INFLECTRA®
(infliximab-dyyb)
for injection

Product information

INFLECTRA

NDC 0069-0809-01

Unit quantity One 20-mL vial containing 100 mg of lyophilized infliximab-dyyb

Unit list price $946.28

Q-code
- Q5102: injection, infliximab, biosimilar, 10 mg
- Modifier “ZB” (Pfizer/Hospira)

Access and support

Pfizer enCompass™ is a comprehensive resource for information and resources related to reimbursement and access for INFLECTRA. It provides a variety of patient support programs, including assistance for eligible uninsured and insured patients who cannot afford their out-of-pocket costs.

For further information or to request assistance, please call 1-844-722-6672, Monday-Friday, 9 AM to 8 PM ET.

Contact your Pfizer Biosimilar representative or visit InflectraHCP.com for more information

Please see full Important Safety Information and Indications on pages 2, 3, and 4.

Please see accompanying full Prescribing Information, including BOXED WARNING and Medication Guide at the end of this document.
IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with infliximab products are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Discontinue INFLECTRA® (infliximab-dyyb) if a patient develops a serious infection or sepsis.

Reported infections include:

- **Active tuberculosis (TB), including reactivation of latent TB.** Patients frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent TB before INFLECTRA® use and during therapy. Treatment for latent infection should be initiated prior to INFLECTRA® use.
- **Invasive fungal infections including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis.** Patients may present with disseminated, rather than localized, disease. 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 TB in patients who tested negative for latent TB infection prior to initiating therapy, who are on treatment for latent TB, or who were previously treated for TB infection.

Risk of infection may be higher in patients greater than 65 years of age, pediatric patients, patients with co-morbid conditions and/or patients taking concomitant immunosuppressant therapy. In clinical trials, other serious infections observed in patients treated with infliximab products included pneumonia, cellulitis, abscess, and skin ulceration.

References:

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

Please see accompanying full Prescribing Information, including BOXED WARNING and Medication Guide at the end of this document.

MALIGNANCIES

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, 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 after the first dose of therapy. Most of the patients were receiving concomitant immunosuppressants.

Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell 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. 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. Almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. Carefully assess the risks and benefits of treatment with INFLECTRA®, especially in these patient types.

In clinical trials of all TNF inhibitors, more cases of lymphoma were observed compared with controls and the expected rate in the general population. However, patients with Crohn’s disease, rheumatoid arthritis, or plaque psoriasis may be at higher risk for developing lymphoma. In clinical trials of some TNF inhibitors, including infliximab products, more cases of other malignancies were observed compared with controls. The rate of these malignancies among patients treated with infliximab products was similar to that expected in the general population, whereas the rate in control patients was lower than expected. Cases of acute and chronic leukemia have been reported with postmarketing TNF-blocker use. As the potential role of TNF inhibitors in the development of malignancies is not known, caution should be exercised when considering treatment of patients with a current or a past history of malignancy or other risk factors such as chronic obstructive pulmonary disease (COPD).

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocker therapy, including infliximab products. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.
IMPORTANT SAFETY INFORMATION
(CONTINUED)

CONTRAINDICATION
INFLECTRA® is contraindicated in patients with moderate to severe (NYHA Class III/IV) congestive heart failure (CHF) at doses greater than 5 mg/kg. Higher mortality rates at the 10 mg/kg dose and higher rates of cardiovascular events at the 5 mg/kg dose have been observed in these patients. INFLECTRA® should be used with caution and only after consideration of other treatment options. Patients should be monitored closely. Discontinue INFLECTRA® if new or worsening CHF symptoms appear. INFLECTRA® should not be (re)administered to patients who have experienced a severe hypersensitivity reaction or to patients with hypersensitivity to murine proteins or other components of the product.

HEPATITIS B REACTIVATION
TNF inhibitors, including infliximab products, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers. Some cases were fatal. Patients should be tested for HBV infection before initiating INFLECTRA®. For patients who test positive, consult a physician with expertise in the treatment of hepatitis B. Exercise caution when prescribing INFLECTRA® for patients identified as carriers of HBV and monitor closely for active HBV infection during and following termination of therapy with INFLECTRA®. Discontinue INFLECTRA® in patients who develop HBV reactivation and initiate antiviral therapy with appropriate supportive treatment. Exercise caution when considering resumption of INFLECTRA® and monitor patients closely.

HEPATOTOXICITY
Severe hepatic reactions, including acute liver failure, jaundice, hepatitis, and cholestasis have been reported rarely in patients receiving infliximab products postmarketing. Some cases were fatal or required liver transplant. Aminotransferase elevations were not noted prior to discovery of liver injury in many cases. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (eg, ≥5 times the upper limit of normal) develop, INFLECTRA® should be discontinued, and a thorough investigation of the abnormality should be undertaken.

HEMATOLOGIC EVENTS
Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia (some fatal) have been reported in patients receiving infliximab products. The causal relationship to infliximab therapy remains unclear. Exercise caution in patients who have ongoing or a history of significant hematologic abnormalities.

Advise patients to seek immediate medical attention if they develop signs and symptoms of blood dyscrasias or infection. Consider discontinuation of INFLECTRA® in patients who develop significant hematologic abnormalities.

HYPERSENSITIVITY
Infliximab products have been associated with hypersensitivity reactions that differ in their time of onset. Acute urticaria, dyspnea, and hypotension have occurred in association with infusions of infliximab products. Serious infusion reactions including anaphylaxis were infrequent. Mediations for the treatment of hypersensitivity reactions should be available.

NEUROLOGIC EVENTS
TNF inhibitors, including infliximab products, have been associated in rare cases with CNS manifestation of systemic vasculitis, seizure, and new onset or exacerbation of CNS demyelinating disorders, including multiple sclerosis and optic neuritis, and peripheral demyelinating disorders, including Guillain-Barré syndrome. Exercise caution when considering INFLECTRA® in patients with these disorders and consider discontinuation if these disorders develop.

AUTOIMMUNITY
Treatment with infliximab products may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. Discontinue treatment with INFLECTRA® if symptoms of a lupus-like syndrome develop.

ADVERSE REACTIONS
In clinical trials with infliximab products, the most common adverse reactions occurring in >10% of patients included infections (eg, upper respiratory, sinusitis, and pharyngitis), infusion-related reactions, headache, and abdominal pain.

USE WITH OTHER DRUGS
Concomitant use of INFLECTRA® with anakinra, abatacept, tocilizumab, or other biologics used to treat the same conditions as INFLECTRA® is not recommended because of the possibility of an increased risk of infection. Care should be taken when switching from one biologic to another, since overlapping biological activity may further increase the risk of infection.

LIVE VACCINES/THERAPEUTIC INFECTIOUS AGENTS
Live vaccines or therapeutic infectious agents should not be given with INFLECTRA® due to the possibility of clinical infections, including disseminated infections. Bring pediatric patients up to date with all vaccinations prior to initiating INFLECTRA®. At least a 6-month waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to infliximab products.

Please see accompanying full Prescribing Information, including BOXED WARNING and Medication Guide at the end of this document.
INDICATIONS

Crohn’s Disease

• Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn’s disease (CD) 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 CD

Pediatric Crohn’s Disease

• 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

Ulcerative Colitis

• 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

Rheumatoid Arthritis

• Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis, in combination with methotrexate

Ankylosing Spondylitis

• Reducing signs and symptoms in patients with active ankylosing spondylitis

Psoriatic Arthritis

• Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis

Plaque Psoriasis

• Treatment of adult patients with chronic severe (ie, 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

INFLECTRA® is a trademark of Hospira UK, a Pfizer company. Remicade® is a registered trademark of Janssen Biotech.

Please see full Important Safety Information on pages 2 and 3. Please see accompanying full Prescribing Information, including BOXED WARNING and Medication Guide at the end of this document.
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 (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)

Ulcereative 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)

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

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

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

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

USE IN SPECIFIC POPULATIONS
- Pediatric Use – INFLECTRA has not been studied in children with Crohn’s disease or ulcerative colitis <6 years of age. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

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

2 DOSAGE AND ADMINISTRATION
2.1 Crohn’s Disease
2.2 Pediatric Crohn’s Disease
2.3 Ulcerative Colitis
2.4 Rheumatoid Arthritis
2.5 Ankylosing Spondylitis
2.6 Psoriatic Arthritis
2.7 Plaque Psoriasis
2.8 Monitoring to Assess Safety

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

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

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience

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

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

9 OVERDOSE

10 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
thereafter for the treatment of adults with moderately to severely active Crohn’s disease or fistulating Crohn’s disease. For adult patients who respond and then lose their response, consideration may be given to treatment with 10 mg/kg. Patients who do not respond by Week 14 are unlikely to respond with continued dosing and consideration should be given to discontinue INFLECTRA in these patients.

2.2 Pediatric Crohn’s Disease

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

2.3 Ulcerative Colitis

The recommended dose of INFLECTRA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter for the treatment of moderate to severely active ulcerative colitis.

2.4 Rheumatoid Arthritis

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

2.5 Ankylosing Spondylitis

The recommended dose of INFLECTRA is 5 mg/kg given as an intravenous induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks thereafter for the treatment of active ankylosing spondylitis.

2.6 Psoriatic Arthritis

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

2.7 Plaque Psoriasis

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

2.8 Monitoring to Assess Safety

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

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 may occur at any time during INFLECTRA infusion. Approximately 20% of patients in all clinical trials of infliximab experienced an infusion reaction compared with 10% of placebo-treated patients [see Adverse Reactions (6.1)]. Prior to infusion with INFLECTRA, premedication may be administered at the physician’s discretion. Premedication could include antihistamines (anti-H1 +/- anti-H2), acetaminophen and/or corticosteroids.

During infusion, mild to moderate infusion reactions may improve following slowing or suspension of the infusion, and upon resolution of the reaction, reinitiation at a lower infusion rate and/or therapeutic administration of antihistamines, acetaminophen, and/or corticosteroids. For patients that do not tolerate the infusion following these interventions, INFLECTRA should be discontinued.

During or following infusion, patients who have severe infusion-related hypersensitivity reactions should be discontinued from further INFLECTRA treatment. The management of severe infusion reactions should be dictated by the signs and symptoms of the reaction. Appropriate personnel and medication should be available to treat anaphylaxis if it occurs.

2.10 General Considerations and Instructions for Preparation and Administration

INFLECTRA is intended for use under the guidance and supervision of a physician. The reconstituted infusion solution should be prepared by a trained medical professional using aseptic technique by the following procedure:

1. Calculate the dose, total volume of reconstituted INFLECTRA solution required and the number of INFLECTRA vials needed. Each INFLECTRA vial contains 100 mg of the infliximab-darbop 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-darbop in a 20 mL vial for injection, for intravenous use.

4. CONTRAINDICATIONS

INFLECTRA at doses >5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating infliximab in patients with moderate to severe heart failure, Mortality 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 re-administered to patients who have experienced a severe hypersensitivity reaction to infliximab products. Additionally, INFLECTRA should not be administered to patients with known hypersensitivity to inactive components of the product or to any murine proteins.

5. WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with infliximab products are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death. Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

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

• with chronic or recurrent infection;

• who have been exposed to tuberculosis;

• with a history of an opportunistic infection;

• who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or

• with underlying conditions that may predispose them to infection.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving infliximab products, including patients who have previously received treatment for latent or active tuberculosis. Cases of active tuberculosis have also occurred in patients being treated with infliximab products during treatment for latent tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating anti-TNF therapy. Treatment at doses >3 mg/kg is contraindicated for patients with a positive test for 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 infection 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.

5.2 Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with INFLECTRA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with INFLECTRA.
INFLECTRA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with INFLECTRA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

**Invasive Fungal Infections**

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

**5.2 Malignancies**

Malignancies, some fatal, have been reported among children, adolescents and young adults who received treatment with TNF blocking agents (initiation of therapy <18 years of age), including infliximab products. Approximately half of these cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphoma. The other cases represented a variety of malignancies (cancer of the breast) in infliximab-treated patients vs. a rate of 0.11/100 patient-years among control patients), 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 based on historical reports of lymphoma risk in 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 therapy in 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 normal population. Patients with Crohn’s disease, rheumatoid arthritis or plaque psoriasis, particularly patients with highly active disease and/or chronic exposure to TNF products concomitantly with other immunosuppressants. When treating patients, consideration of whether to use INFLECTRA alone or in combination with other immunosuppressants such as azathioprine or 6-mercaptopurine concomitantly with a TNF-blocker at or prior to diagnosis. The majority of reported cases have been observed in patients with Crohn’s disease or ulcerative colitis and most were in adolescent and young adult males. It is uncertain whether the occurrence of HSTCL is related to TNF blockers or TNF blockers in combination with other immunosuppressants. When treating patients, consideration of whether to use INFLECTRA therapy in conjunction with other TNF blockers or infliximab in patients with active infection. When feasible, the decision to administer empiric antifungal therapy should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

**5.3 Hepatitis B Virus Reactivation**

Use of TNF blockers, including infliximab products, has been associated with reactivation of hepatitis B virus infection 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 potential role of TNF blocking therapy in the development of malignancies is not known [see Adverse Reactions (6.1)]. Rates in clinical trials for infliximab cannot be compared to rates in clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Caution should be exercised in considering INFLECTRA treatment in patients with a history of malignancy or in continuing treatment in patients who develop malignancy while receiving INFLECTRA.

For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy. 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 efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy. 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 efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy. 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 efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy. 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 efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy. 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 efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy. 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 efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy. 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 efficacy or safety 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 considered. In patients who develop HBV reactivation while taking TNF blockers, reactivation should be confirmed before resuming TNF blocker therapy.
and/or dysphagia. These reactions were associated with a marked increase in antibodies to infliximab product, loss of detectable serum concentrations of infliximab products, and possible loss of drug efficacy. INFLECTRA should be discontinued for severe hypersensitivity reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be administered for immediate use in the event of a reaction [see Adverse Reactions (6.1)].

In rheumatoid arthritis, Crohn’s disease and psoriasis clinical trials, readministration of infliximab after a period of no treatment resulted in a higher incidence of infusion reactions relative to 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 associated with 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 TNF-blocking agent, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse reactions seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. Therefore, the combination of INFLECTRA and anakinra is not recommended.

5.10 Use with Abatacept
In 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 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 should be considered in clinical infections, including disseminated infections. The concurrent administration of live vaccines with INFLECTRA is not recommended. Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after in utero exposure to infliximab products. Infliximab products are known to cross the placenta and have been detected up to 6 months following birth. At least a six month waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to infliximab products. Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG blader instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with INFLECTRA. It is recommended that all pediatric patients be brought up to date with all vaccinations prior to initiating INFLECTRA therapy. The interval between vaccination and initiation of INFLECTRA therapy should be in accordance with current vaccination guidelines.

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

6.2 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).

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

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

Patients who became positive for antibodies to infliximab were more likely (approximately two to three-fold) to have an infusion reaction than 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 to moderate to severe psoriasis designed to assess the efficacy of long-term maintenance therapy versus re-treatment with an induction regimen of infliximab therapy, patients who had discontinued treatment with infliximab 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 flushing, headache, rash, hypotension. In a subset of patients, 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 delayed hyperosensitivity 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 pneumoystosis, cytomegalovirus, nocardiosis and cytomegalovirus. Tuberculosis was reported in 14 patients, 4 of whom (2.5%) 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 flushing, headache, rash, hypotension. In a subset of patients, treatment with infliximab was discontinued and/or other treatment instituted with complete resolution of signs and symptoms.

Autoimmune Diseases
Autoimmune diseases are more common in patients receiving infliximab compared to placebo. In psoriasis Study I, the rates of new and/or exacerbation of clinical symptoms suggestive of lupus-like syndrome following treatment with INFLECTRA, treatment should be discontinued [see Adverse Reactions (6.1)].

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

5.13 Autoimmunity
Treatment with 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 should be considered in clinical infections, including disseminated infections. The concurrent administration of live vaccines with INFLECTRA is not recommended.

Fatal outcome due to disseminated BCG infection has been reported in an infant who received a BCG vaccine after in utero exposure to infliximab products. Infliximab products are known to cross the placenta and have been detected up to 6 months following birth. At least a six month waiting period following birth is recommended before the administration of any live vaccine to infants exposed in utero to infliximab products.

Other uses of therapeutic infectious agents such as live attenuated bacteria (e.g., BCG blader instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious agents not be given concurrently with INFLECTRA.

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

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

Autoimmune Diseases
Autoimmune diseases are more common in patients receiving infliximab compared to placebo. In psoriasis Study I, the rates of new and/or exacerbation of clinical symptoms suggestive of lupus-like syndrome following treatment with INFLECTRA, treatment should be discontinued [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).
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 CDP who were either current smokers or ex-smokers, 157 patients were treated with infliximab at doses similar to those used in rheumatoid arthritis and Crohn's disease. Of these patients treated with infliximab, 9 developed a malignancy, including 1 lymphoma, for a rate of 7.67 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% confidence interval [CI] 3.51 - 14.56). There was 1 reported malignancy among 77 control patients for a rate of 1.83 cases per 100 patient-years of follow-up (median duration of follow-up 0.8 years; 95% CI 0.04 - 9.10). The majority of the malignancies developed in the lung or head and neck.

Patients with Heart Failure
In a randomized study evaluating infliximab in moderate to severe heart failure (NYHA Class III/IV; left ventricular ejection fraction ≤ 35%), 150 patients were randomized to receive treatment with 3 infusions of infliximab at 10 mg/kg, 5 mg/kg, or placebo, at 0, 2, and 6 weeks. Higher incidences of mortality and hospitalization due to worsening heart failure were observed in patients who received infliximab at 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 patients treated with 3 mg/kg induction. Despite the increase in antibody formation, the infusion reaction 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.

Table 1 Proportion of patients with elevated ALT in clinical trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Infliximab</th>
<th>Placebo</th>
<th>Infliximab</th>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>24%</td>
<td>34%</td>
<td>3%</td>
<td>4%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Crohn's disease</td>
<td>34%</td>
<td>39%</td>
<td>4%</td>
<td>5%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>12%</td>
<td>17%</td>
<td>1%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>15%</td>
<td>51%</td>
<td>0%</td>
<td>10%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>16%</td>
<td>50%</td>
<td>0%</td>
<td>7%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Plaque psoriasis</td>
<td>24%</td>
<td>49%</td>
<td>&lt;1%</td>
<td>8%</td>
<td>0%</td>
<td>3%</td>
</tr>
</tbody>
</table>

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 2 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 24 weeks for the placebo group and 102 weeks for infliximab group.
d Median follow-up was 39 weeks for infliximab group and 16 weeks for the placebo group.
e ALT values are obtained in 2 Phase 3 psoriasis studies with median follow-up of 30 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 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 NMS 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 172 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.
Table 2 Adverse reactions occurring in 5% or more of patients receiving 4 or more infusions for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=350)</td>
<td>(n=1129)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>20%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>25%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>8%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>8%</td>
</tr>
<tr>
<td>Coughing</td>
<td>8%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>9%</td>
</tr>
<tr>
<td>Skin and appendages disorders</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>7%</td>
</tr>
<tr>
<td>Pain</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Resistance mechanism disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>4%</td>
</tr>
<tr>
<td>Moniliasis</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Central and peripheral nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Musculoskeletal system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Urinary system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Cardiovascular disorders, general</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5%</td>
</tr>
</tbody>
</table>

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 ≥2.0% or clinically significant adverse reactions by body system were as follows:

- **Body as a whole**: allergic reaction, edema
- **Blood & lymphopoiesis**: thrombocytopenia
- **Cardiovascular**: hypotension
- **Gastrointestinal**: constipation, intestinal obstruction
- **Central and Peripheral Nervous System**: dizziness
- **Heart Rate and Rhythm**: bradycardia
- **Liver and Biliary**: hepatitis
- **Metabolic and Nutritional**: dehydration
- **Neoplasms**: lymphoma
- **Respiratory**: upper 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 (5%), 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 every 8-week and 1 in the every 12-week maintenance treatment groups). Herpes zoster was reported for 2 patients in the every 8-week maintenance treatment group.

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 (5.8)], interstitial lung disease (including pulmonary fibrosis/interstitial pneumonitis and very rare rapidly progressive disease), idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, paracutaneous 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 life threatening reactions include anaphylaxis, serious infections [see Warnings and Precautions (5.1)], malignancies, including melanoma and Merkel cell carcinoma [see Warnings and Precautions (5.2)], and serum sickness [see Warnings and Precautions (5.4)]. Serious infections may result from combination of bovine tuberculosis (disseminated BCG infection) following vaccination in an infant exposed in utero to infliximab [see Warnings and Precautions (5.14)].

Infusion-related Reactions

In postmarketing experiences, 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 HSCTL [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 (5.10)].

7.2 Use with Tocilizumab

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

7.3 Use with Other Biological Therapeutics

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

7.4 Methotrexate (MTX) and Other Concomitant Medications

Specific drug interaction studies, including interactions with MTX, have not been conducted. The majority of patients in rheumatoid arthritis or Crohn’s disease clinical studies received one or more concomitant medications. In rheumatoid arthritis, concomitant medications besides MTX were nonsteroidal anti-inflammatory agents (NSAIDs), folic acid, corticosteroids and/or narcotics. Concomitant Crohn’s disease medications were antibiotics, anti-virals, corticosteroids, 6-MP/AZA and aminosalicylates. In pediatric 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 amnolacysalizes.

7.6 CYTOKINE STORM SYNDROME

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, 

7.7 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)].
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 utero exposure to infliximab products for at least 6 months [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 reproductive capacity. INFLECTRA should not 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 mice using an analogus antibody that selectively inhibits the functional activity of mouse TNFα.

Doses of 10 to 15 mg/kg in pharmacodynamic animal models with the anti-TNFα 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)].

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 has 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. Pediatric Crohn’s Disease

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 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 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 than expected 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 in combination with MTX over 38 weeks. The most commonly reported infections were upper respiratory tract infection and pharyngitis, and the most commonly reported serious infection was pneumonia. Other notable infections included primary varicella infection in 1 patient and herpes zoster in 1 patient.

8.5 Geriatric Use

In rheumatoid arthritis and plaque psoriasis clinical trials, no overall differences were observed in effectiveness or safety in 181 patients with rheumatoid arthritis and 75 patients with plaque psoriasis, aged 65 or older who received infliximab, compared to patients who were younger. However, a higher rate of immunogenicity than what has been observed in adults. Additionally, a higher rate of serious infusion reactions was observed in elderly patients who received infliximab 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 of age and older who received 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 IgG1x 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 diphosphate 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 receptor. In pharmacodynamic animal models with the anti-TNFα analogous antibody products do not neutralize TNFp7 (lymphotoxin-α), a related cytokine that utilizes the 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 leucocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as promotion of synovial membrane vascularity. Treatment with infliximab products 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 anti-TNFα antibodies have also reduced resident numbers of mononuclear cells within the colon of mice injected with TNFα.

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 results in regression of inflammatory cells into involved tissue and a reduction in the levels of TNFα, IL-6 and other pro-inflammatory cytokines. Treatment with infliximab products results in a reduction of synovial fluid levels of TNFα and IL-6, compared to untreated patients. In psoriatic arthritis, treatment with infliximab products resulted in...
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 3 mg/kg of infliximab, the steady state area under the concentration curve (AUCss) 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 in 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 is an analogous antibody that inhibits the function of TNFαα. CV1q is an analogous antibody that inhibits the function of TNFαα.

In the single-dose trial of 108 patients, 16% (4/25) of placebo patients achieved a clinical response 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)].

14 CLINICAL STUDIES

14.1 Crohn's Disease

Active Crohn's Disease

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.

In the first trial, 94 patients received 3 doses of either placebo or infliximab at Weeks 0, 2 and 6. 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

In the single-dose trial of 108 patients, 16% (4/25) of placebo patients achieved a clinical response 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)].

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 placebo or infliximab at Weeks 0, 2 and 6. Patients who did not respond by Week 14, additional therapy did not result in significantly more responses [see Dosage and Administration (2)].

Table 3 Clinical remission and steroid withdrawal

<table>
<thead>
<tr>
<th>Week 30</th>
<th>Single 5-mg/kg Dose</th>
<th>Three-Dose Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Maintenance</td>
<td>25/102</td>
<td>41/104</td>
</tr>
<tr>
<td>Infliximab Maintenance q 8wks</td>
<td>25%</td>
<td>39%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 54</th>
<th>Single 5-mg/kg Dose</th>
<th>Three-Dose Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Maintenance</td>
<td>14/56</td>
<td>18/53</td>
</tr>
<tr>
<td>Infliximab Maintenance q 8wks</td>
<td>11%</td>
<td>25%</td>
</tr>
</tbody>
</table>

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

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

In the current study, 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.

In the first trial, 94 patients received 3 doses of either placebo or infliximab at Weeks 0, 2 and 6. 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

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 placebo or infliximab at Weeks 0, 2 and 6. Patients who did not respond by Week 14, additional therapy did not result in significantly more responses [see Dosage and Administration (2)].

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 placebo or infliximab at Weeks 0, 2 and 6. Patients who did not respond by Week 14, additional therapy did not result in significantly more responses [see Dosage and Administration (2)].

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 placebo or infliximab at Weeks 0, 2 and 6. Patients who did not respond by Week 14, additional therapy did not result in significantly more responses [see Dosage and Administration (2)].
Week 14 and then every 8 weeks through Week 46. Patients who were in fistula response (fistula response was defined the same as in the first trial) at both Weeks 10 and 14 were randomized separately from those not in response. The primary endpoint was time from randomization to loss of response among those patients who were in fistula response.

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

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

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

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

Patients who had not achieved a response by Week 14 were unlikely to respond to additional doses of infliximab. Similar proportions of patients in either group developed new fistulas (17% overall) and similar numbers developed abscesses (15% overall).

### 14.2 Pediatric Crohn’s Disease

The safety and efficacy of infliximab were assessed in a randomized, open-label study (Study Peds Crohn’s) in 112 pediatric patients aged 6 to 17 years old with moderately to severely active 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 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 10 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

<table>
<thead>
<tr>
<th></th>
<th>Every 8 Week Treatment Group</th>
<th>Every 12 Week Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients randomized</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Response¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 30</td>
<td>73%*</td>
<td>47%</td>
</tr>
<tr>
<td>Week 54</td>
<td>64%*</td>
<td>35%</td>
</tr>
<tr>
<td>Clinical Remission²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 30</td>
<td>60%*</td>
<td>35%</td>
</tr>
<tr>
<td>Week 54</td>
<td>56%*</td>
<td>24%</td>
</tr>
</tbody>
</table>

¹ Defined as a decrease from baseline in the PCDAI score of ≥15 points and total score of ≤30 points.
² Defined as a PCDAI score of ≤10 points.

### 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) (Study 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. 10% in placebo group in Study UC II). In Study UC II, 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.

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

<table>
<thead>
<tr>
<th></th>
<th>Study UC I</th>
<th>Study UC II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients randomized</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Response⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>37%*</td>
<td>29%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>30%*</td>
<td>26%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>20%*</td>
<td>NA</td>
</tr>
<tr>
<td>Sustained Response⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Clinical response at both Week 8 and 30)</td>
<td>23%*</td>
<td>15%*</td>
</tr>
<tr>
<td>Clinical Remission⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>15%*</td>
<td>6%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>16%*</td>
<td>11%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%*</td>
<td>NA</td>
</tr>
<tr>
<td>Sustained Remission⁶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Clinical response at both Week 8 and 30)</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Mucosal Healing⁷</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 8</td>
<td>25%*</td>
<td>30%*</td>
</tr>
<tr>
<td>Week 30</td>
<td>34%*</td>
<td>31%*</td>
</tr>
<tr>
<td>Week 54</td>
<td>18%*</td>
<td>48%**</td>
</tr>
</tbody>
</table>

⁵ 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.
⁶ Defined as a PCDAI score of ≤10 points.
⁷ 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.

**Table 5 Response, remission and mucosal healing in ulcerative colitis studies**
The improvement with infliximab was consistent across all Mayo subscores through Week 54 (Study UC I shown in Table 6; Study UC II through Week 30 was similar).

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

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + MTX</th>
<th>Infliximab + MTXa</th>
<th>Infliximab + MTXb</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACR 20</strong> Week 30</td>
<td>20%</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>Week 54</td>
<td>17%</td>
<td>42%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>ACR 50</strong> Week 30</td>
<td>5%</td>
<td>27%</td>
<td>31%</td>
</tr>
<tr>
<td>Week 54</td>
<td>9%</td>
<td>21%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>ACR 70</strong> Week 30</td>
<td>0%</td>
<td>8%</td>
<td>18%</td>
</tr>
<tr>
<td>Week 54</td>
<td>2%</td>
<td>11%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>Major clinical response</strong>a</td>
<td>0%</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>No. of Tender Joints</strong></td>
<td>24</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>6.7</td>
<td>6.1</td>
<td>6.8</td>
</tr>
<tr>
<td><strong>Physician’s Global Assessment</strong>b</td>
<td>6.5</td>
<td>5.2</td>
<td>6.2</td>
</tr>
<tr>
<td><strong>CRP (mg/dL)</strong></td>
<td>3.0</td>
<td>2.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Parameter (medians)</th>
<th>Placebo + MTX (n=88)</th>
<th>Infliximab + MTX (n=340)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Tender Joints</strong></td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td><strong>No. of Swollen Joints</strong></td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td><strong>Physician’s Global Assessment</strong></td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td><strong>CRP (mg/dL)</strong></td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

### 14.4 Rheumatoid Arthritis

The safety and efficacy of infliximab were assessed in 2 multicenter, randomized, double-blind, pivotal trials: ATTRACT (Study RA I) and ASPIRE (Study RA II). Concurrent use of stable doses of folic acid, oral corticosteroids (≤10 mg/day) and/or non-steroidal anti-inflammatory drugs (NSAIDs) was permitted. Study RA I was a placebo-controlled study of 428 patients with active rheumatoid arthritis despite treatment with MTX. Patients enrolled had a median age of 54 years, median disease duration of 8.4 years, median swollen and tender joint count of 20 and 31 respectively, and were on a median dose of 15 mg/wk of MTX. Patients received either placebo + MTX or one of 4 doses/schedules of the infliximab + MTX: 3 mg/kg or 10 mg/kg infliximab by intravenous infusion at Weeks 0, 2 and 6 followed by additional infusions every 4 or 8 weeks in combination with MTX. Study RA II was a placebo-controlled study of 3 active treatment arms in 1004 MTX 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).
At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving infliximab, compared to 9% and 4%, respectively, for patients receiving placebo (P < 0.001, infliximab vs. placebo). A low level of disease activity (defined as a value < 20 [on a scale of 0 - 100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of patients treated with infliximab vs. 1% in placebo-treated patients (P < 0.001).

### Table 10 Components of ankylosing spondylitis disease activity

<table>
<thead>
<tr>
<th>Criteria (Mean)</th>
<th>Placebo (n=78)</th>
<th>Infliximab 5 mg/kg (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAS 20 response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Global Assessment</td>
<td>6.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Spinal pain</td>
<td>7.3</td>
<td>6.5</td>
</tr>
<tr>
<td>BASFI</td>
<td>5.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Inflammation</td>
<td>6.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Acute Phase Reactants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median CRP (mg/dL)</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Spinal Mobility (cm, Mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Schober’s test</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Chest expansion</td>
<td>3.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Tragus to wall</td>
<td>17.3</td>
<td>17.4</td>
</tr>
<tr>
<td>Lateral spinal flexion</td>
<td>10.6</td>
<td>11.0</td>
</tr>
</tbody>
</table>

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

### 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 < 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. Patients were to have had active disease as evidenced by both a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score >4 (possible range 0–10) and spinal pain >4 (on a Visual Analog Scale [VAS] of 0–10). Patients with complete ankylosis of the spine were excluded from study participation, and the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) and systemic corticosteroids were prohibited. Doses of 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).
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.

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

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

Across all treatment groups, the median baseline PASI score was 21 and the baseline Stati
g to Physician Global Assessment (sPGA) score ranged from moderate (52%) 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 already received either psoralen plus ultraviolet A treatment (PUVA) or other systemic therapy for their psoriasis. These patients were randomized to receive either placebo or infliximab at doses of 3 mg/kg or 5 mg/kg at Weeks 0, 2, and 6. At Week 26, patients with a PASI score of moderate or worse (greater than or equal to 3) received the Week 15 dose and continued treatment. Across all treatment groups, the median baseline PASI score was 19, and the baseline PASI score ranged from moderate (62%) to severe (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 with the 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 5-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 (sPGA). The PASI is a 5-category scale ranging from “0 = worse” to “1 = clear” that was assessed relative to baseline.

Overall lesions were graded with consideration to the percent of body involvement as well as overall induration, scaling, and erythema. Treatment success, defined as “clear” or “excellent,” consisted of some residual pinkness or pigmentation to marked improvement (nearly normal skin texture; some erythema may be present). The results of these studies are presented in Table 12.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>3 mg/kg</th>
<th>5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75</td>
<td>77</td>
<td>2 (3%)</td>
<td>242 (80%)*</td>
</tr>
<tr>
<td>sPGA</td>
<td>3 (4%)</td>
<td>242 (80%)*</td>
<td></td>
</tr>
<tr>
<td>PASI 75</td>
<td>208</td>
<td>313</td>
<td>314</td>
</tr>
<tr>
<td>sPGA</td>
<td>4 (2%)</td>
<td>220 (70%)*</td>
<td>237 (75%)*</td>
</tr>
<tr>
<td>PASI 75</td>
<td>2 (1%)</td>
<td>217 (69%)*</td>
<td>234 (75%)*</td>
</tr>
<tr>
<td>sPGA</td>
<td>3 (6%)</td>
<td>71 (72%)*</td>
<td>87 (88%)*</td>
</tr>
</tbody>
</table>

* P<0.001 compared with placebo

---

**Radiographic response**

Structural damage in both hands and feet was assessed radiographically by the change from baseline in the van der Heijde-Sharp (vHS-S) score, modified by the addition of hand DIP joints. The total modified vHS-S score is a composite score of structural damage that measures the number and size of joint erosions and the degree of joint space narrowing (JSN) in the hands and feet. At Week 24, patients treated with infliximab had less radiographic progression than placebo-treated patients (mean change of -0.70 vs. -0.82, P<0.001). Patients treated with infliximab also had less progression in their erosion scores (-0.56 vs 0.51) and JSN scores (-0.14 vs 0.31). The patients in infliximab group demonstrated continued inhibition of structural damage at Week 54. Most patients showed little or no change in the vHS-S score using a sub-study (median change of 0 in both patients who initially received infliximab or placebo). More patients in the placebo group (12%) had radiographically progressive 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 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.
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.

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

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.
Serious Infections

INFLECTRA can cause serious side effects, including:

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?”.

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 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 is the most important information I should know about INFLECTRA?

INFLECTRA can cause serious side effects, including:

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
- weakness in your arms or legs
- numbness or tingling in any part of your body
- 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.


Distributed by
Pfizer Labs
Division of Pfizer Inc, NY, NY 10017

For more information call 1-800-383-7504.
This Medication Guide has been approved by the U.S. Food and Drug Administration
Issued: 08/2016

71001228