, and 1.6% in the 5 mg/kg infliximab group.

Among patients in the 2 Phase 3 studies, 12.4% of patients receiving infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 SAE in Study I. In Study II, 4.1% and 4.7% of patients receiving infliximab 3 mg/kg and 5 mg/kg every 8 weeks, respectively, through 1 year of maintenance treatment experienced at least 1 SAE.

One death due to bacterial sepsis occurred 25 days after the second infusion of 5 mg/kg of infliximab. Serious infections included sepsis, and abscesses. In Study I, 2.7% of patients receiving infliximab 5 mg/kg every 8 weeks through 1 year of maintenance treatment experienced at least 1 serious infection. In Study II, 1.0% and 1.3% of patients receiving infliximab 3 mg/kg and 5 mg/kg, respectively, through 1 year of treatment experienced at least 1

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serious infection. The most common serious infection (requiring hospitalization) was abscess (skin, throat, and peri-rectal) reported by 5 (0.7%) patients in the 5 mg/kg infliximab group. Two active cases of tuberculosis were reported: 6 weeks and 34 weeks after starting infliximab.

In the placebo-controlled portion of the psoriasis studies, 7 of 1123 patients who received infliximab at any dose were diagnosed with at least one NMSC compared to 0 of 334 patients who received placebo.

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

Other Adverse Reactions

Safety data are available from 4779 adult patients treated with infliximab, including 1304 with rheumatoid arthritis, 1106 with Crohn's disease, 484 with ulcerative colitis, 202 with ankylosing spondylitis, 293 with psoriatic arthritis, 1373 with plaque psoriasis and 17 with other conditions. [For information on other adverse reactions in pediatric patients, see *Adverse Reactions (6.1)*]. Adverse reactions reported in ≥5% of all patients with rheumatoid arthritis receiving 4 or more infusions are in Table 2. The types and frequencies of adverse reactions observed were similar in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis and Crohn's disease patients treated with infliximab except for abdominal pain, which occurred in 26% of patients with Crohn's disease. In the Crohn's disease studies, there were insufficient numbers and duration of follow-up for patients who never received infliximab to provide meaningful comparisons.

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

	Placebo	Infliximab
	(n=350)	(n=1129)
Average weeks of follow-up	59	66
Gastrointestinal		
Nausea	20%	21%
Abdominal pain	8%	12%
Diarrhea	12%	12%
Dyspepsia	7%	10%
Respiratory		
Upper respiratory tract infection	25%	32%
Sinusitis	8%	14%
Pharyngitis	8%	12%
Coughing	8%	12%
Bronchitis	9%	10%
Skin and appendages disorders		
Rash	5%	10%
Pruritus	2%	7%
Body as a whole-general disorder		
Fatigue	7%	9%
Pain	7%	8%
Resistance mechanism disorders		
Fever	4%	7%
Moniliasis	3%	5%
Central and peripheral nervous system disorders		
Headache	14%	18%
Musculoskeletal system disorders		
Arthralgia	7%	8%
Urinary system disorders		
Urinary tract infection	6%	8%
Cardiovascular disorders, general		
Hypertension	5%	7%

The most common serious adverse reactions observed in clinical trials of infliximab were infections [see *Adverse Reactions (6.1)*]. Other serious, medically relevant adverse reactions ≥0.2%

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or clinically significant adverse reactions by body system were as follows:

Body as a whole: allergic reaction, edema
Blood: pancytopenia
Cardiovascular: hypotension
Gastrointestinal: constipation, intestinal obstruction
Central and Peripheral Nervous: dizziness
Heart Rate and Rhythm: bradycardia
Liver and Biliary: hepatitis
Metabolic and Nutritional: dehydration
Platelet, Bleeding and Clotting: thrombocytopenia
Neoplasms: lymphoma
Red Blood Cell: anemia, hemolytic anemia
Resistance Mechanism: cellulitis, sepsis, serum sickness, sarcoidosis
Respiratory: lower respiratory tract infection (including pneumonia), pleurisy, pulmonary edema
Skin and Appendages: increased sweating
Vascular (Extracardiac): thrombophlebitis
White Cell and Reticuloendothelial: leukopenia, lymphadenopathy

Adverse Reactions in Pediatric Patients

Pediatric Crohn's Disease

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

The following adverse reactions were reported more commonly in 103 randomized pediatric Crohn's disease patients administered 5 mg/kg infliximab through 54 weeks than in 385 adult Crohn's disease patients receiving a similar treatment regimen: anemia (11%), leukopenia (9%), flushing (9%), viral infection (8%), neutropenia (7%), bone fracture (7%), bacterial infection (6%), and respiratory tract allergic reaction (6%).

Infections were reported in 56% of randomized pediatric patients in Study Peds Crohn's and in 50% of adult patients in Study Crohn's I. In Study Peds Crohn's, infections were reported more frequently for patients who received every 8-week as opposed to every 12-week infusions (74% and 38%, respectively), while serious infections were reported for 3 patients in the every 8-week and 4 patients in the every 12-week maintenance treatment group. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was abscess. Pneumonia was reported for 3 patients, (2 in the every 8-

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week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group.

In Study Peds Crohn's, 18% of randomized patients experienced 1 or more infusion reactions, with no notable difference between treatment groups. Of the 112 patients in Study Peds Crohn's, there were no serious infusion reactions, and 2 patients had non-serious anaphylactoid reactions. In Study Peds Crohn's, in which all patients received stable doses of 6-MP, AZA, or MTX, excluding inconclusive samples, 3 of 24 patients had antibodies to infliximab. Although 105 patients were tested for antibodies to infliximab, 81 patients were classified as inconclusive because they could not be ruled as negative due to assay interference by the presence of infliximab in the sample.

Elevations of ALT up to 3 times the upper limit of normal (ULN) were seen in 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 (5.6)*], 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 neuropathies (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 including bovine tuberculosis (disseminated BCG infection) following vaccination in an infant exposed in utero to infliximab [see *Warnings and Precautions* (5.14)].

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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 (5.2)*], transient hepatic enzyme abnormalities, lupus-like syndromes, and the development of autoantibodies.

7 DRUG INTERACTIONS

7.1 Use with Anakinra or Abatacept

An increased risk of serious infections was seen in clinical studies of other TNFα blocking agents used in combination with anakinra or abatacept, with no added clinical benefit. 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

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MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn's disease medications were antibiotics, anti-virals, 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, it is expected that for a molecule that antagonizes cytokine activity, such as infliximab products, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of INFLECTRA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

7.7 Live Vaccines/Therapeutic Infectious Agents

It is recommended that live vaccines not be given concurrently with INFLECTRA. It is also recommended that live vaccines not be given to infants after *in utero* exposure to infliximab products for at least 6 months following birth [see *Warnings and Precautions (5.14)*].

It is recommended that therapeutic infectious agents not be given concurrently with INFLECTRA [see *Warnings and Precautions (5.14)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. It is not known whether infliximab products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. INFLECTRA should be given to a pregnant woman only if clearly needed. Because infliximab products do not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with infliximab products. No evidence of maternal toxicity, embryotoxicity or teratogenicity was observed in a developmental toxicity study conducted in

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mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα.

Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNF analogous antibody produced maximal pharmacologic effectiveness. Doses up to 40 mg/kg were shown to produce no adverse effects in animal reproduction studies.

As with other IgG antibodies, infliximab products cross the placenta. Infliximab has been detected in the serum of infants at up to 6 months following birth. Consequently, these infants may be at increased risk of infection, including disseminated infection which can become fatal. At least a six month waiting period following birth is recommended before the administration of live vaccines (e.g., BCG vaccine or other live vaccines, such as the rotavirus vaccine) to these infants [see *Warnings and Precautions (5.14)*].

8.3 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.

8.4 Pediatric Use

The safety and effectiveness 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 ulcerative colitis <6 years of age.

<u>Pediatric Crohn's Disease</u>

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

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

A pediatric assessment for INFLECTRA demonstrates that INFLECTRA is safe and effective in

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another pediatric indication. However, INFLECTRA is not approved for such indication due to marketing exclusivity for REMICADE (infliximab).

Juvenile Rheumatoid Arthritis (JRA)

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

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

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

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

A total of 68% (41/60) of patients who received 3 mg/kg of infliximab in combination with MTX experienced an infection over 52 weeks compared with 65% (37/57) of patients who received 6 mg/kg of infliximab in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella

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infection in 1 patient and herpes zoster in 1 patient.

8.5 Geriatric Use

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

10 OVERDOSAGE

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

11 DESCRIPTION

Infliximab-dyyb, the active ingredient in INFLECTRA, is a chimeric IgG1κ monoclonal antibody (composed of human constant and murine variable regions) specific for human tumor necrosis factor-alpha (TNFα). It has a molecular weight of approximately 149.1 kilodaltons. Infliximab-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 dihydrogen phosphate monohydrate, and 6.1 mg di-Sodium hydrogen phosphate dihydrate. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Infliximab products neutralize the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibit binding of TNFα with its receptors. Infliximab products do not neutralize TNFβ (lymphotoxin-α), a related cytokine that utilizes the

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same receptors as TNFα. Biological activities attributed to TNFα include: induction of proinflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab products can be lysed *in vitro* or *in vivo*. Infliximab products inhibit the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. The relationship of these biological response markers to the mechanism(s) by which infliximab products exert their clinical effects is unknown. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab products prevent disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal.

12.2 Pharmacodynamics

Elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and plaque psoriasis. In rheumatoid arthritis, treatment with infliximab products reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion [E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)], chemoattraction [IL-8 and monocyte chemotactic protein (MCP-1)] and tissue degradation [matrix metalloproteinase (MMP) 1 and 3]. In Crohn's disease, treatment with infliximab products reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine, and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon. After treatment with infliximab products, patients with rheumatoid arthritis or Crohn's disease exhibited decreased levels of serum IL-6 and C-reactive protein (CRP) compared to baseline. Peripheral blood lymphocytes from infliximab product-treated patients showed no significant decrease in number or in proliferative responses to *in vitro* mitogenic stimulation when compared to cells from untreated patients. In psoriatic arthritis, treatment with infliximab products resulted in a reduction in the number of T-cells and blood vessels in the synovium and psoriatic skin lesions as well as a reduction of macrophages in the synovium. In plaque psoriasis, 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.

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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 a body weight of up to 35 kg receiving 6 mg/kg of infliximab and children with JRA with body weight greater than 35 kg up to adult body weight receiving 3mg/kg infliximab product, the steady state area under the concentration curve (AUC_{ss}) was similar to that observed in adults receiving 3 mg/kg of infliximab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The significance of the results of nonclinical studies for human risk is unknown. A repeat dose toxicity study was conducted with mice given cV1q anti-mouse TNFα to evaluate tumorigenicity. CV1q is an analogous antibody that inhibits the function of TNFα in mice. Animals were assigned to 1 of 3 dose groups: control, 10 mg/kg or 40 mg/kg cV1q given weekly for 6 months. The weekly doses of 10 mg/kg and 40 mg/kg are 2 and 8 times, respectively, the human dose of 5 mg/kg for Crohn's disease. Results indicated that cV1q did not cause tumorigenicity in mice. No clastogenic or mutagenic effects of infliximab were observed in the *in vivo* mouse

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micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes. It is not known whether infliximab products can impair fertility in humans. No impairment of fertility was observed in a fertility and general reproduction toxicity study with the analogous mouse antibody used in the 6-month chronic toxicity study.

14 CLINICAL STUDIES

14.1 Crohn's Disease

Active Crohn's Disease

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

In the single-dose trial of 108 patients, 16% (4/25) of placebo patients achieved a clinical response (decrease in CDAI ≥70 points) at Week 4 vs. 81% (22/27) of patients receiving 5 mg/kg infliximab (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 (CDAI<150) at Week 4.

In a multidose trial (ACCENT I [Study Crohn's I]), 545 patients received 5 mg/kg at Week 0 and were then randomized to one of three treatment groups; the placebo maintenance group received placebo at Weeks 2 and 6, and then every 8 weeks; the 5 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then every 8 weeks; and the 10 mg/kg maintenance group received 5 mg/kg at Weeks 2 and 6, and then 10 mg/kg every 8 weeks. Patients in response at Week 2 were randomized and analyzed separately from those not in responses at Week 2. Corticosteroid taper was permitted after Week 6.

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

Additionally, a significantly greater proportion of patients in the 5 mg/kg and 10 mg/kg maintenance groups of infliximab were in clinical remission and were able to discontinue corticosteroid use compared to patients in the placebo maintenance group at Week 54 (Table 3).

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Table 3 Clinical remission and steroid withdrawal

	Single 5-mg/kg Dose[a]	Three-Dose Induction[b]	
	Placebo Maintenance	Infliximab Maintenance q 8wks	
		5 mg/kg	10 mg/kg
Week 30			
Clinical remission	25/102 25%	41/104 39%	48/105 46%
P-value[c]		0.022	0.001
Week 54			
Patients in remission able to discontinue corticosteroid use[d]	6/54 11%	14/56 25%	18/53 34%
P-value[c]		0.059	0.005

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

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 improvement from baseline was 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.

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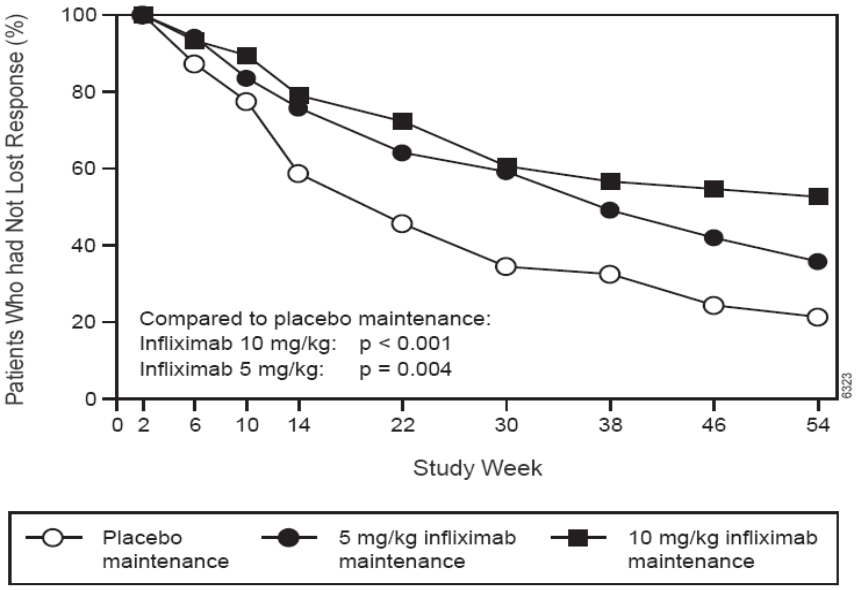

Figure 1 Kaplan-Meier estimate of the proportion of patients who had not lost response through Week 54

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)*].

Fistulizing 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.

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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. Patients received maintenance doses at Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

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

At Week 14, 65% (177/273) of patients were in fistula response. Patients randomized to 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.

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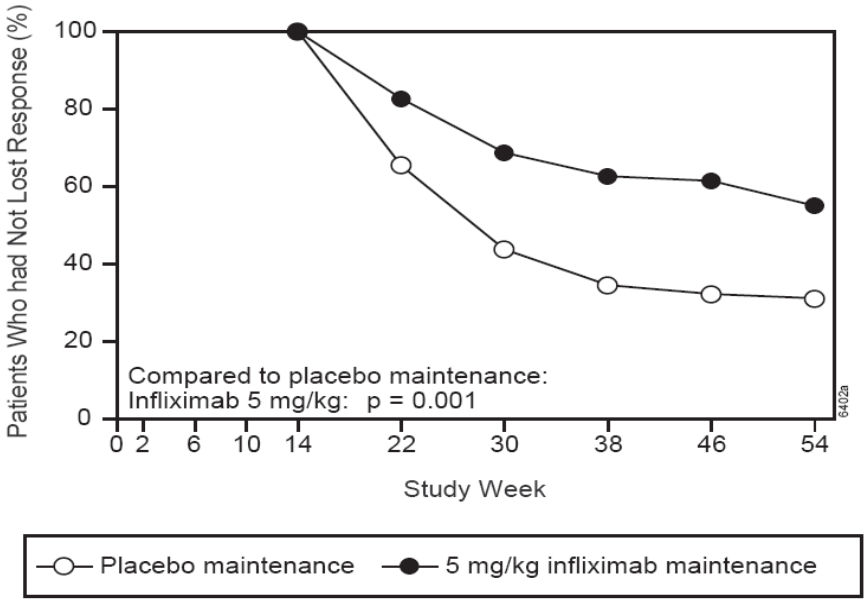

Figure 2 Life table estimates of the proportion of patients who had not lost fistula response through Week 54

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 Crohn's disease and an inadequate response to conventional therapies. The median age was 13 years and the median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 (on a scale of 0 to 100). All patients were required to be on a stable dose of 6-MP, AZA, or MTX; 35% were also receiving corticosteroids at baseline.

All patients received induction dosing of 5 mg/kg of infliximab at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of 5 mg/kg of infliximab given either

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every 8 weeks or every 12 weeks.

At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥15 points and total PCDAI score of ≤30 points), and 59% were in clinical remission (defined as PCDAI score of ≤10 points).

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

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

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

Table 4 Response and remission in study peds Crohn's

	5 mg/kg Infliximab	
	Every 8 Week Treatment Group	**Every 12 Week Treatment Group**
Patients randomized	52	51
Clinical Response[a]		
Week 30	73%[d]	47%
Week 54	64%[d]	33%
Clinical Remission[b]		
Week 30	60%[c]	35%
Week 54	56%[d]	24%

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

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14.3 Ulcerative Colitis

The safety and efficacy of infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 patients with moderately to severely active ulcerative colitis (UC) (Mayo score[5] 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 8. 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 treatments and/or aminosalicylates. Similar proportions of patients in Studies UC I and UC II were receiving corticosteroids (61% and 51%, respectively), 6-MP/AZA (49% and 43%) and aminosalicylates (70% and 75%) at baseline. More patients in Study UC II than UC I were taking solely aminosalicylates for UC (26% vs. 11%, respectively). Clinical response was defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Clinical Response, Clinical Remission, and Mucosal Healing

In both Study UC I and Study UC II, greater percentages of patients in both 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. 3% in placebo group in Study UC II). In Study UC I, this effect was maintained through Week 54 (21% in infliximab treatment groups vs. 9% in placebo group). The infliximab-associated response was generally similar in the 5 mg/kg and 10 mg/kg dose groups.

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

	Study UC I			Study UC II		
	Placebo	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**	**Placebo**	**5 mg/kg Infliximab**	**10 mg/kg Infliximab**
Patients randomized	121	121	122	123	121	120
Clinical Response[a,d]						
Week 8	37%	69%*	62%*	29%	65%*	69%*
Week 30	30%	52%*	51%**	26%	47%*	60%*
Week 54	20%	45%*	44%*	NA	NA	NA
Sustained Response[d]						
(Clinical response at both Week 8 and 30)	23%	49%*	46%*	15%	41%*	53%*
(Clinical response at both Week 8, 30 and 54)	14%	39%*	37%*	NA	NA	NA
Clinical Remission[b,d]						
Week 8	15%	39%*	32%**	6%	34%*	28%*
Week 30	16%	34%**	37%*	11%	26%**	36%*
Week 54	17%	35%**	34%**	NA	NA	NA
Sustained Remission[d]						
(Clinical remission at both Week 8 and 30)	8%	23%**	26%*	2%	15%*	23%*
(Clinical remission at Weeks 8, 30 and 54)	7%	20%**	20%**	NA	NA	NA
Mucosal Healing[c,d]						
Week 8	34%	62%*	59%*	31%	60%*	62%*
Week 30	25%	50%*	49%*	30%	46%**	57%*
Week 54	18%	45%*	47%*	NA	NA	NA

* $P<0.001$, ** $P<0.01$

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. (The Mayo score consists of the sum of four subscores: stool frequency, rectal bleeding, physician's global assessment and endoscopy findings.)

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

c Defined as a 0 or 1 on the endoscopy subscore of the Mayo score.

d Patients who had a prohibited change in medication, had an ostomy or colectomy, or discontinued study infusions due to lack of efficacy are considered to not be in clinical response, clinical remission or mucosal healing from the time of the event onward.

The improvement with 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).

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

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

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

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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 naïve 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 8) and either placebo, 3 mg/kg or 6 mg/kg of infliximab at Weeks 0, 2, and 6 and every 8 weeks thereafter.

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

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

	Study RA I					**Study RA II**		
		Infliximab + MTX					**Infliximab + MTX**	
		3 mg/kg		**10 mg/kg**			**3 mg/kg**	**6 mg/kg**
Response	Placebo +MTX (n=88)	q8 wks (n=86)	q4 wks (n=86)	q8 wks (n=87)	q4 wks (n=81)	Placebo +MTX (n=274)	q8 wks (n=351)	q8 wks (n=355)
ACR 20								
Week 30	20%	50%[a]	50%[a]	52%[a]	58%[a]	N/A	N/A	N/A
Week 54	17%	42%[a]	48%[a]	59%[a]	59%[a]	54%	62%[c]	66%[a]

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ACR 50								
Week 30	5%	27% [a]	29% [a]	31% [a]	26% [a]	N/A	N/A	N/A
Week 54	9%	21% [c]	34% [a]	40% [a]	38% [a]	32%	46% [a]	50% [a]
ACR 70								
Week 30	0%	8% [b]	11% [b]	18% [a]	11% [a]	N/A	N/A	N/A
Week 54	2%	11% [c]	18% [a]	26% [a]	19% [a]	21%	33% [b]	37% [a]
Major clinical response[#]	0%	7% [c]	8% [b]	15% [a]	6% [c]	8%	12%	17% [a]

A major clinical response was defined as a 70% ACR response for 6 consecutive months (consecutive visits spanning at least 26 weeks) through Week 102 for Study RA I and Week 54 for Study RA II.

a $P \leq 0.001$

b $P < 0.01$

c $P < 0.05$

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

	Placebo + MTX (n=88)		**Infliximab + MTX[a] (n=340)**	
Parameter (medians)	**Baseline**	**Week 54**	**Baseline**	**Week 54**
No. of Tender Joints	24	16	32	8
No. of Swollen Joints	19	13	20	7
Pain[b]	6.7	6.1	6.8	3.3
Physician's Global Assessment[b]	6.5	5.2	6.2	2.1
Patient's Global Assessment[b]	6.2	6.2	6.3	3.2
Disability Index (HAQ-DI)[c]	1.8	1.5	1.8	1.3
CRP (mg/dL)	3.0	2.3	2.4	0.6

a All doses/schedules of infliximab + MTX

b Visual Analog Scale (0=best, 10=worst)

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

Radiographic Response

Structural damage in both hands and feet was assessed radiographically at Week 54 by the change from baseline in the van der Heijde-modified Sharp (vdH-S) score, a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet.[3]

In Study RA I, approximately 80% of patients had paired X-ray data at 54 weeks and

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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 vdH-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 vdH-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 (vdH-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%).

Table 9 Radiographic change from baseline to Week 54

	Study RA I			**Study RA II**		
		Infliximab + MTX			**Infliximab + MTX**	
		3 mg/kg	**10 mg/kg**		**3 mg/kg**	**6 mg/kg**
	Placebo + MTX (n=64)	**q8 wks (n=71)**	**q8 wks (n=77)**	**Placebo + MTX (n=282)**	**q8 wks (n=359)**	**q8 wks (n=363)**
Total Score						
Baseline						
Mean	79	78	65	11.3	11.6	11.2
Median	55	57	56	5.1	5.2	5.3
Change from baseline						
Mean	6.9	1.3[a]	0.2[a]	3.7	0.4[a]	0.5[a]
Median	4.0	0.5	0.5	0.4	0.0	0.0
Erosion Score						
Baseline						
Mean	44	44	33	8.3	8.8	8.3
Median	25	29	22	3.0	3.8	3.8

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Change from baseline						
Mean	4.1	0.2[a]	0.2[a]	3.0	0.3[a]	0.1[a]
Median	2.0	0.0	0.5	0.3	0.0	0.0
JSN Score						
Baseline						
Mean	36	34	31	3.0	2.9	2.9
Median	26	29	24	1.0	1.0	1.0
Change from baseline						
Mean	2.9	1.1[a]	0.0[a]	0.6	0.1[a]	0.2
Median	1.5	0.0	0.0	0.0	0.0	0.0

a P<0.001 for each outcome against placebo.

Physical Function Response

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

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

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

14.5 Ankylosing Spondylitis

The safety and efficacy of infliximab were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. Patients were between 18 and 74 years of age, and had ankylosing spondylitis as defined by the modified New York criteria for Ankylosing Spondylitis.[4] Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0-10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0-10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying

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Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of 5 mg/kg of infliximab or placebo were administered intravenously at Weeks 0, 2, 6, 12 and 18.

At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by the proportion of patients achieving a 20% improvement in ASAS response criteria (ASAS 20), was seen in 60% of patients in infliximab group vs. 18% of patients in the placebo group (p<0.001). Improvement was observed at Week 2 and maintained through Week 24 (Figure 3 and Table 10).

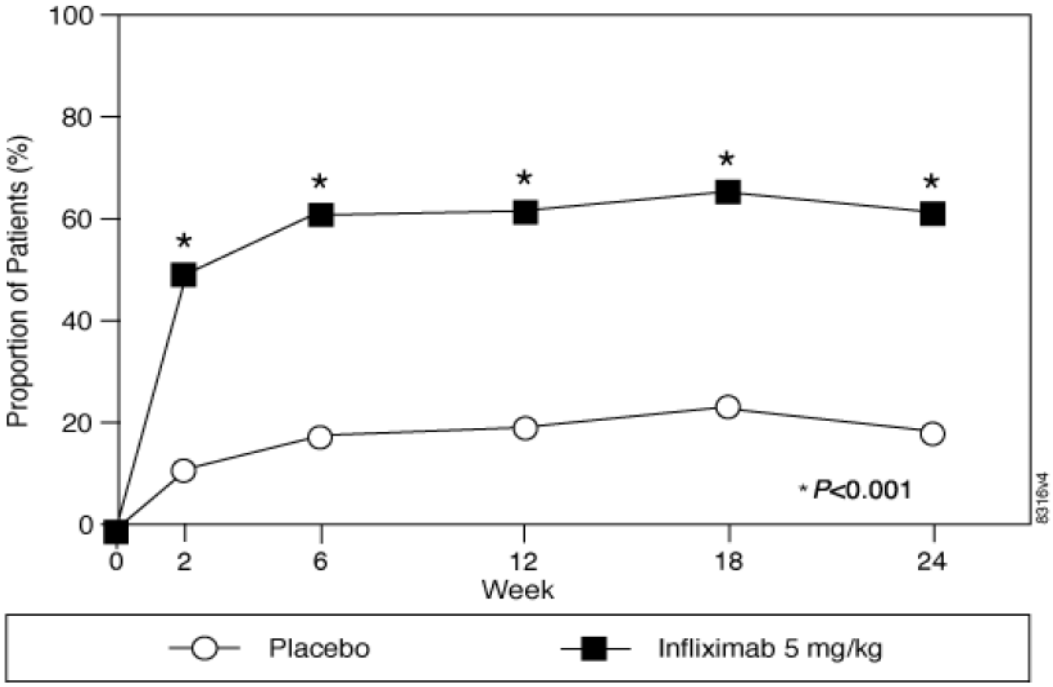

Figure 3 Proportion of patients achieving ASAS 20 response

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).

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Table 10 Components of ankylosing spondylitis disease activity

	Placebo (n=78)		Infliximab 5 mg/kg (n=201)		
	Baseline	**24 Weeks**	**Baseline**	**24 Weeks**	**P-value**
ASAS 20 response					
Criteria (Mean)					
Patient Global Assessment[a]	6.6	6.0	6.8	3.8	<0.001
Spinal pain[a]	7.3	6.5	7.6	4.0	<0.001
BASFI[b]	5.8	5.6	5.7	3.6	<0.001
Inflammation[c]	6.9	5.8	6.9	3.4	<0.001
Acute Phase Reactants					
Median CRP[d] (mg/dL)	1.7	1.5	1.5	0.4	<0.001
Spinal Mobility (cm, Mean)					
Modified Schober's test[e]	4.0	5.0	4.3	4.4	0.75
Chest expansion[e]	3.6	3.7	3.3	3.9	0.04
Tragus to wall[e]	17.3	17.4	16.9	15.7	0.02
Lateral spinal flexion[e]	10.6	11.0	11.4	12.9	0.03

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 BASDAI

d CRP normal range 0–1.0 mg/dL

e Spinal mobility normal values: modified Schober's test: >4 cm; chest expansion:>6 cm; tragus to wall: <15 cm; lateral spinal flexion: >10 cm

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), polyarticular arthritis (n=100), and spondylitis with peripheral arthritis (n=8). Patients

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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 mutilans 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.

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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

Patients Randomized	Placebo (n=100)		Infliximab 5mg/kg[a] (n=100)	
	Baseline	Week 24	Baseline	Week 24
Parameter (medians)	24	20	20	6
No. of Tender Joints[b]	12	9	12	3
No. of Swollen Joints[c]	6.4	5.6	5.9	2.6
Pain[d]	6.0	4.5	5.6	1.5
Physician's Global Assessment[d]	6.1	5.0	5.9	2.5
Disability Index (HAQ-DI)[e]	1.1	1.1	1.1	0.5
CRP (mg/dL)[f]	1.2	0.9	1.0	0.4
% Patients with 1 or more digits with dactylitis	41	33	40	15
% Patients with enthesopathy	35	36	42	22

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

b Scale 0-68

c Scale 0-66

d Visual Analog Scale (0=best, 10=worst)

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

f Normal range 0-0.6 mg/dL

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 (14.8)*].

Radiographic response

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vdH-S) score, modified by the addition of hand DIP joints. The total modified vdH-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and

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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 vdH-S score during this 12-month study (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 (HAQ-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, stable plaque psoriasis involving ≥10% BSA, a minimum PASI score of 12, and who were candidates for systemic therapy or phototherapy. Patients with guttate, pustular, or erythrodermic psoriasis were excluded from these studies. No concomitant anti-psoriatic therapies were allowed during the study, with the exception of low-potency topical corticosteroids on the face and groin after Week 10 of study initiation.

Study I (EXPRESS) evaluated 378 patients who received placebo or 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)

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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 sPGA score of moderate or worse (greater than or equal to 3 on a scale of 0 to 5) received an additional dose of the randomized treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline sPGA score ranged from moderate (62% of patients) to marked (22%) to severe (3%). In addition, 75% of patients had a BSA >20%. Of the enrolled patients, 114 (46%) received the Week 26 additional dose.

In Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at Week 10 by the PASI (PASI 75). In Study I and Study III, another evaluated outcome included the proportion of patients who achieved a 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 <5% 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 “6 = worse” to “1 = clear” that was assessed relative to baseline. Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as “clear” or “excellent,” consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

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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

	Placebo	Infliximab	
		3 mg/kg	5 mg/kg
Psoriasis Study I - patients randomized[a]	77	---	301
PASI 75	2 (3%)	---	242 (80%)*
sPGA	3 (4%)	---	242 (80%)*
Psoriasis Study II - patients randomized[a]	208	313	314
PASI 75	4 (2%)	220 (70%)*	237 (75%)*
rPGA	2 (1%)	217 (69%)*	234 (75%)*
Psoriasis Study IIII - patients randomized[b]	51	99	99
PASI 75	3 (6%)	71 (72%)*	87 (88%)*
sPGA	5 (10%)	71 (72%)*	89 (90%)*

* *P*<0.001 compared with placebo

a Patients with missing data at Week 10 were considered as nonresponders.

b Patients with missing data at Week 10 were imputed by last observation.

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

In Study II, in the subgroup of patients with more extensive psoriasis who had previously received phototherapy, 72% and 77% of patients on 3 mg/kg and 5 mg/kg 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 2% on placebo.

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

The groups that received a maintenance dose every 8 weeks appear to have a greater percentage of patients maintaining a PASI 75 through week 50 as compared to patients who received the as-

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needed or PRN doses, and the best response was maintained with the 5 mg/kg every 8-week dose. These results are shown in Figure 4. At Week 46, when infliximab serum concentrations were at trough level, in the every 8-week dose group, 54% of patients in the 5 mg/kg group compared to 36% in the 3 mg/kg group achieved PASI 75. The lower percentage of PASI 75 responders in the 3 mg/kg every 8-week dose group compared to the 5 mg/kg group was associated with a lower percentage of patients with detectable trough serum infliximab levels.

This may be related in part to higher antibody rates [see *Adverse Reactions (6.1)*]. In addition, in a subset of patients who had achieved a response at Week 10, maintenance of response appears to be greater in patients who received 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.

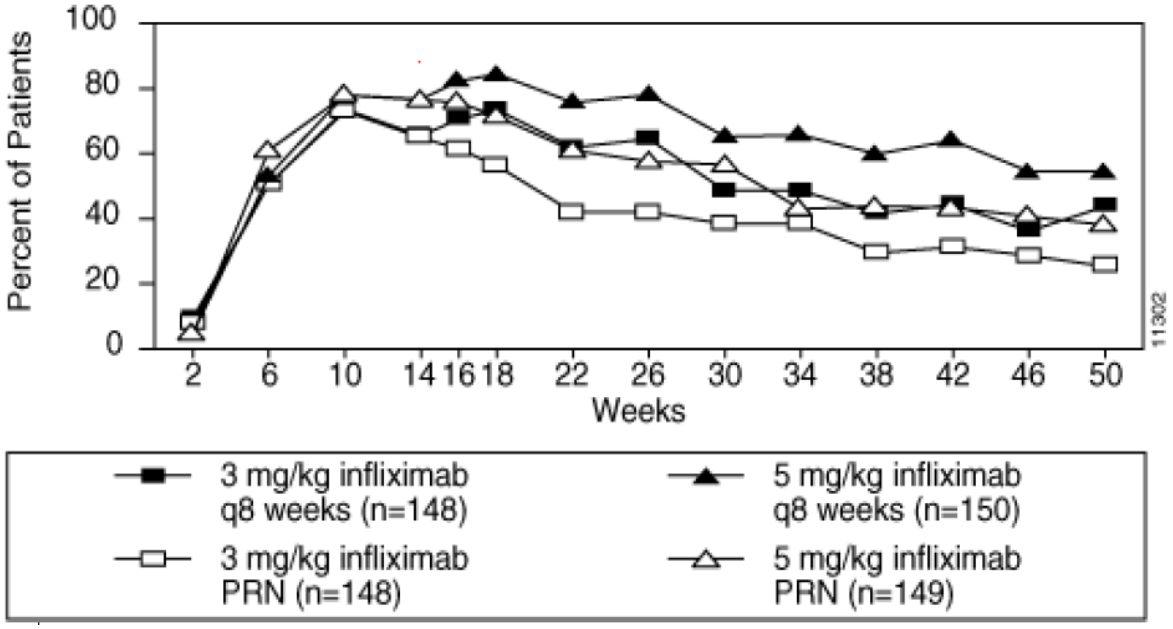

Figure 4 Proportion of patients achieving ≥75% improvement in PASI from baseline through Week 50; patients randomized at Week 14

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

Reference ID: 3912620

15 REFERENCES

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3. van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic assessments of hands and feet in a three-year prospective follow-up of patients with early rheumatoid arthritis. *Arthritis Rheum.* 1992;35(1):26-34.

4. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum.* 1984;27(4):361-368.

5. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med*. 1987;317(26):1625-1629.

16 HOW SUPPLIED/STORAGE AND HANDLING

Each INFLECTRA 20 mL vial is individually packaged in a carton. INFLECTRA for injection is supplied in an accumulator carton containing 10 vials.

NDC 32228-001-01 100 mg vial

Each single use vial contains 100 mg of infliximab-dyyb for final reconstitution volume of 10 mL.

Storage and Stability

INFLECTRA must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Do not use INFLECTRA beyond the expiration date (Exp) located on the carton and the vial. This product contains no preservative.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Medication Guide)

Patient Counseling

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

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

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

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CELLTRION, Inc.
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Yeonsu-gu, Incheon
406-840, Republic of Korea
U.S. License No. 1996

for
Hospira, a Pfizer Company
275 Field Drive
Lake Forest, IL 60045

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Reference ID: 3912620

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.

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.

What should I tell my doctor before starting treatment with INFLECTRA?

Your doctor will assess your health before each treatment.

Tell your doctor about all of your medical conditions, including if you:

- have an infection (see "**What is the most important information I should know about 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.
- are breast-feeding or planning to breast-feed. It is not known whether INFLECTRA passes into your breast milk. Talk to your doctor about the best way to feed your baby while taking INFLECTRA. You should not breast-feed while taking INFLECTRA.

If you have a baby and you were using INFLECTRA during your pregnancy, it is important to tell your baby's doctor and other health care professionals about your INFLECTRA use so they can decide when your baby should receive any vaccine. Certain vaccinations can cause infections.

If you received INFLECTRA while you were pregnant, your baby may be at higher risk for getting an infection. If your baby receives a live vaccine within 6 months after birth, your baby may develop infections with serious complications that can lead to death. This includes live vaccines such as the BCG, rotavirus, or any other live vaccines. For other types of vaccines, talk with your doctor.

How should I receive INFLECTRA?

- You will be given INFLECTRA through a needle placed in a vein (IV or intravenous infusion) in your arm.
- Your doctor may decide to give you medicine before starting the INFLECTRA infusion to prevent or lessen side effects.
- Only a healthcare professional should prepare the medicine and administer it to you.
- INFLECTRA will be given to you over a period of about 2 hours.
- If you have side effects from INFLECTRA, the infusion may need to be adjusted or stopped. In addition, your healthcare professional may decide to treat your symptoms.
- A healthcare professional will monitor you during the INFLECTRA infusion and for a period of time afterward for side effects. Your doctor may do certain tests while you are taking INFLECTRA to monitor you for side effects and to see how well you respond to the treatment.
- Your doctor will determine the right dose of INFLECTRA for you and how often you should receive it. Make sure to discuss with your doctor when you will receive infusions and to come in for all your infusions and follow-up appointments.

What should I avoid while receiving INFLECTRA?

Do not take INFLECTRA together with medicines such as KINERET (anakinra), ORENCIA (abatacept), ACTEMRA

(tocilizumab), or other medicines called biologics that are used to treat the same conditions as INFLECTRA.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. These include any other medicines to treat Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis or psoriasis.

Know the medicines you take. Keep a list of your medicines and show them to your doctor and pharmacist when you get a new medicine.

What are the possible side effects of INFLECTRA?

INFLECTRA can cause serious side effects, including:

See "**What is the most important information I should know about INFLECTRA?**".

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:
  - a fever
  - feel very tired
  - have a cough
  - have flu-like symptoms
  - warm, red, or painful skin
- Your doctor will examine you for TB and perform a test to see if you have TB. If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with 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:
  - feel unwell
  - poor appetite
  - tiredness (fatigue)
  - fever, skin rash, or joint pain

Heart Failure

If you have a heart problem called congestive heart failure, your doctor should check you closely while you are taking 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:

- shortness of breath
- swelling of ankles or feet
- 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

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

Blood Problems

In some patients taking INFLECTRA, the body may not make enough of the blood cells that help fight infections or help stop bleeding. Tell your doctor if you

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

Nervous System Disorders

In rare cases, patients taking infliximab products have developed problems with their nervous system. Tell your doctor if you have

- changes in your vision
- numbness or tingling in any part of your body

- weakness in your arms or legs
- seizures

Allergic Reactions

Some patients have had allergic reactions to 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

Children with Crohn’s disease showed some differences in side effects of treatment compared with adults with Crohn's disease. The side effects that happened more in children were: anemia (low red blood cells), leukopenia (low white blood cells), flushing (redness or blushing), viral infections, neutropenia (low neutrophils, the white blood cells that fight infection), bone fracture, bacterial infection and allergic reactions of the breathing tract.

Tell your doctor about any side effect that bothers you or does not go away.

These are not all of the side effects with INFLECTRA. Ask your doctor or pharmacist for more information.

General information about INFLECTRA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use INFLECTRA for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about INFLECTRA. You can ask your doctor or pharmacist for information about INFLECTRA that is written for health professionals.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What are the ingredients in INFLECTRA?

The active ingredient is infliximab-dyyb.

The inactive ingredients in INFLECTRA include: sucrose, polysorbate 80, sodium dihydrogen phosphate monohydrate, and di-Sodium hydrogen phosphate dihydrate. No preservatives are present.

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For Hospira, a Pfizer Company, 275 Field Drive, Lake Forest, IL 60045

For more information call 1-800-383-7504.

This Medication Guide has been approved by the U.S. Food and Drug Administration Issued: 04/2016

(b) (4)

Unit(mm)

180

10.5 | 45 | 40 | 45 | 39.5

153 | 39 | 75 | 39

34

37

20 | 73 | 20 | 20

28

Pharmacodes

Item No.

Pharmacodes

Inflectra™
(infliximab-dyyb)
For Injection

100 mg per vial
For Intravenous Infusion Only
Single-use vial –
Discard unused portion

NDC 32228-001-01

Inflectra™
(infliximab-dyyb)
For Injection

100 mg per vial
For Intravenous Infusion Only
Single-use vial –
Discard unused portion

Dispense the enclosed Medication Guide to each patient.

Reconstitute and Dilute Before Intravenous Infusion.
Infuse over at least 2 hours with an in-line filter.
Rx only

Usual Dosage: See prescribing information.

Reconstitute each vial with 10 mL Sterile Water for Injection, USP. The resulting concentration is 10 mg/mL. Do NOT shake reconstituted solution. Further dilute with 0.9% Sodium Chloride Injection, USP. See insert for full preparation instructions. Once reconstituted, each mL contains infliximab-dyyb 10 mg, di-sodium hydrogen phosphate dihydrate 0.61 mg, polysorbate 80 0.05 mg, sodium dihydrogen phosphate monohydrate 0.22 mg, and sucrose 50 mg.

Contains no preservative.

NDC 32228-001-01

Inflectra™
(infliximab-dyyb)
For Injection

100 mg per vial
For Intravenous Infusion Only
Single-use vial –
Discard unused portion

Dispense the enclosed Medication Guide to each patient.

Reconstitute and Dilute Before Intravenous Infusion.
Infuse over at least 2 hours with an in-line filter.
Rx only

Store in refrigerator at 2°C - 8°C (36°F - 46°F).
No U.S. standard of potency.

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for
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275 Field Drive
Lake Forest, IL 60045

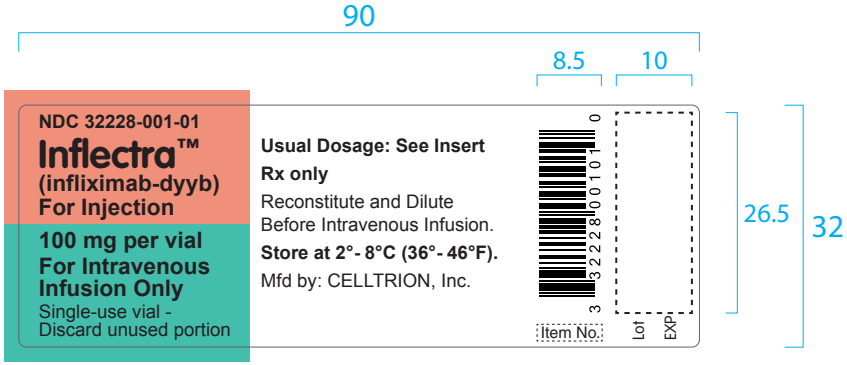
3 32228 00101 0

Lot / EXP

Inflectra 100mg Carton Box (US)

Reference ID: 3912620

(b) (4)



Inflectra 100mg Vial (US)

25 | 230 | 84 | 230 | 83.3

Unit(mm)

(b) (4)

27 | 82 | 79.3 | 25 | 9.5 | 27 | 62 | 25.5

50 | 79 | 20 | 42

Pharmacodes

NDC 32228-001-01
Inflectra™
(infliximab-dyyb)
For Injection
Contains 10 vials
100 mg per vial
For Intravenous Infusion Only
Single-use vial – Discard unused portion
Dispense the enclosed Medication Guide to each patient.
Store in refrigerator at 2°C - 8°C (36°F - 46°F).

Item No.

Pharmacodes

NDC 32228-001-01
Inflectra™
(infliximab-dyyb)
For Injection
Contains 10 vials

100 mg per vial
For Intravenous Infusion Only
Single-use vial – Discard unused portion

Dispense the enclosed Medication Guide to each patient.
Reconstitute and Dilute Before Intravenous Infusion.
Infuse over at least 2 hours with an in-line filter.
Rx only

Usual Dosage: See prescribing information.
Reconstitute each vial with 10 mL Sterile Water for Injection, USP. The resulting concentration is 10 mg/mL. Do NOT shake reconstituted solution. Further dilute with 0.9% Sodium Chloride Injection, USP. See insert for full preparation instructions. Once reconstituted, each mL contains infliximab-dyyb 10 mg, di-sodium hydrogen phosphate dihydrate 0.61 mg, polysorbate 80 0.05 mg, sodium dihydrogen phosphate monohydrate 0.22 mg, and sucrose 50 mg.
Contains no preservative.

Lot / EXP

NDC 32228-001-01
Inflectra™
(infliximab-dyyb)
For Injection
Contains 10 vials

100 mg per vial
For Intravenous Infusion Only
Single-use vial – Discard unused portion

Dispense the enclosed Medication Guide to each patient.
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Infuse over at least 2 hours with an in-line filter.
Rx only

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28

51.5 | 37 | 141.5 | 37

Inflectra 100mg Semi Carton Box - 10 vials (US)

Reference ID: 3912620

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/s/

BADRUL A CHOWDHURY
04/05/2016