REMICADE™

INFLIXIMAB

for IV Injection

DESCRIPTION:

Remicade (Infliximab) is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 10^{10} M^{-1}. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

Remicade is supplied as a sterile, white, lyophilized powder for intravenous infusion. Following reconstitution with 10 mL of Sterile Water for Injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg Infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate and 6.1 mg dibasic sodium phosphate. No preservatives are present.

CLINICAL PHARMACOLOGY:

General

Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors.[1-3] Infliximab does not neutralize TNFβ (lymphotoxin α),[1] a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of pro-inflammatory cytokines such as IL-1 and IL-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, and induction of acute phase and other liver proteins.[4] Cells expressing transmembrane TNFα bound by Infliximab can be lysed *in vitro* by complement or effector cells.[2] Anti-TNFα antibodies reduce disease activity in a cotton-top tamarin colitis model.[5] Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils,[3] B and T lymphocytes[6,7] and epithelial cells.[8]

Pharmacodynamics

Elevated concentrations of TNFα have been found in the stools of Crohn's disease patients and correlate with elevated disease activity.[9] Treatment with Infliximab reduced infiltration of inflammatory cells and TNFα production in inflamed areas of the intestine,[8] and reduced the proportion of mononuclear cells from the lamina propria able to express TNFα and interferon γ.[10] After treatment with Infliximab, patients with Crohn's disease have decreased levels of serum IL-6 and C-reactive protein compared to baseline.[8] Peripheral blood lymphocytes from Infliximab-treated patients, however, showed no decrease in proliferative responses to *in vitro* mitogenic stimulation when

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compared to cells from untreated patients.[8]

Pharmacokinetics

Data from a study of single intravenous infusions of 1, 5, 10 or 20 mg/kg showed a direct and linear relationship between the dose administered and the maximum serum concentration (C_{max}) and area under the concentration-time curve. The volume of distribution at steady state (V_d), clearance and mean residence time were independent of the administered dose. Infliximab has a prolonged terminal half-life and is predominantly distributed within the vascular compartment. A single infusion of the recommended dose of 5 mg/kg resulted in a median C_{max} of 118 μg/mL, a median V_d equal to 3.0 liters and a terminal half-life of 9.5 days. During the clinical studies, no pharmacokinetic differences were observed in patient subgroups defined by gender, age, weight or hepatic or renal function. Corticosteroid use significantly increased the V_d of Infliximab from 2.8 to 3.3 liters (a 17% increase, possibly secondary to corticosteroid-mediated changes in electrolyte balance and fluid retention). No evidence of accumulation was observed after repeated dosing in patients with fistulizing disease given 5 mg/kg Infliximab at weeks 0, 2 and 6, or in patients with moderate or severe Crohn's disease retreated with 4 infusions of 10 mg/kg Infliximab at 8-week intervals.

CLINICAL STUDIES:

Active Crohn's Disease

The safety and efficacy of Infliximab were assessed in a randomized, double-blind, placebo-controlled dose ranging study of 108 patients with moderate to severe active Crohn's disease[11] [Crohn's Disease Activity Index (CDAI) ≥220≤400].[12] All patients had experienced an inadequate response to prior conventional therapies, including corticosteroids (60% of patients), 5-aminosalicylates (5-ASA)(60%) and/or 6-mercaptopurine/azathioprine (6-MP/AZA)(37%). Concurrent use of stable dose regimens of corticosteroids, 5-ASA, 6-MP and/or AZA was permitted and 92% of patients continued to receive at least one of these medications.

The study was divided into three phases. In the first phase, patients were randomized to receive a single intravenous (IV) dose of either placebo, 5, 10 or 20 mg/kg of Infliximab. The primary endpoint was the proportion of patients who experienced a clinical response, defined as a decrease in CDAI by ≥70 points from baseline at the 4-week evaluation and without an increase in Crohn's disease medications or surgery for Crohn's disease. Patients who responded at week 4 were followed to week 12. Secondary endpoints included the proportion of patients who were in clinical remission at week 4 (CDAI <150), and clinical response over time.

At week 4, four of twenty-five (16%) of the placebo patients achieved a clinical response vs. twenty-two of twenty-seven (82%) of the patients at 5 mg/kg Infliximab ($p < 0.001$, two-sided, Fisher's Exact test). One of twenty-five (4%) placebo patients and thirteen of twenty-seven (48%) patients receiving 5 mg/kg Infliximab achieved a CDAI <150 at week 4. The maximum response to any dose of Infliximab was observed within 2 to 4 weeks. The proportion of patients in response gradually diminished over the 12 weeks of the evaluation period. There was no evidence of a dose response; doses higher than 5 mg/kg did not result in a greater proportion of responders. Results are shown in Figure 1.

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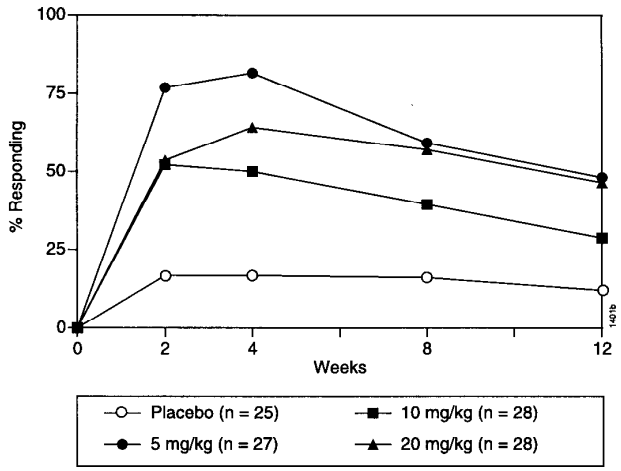

Figure 1. Response (≥70 point decrease in CDAI) to a Single IV Infliximab or Placebo Dose

During the 12-week period following infusion, patients treated with Infliximab compared to placebo demonstrated improvement in quality of life as measured by the Inflammatory Bowel Disease Questionaire.[13]

In the second phase, 29 patients who did not respond to the single dose of 5, 10 or 20 mg/kg of Infliximab entered the open label phase and received a single 10 mg/kg dose of Infliximab 4 weeks after the initial dose. Ten of twenty-nine (34%) patients experienced a response 4 weeks after receiving the second dose.

Patients, who remained in clinical response at week 8 during the first or second phase, were eligible for the retreatment phase. Seventy-three patients were re-randomized at week 12 to receive 4 infusions of placebo or 10 mg/kg Infliximab at 8-week intervals (weeks 12, 20, 28, 36) and were followed to week 48. In the limited data set available, no significant differences were observed between the Infliximab and placebo-treated groups..

Fistulizing Crohn's Disease

The safety and efficacy of Infliximab were assessed in a randomized, double-blind, placebo controlled study of 94 patients with fistulizing Crohn's disease with fistula(s) that were of at least 3 months duration. Concurrent use of stable doses of corticosteroids, 5-ASA, antibiotics, methotrexate, 6-MP and/or AZA was permitted, and 83% of patients continued to receive at least one of these medications. Fifty-two (55%) had multiple cutaneously draining fistulas; 90% of patients had fistula(s) in the perianal area and 10% had abdominal fistula(s).

Patients received 3 doses of either placebo, 5 or 10 mg/kg Infliximab at weeks 0, 2 and 6 and were followed up to 26 weeks. The primary endpoint was the proportion of patients who experienced a clinical response, defined as ≥50% reduction from baseline in the number of fistula(s) draining upon gentle compression, on at least two consecutive visits, without an increase in medication for Crohn's disease, or surgery for Crohn's disease.

Eight of thirty-one (26%) patients in the placebo arm achieved a clinical response vs. twenty-one of the thirty-one (68%) patients in the 5 mg/kg Infliximab arm ($p = 0.002$, two-sided, Fisher's Exact test).

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Eighteen of thirty-two (56%) patients in the 10 mg/kg arm achieved a clinical response.

The median time to onset of response in the Infliximab-treated group was 2 weeks. The median duration of response was 12 weeks; after 22 weeks there was no difference between either dose of Infliximab and placebo in the proportion of patients in response (Figure 2). New fistula(s) developed in approximately 15% of both Infliximab and placebo-treated patients.

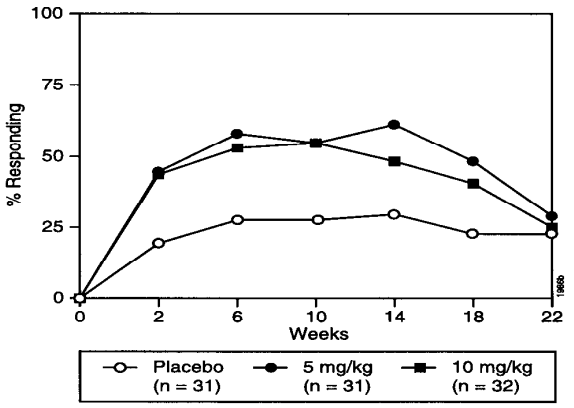

Figure 2. Response [fistula(s) closure] with Three Doses of Infliximab or Placebo

Seven of sixty (12%) evaluable Infliximab-treated patients, compared to one of thirty-one (3.5%) placebo-treated patients, developed an abscess in the area of fistulas between 8 and 16 weeks after the last infusion of Infliximab. Six of the Infliximab patients who developed an abscess had experienced a clinical response. (See *ADVERSE REACTIONS, Infections*).

Dose regimens other than dosing at weeks 0, 2 and 6 have not been studied. Studies have not been done to assess the effects of Infliximab on healing of the internal fistular canal, on closure of non-cutaneously draining fistulas (e.g., entero-entero), or on cutaneously draining fistulas in locations other than perianal and periabdominal.

INDICATIONS AND USAGE:

Infliximab is indicated for:

1. treatment of moderately to severely active Crohn's disease for the reduction of the signs and symptoms, in patients who have an inadequate response to conventional therapy.

   The safety and efficacy of therapy continued beyond a single dose have not been established (See *DOSAGE AND ADMINISTRATION*).

2. treatment of patients with fistulizing Crohn's disease for the reduction in the number of draining enterocutaneous fistula(s).

   The safety and efficacy of therapy continued beyond three doses have not been studied

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(See *DOSAGE AND ADMINISTRATION*).

CONTRAINDICATIONS:

Infliximab should not be administered to patients with known hypersensitivity to any murine proteins or other component of the product.

WARNINGS:

Hypersensitivity

Infliximab has been associated with hypersensitivity reactions. Urticaria, dyspnea and hypotension have occurred in association with Infliximab infusion. Infliximab should be discontinued for severe reactions. Medications for the treatment of hypersensitivity reactions (e.g., acetaminophen, antihistamines, corticosteroids and/or epinephrine) should be available for immediate use in the event of a reaction (see *ADVERSE REACTIONS, Infusion-related Reactions).*

Autoimmunity

Anti-TNF therapy may result in the formation of autoimmune antibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Infliximab and is positive for antibodies against double-stranded DNA, treatment should be discontinued (see *ADVERSE REACTIONS, Auto-antibodies/Lupus-like Syndrome).* In clinical trials, patients who developed anti-double-stranded DNA (dsDNA) antibodies and/or symptoms suggestive of a lupus-like syndrome have had resolution of symptoms and disappearance of the anti-dsDNA after discontinuation of Infliximab therapy.

PRECAUTIONS:

Immunosuppression

TNFα mediates inflammation and modulates cellular immune response; therefore, the possibility exists for anti-TNF therapies, including Infliximab, to affect normal immune responses.

Malignancy/Infection

Patients with long duration of Crohn's disease and chronic exposure to immunosuppressant therapies are more prone to develop lymphomas and infections (see *ADVERSE REACTIONS, Lymphoproliferative Disorders and Infections).* The impact of Infliximab treatment on these phenomena is unknown.

Human Antichimeric Antibody (HACA) Development

One-hundred thirty-four of the 199 Crohn's disease patients treated with Infliximab were evaluated for HACA; 18 (13%) were HACA-positive (the majority at low titer, ≤1:20). Patients who were HACA-positive were more likely to experience an infusion reaction (see *ADVERSE REACTIONS, Infusion-related Reactions*). The incidence of positive HACA responses was lower among Crohn's disease patients receiving immunosuppressant therapies such as 6-MP, AZA or corticosteroids [10/99 (10%)

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of these patients developed positive HACA responses] than among those not receiving these agents [8/35 (23%) of these patients developed positive HACA responses].

Drug Interactions

Specific studies on drug interactions with Infliximab have not been conducted. The majority of patients in Crohn's disease clinical trials received one or more of the following concomitant medications: antibiotics, antivirals, corticosteroids, 6-MP/AZA and aminosalicylates, all medications commonly used in Crohn's disease. Patients receiving immunosuppressants tended to experience fewer infusion reactions as compared to patients on no immunosuppressants (see *PRECAUTIONS, HACA Development* and *ADVERSE REACTIONS, Infusion-related Reactions).*

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential or effects on potential impairment of fertility in male and female animals. No clastogenic or mutagenic effects of Infliximab were observed in the *in vivo* mouse micronucleus test or the *Salmonella-Escherichia coli* (Ames) assay, respectively. Chromosomal aberrations were not observed in an assay performed using human lymphocytes.

Pregnancy Category C

Since Infliximab does not cross-react with TNFα in species other than humans and chimpanzees, animal reproduction studies have not been conducted with Infliximab. It is not known whether Infliximab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Infliximab should be given to a pregnant woman only if clearly needed. In a developmental toxicity study conducted in mice using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, no evidence of maternal toxicity, embryotoxicity or teratogenicity was observed.

Nursing Mothers

It is not known whether Infliximab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Infliximab, 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.

Pediatric Use

Safety and effectiveness of Infliximab in pediatric patients have not been established.

Geriatric Use

Clinical studies of Infliximab did not include sufficient numbers of Crohn's disease patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. As the impact of Infliximab treatment on the incidence of infections is unknown and there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly[14] (see

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ADVERSE REACTIONS, Infections).

ADVERSE REACTIONS:

In clinical trials, a total of 533 patients were treated with Infliximab doses up to 20 mg/kg; 199 in Crohn's disease trials, 334 in investigational trials for other disease. Approximately one-third of the patients received only a single infusion of Infliximab while the remaining patients received multiple infusions, up to a maximum of five. One-hundred fifty-eight patients were followed for at least 2 years, of whom only 30 patients were in Crohn's disease trials.

In studies in Crohn's disease, approximately 5% of patients discontinued scheduled Infliximab infusions due to an adverse experience. The most common reasons for discontinuation of treatment were infusion reactions and infections.

Infusion-related Reactions

An infusion reaction was defined as any adverse event occurring during the infusion or the 2-hour post-infusion observation period. Sixteen percent of Infliximab-treated patients in all clinical trials experienced an infusion reaction compared to 6% of placebo-treated patients. Among the 1,207 Infliximab infusions, 5% (58/1207) were accompanied by nonspecific symptoms such as fever or chills, 1% were accompanied by pruritus or urticaria, 1% were accompanied by cardiopulmonary reactions (primarily chest pain, hypotension, hypertension or dyspnea), and 0.2% were accompanied by combined symptoms of pruritus/urticaria and cardiopulmonary reactions. Nine infusion reactions resulted in discontinuation of Infliximab; all patients recovered with treatment and/or discontinuation of infusion. Seven percent of patients experienced an infusion reaction during the initial infusion and 10% experienced an infusion reaction during the second Infliximab infusion. Subsequent Infliximab infusions beyond two were not associated with a higher incidence of reactions.

Patients who became positive for human antichimeric antibodies (HACA) were more likely to develop infusion reactions than those who remained HACA negative (36% vs. 11% respectively). Use of concomitant immunosuppressant agents appeared to reduce the frequency of infusion

reactions (see *PRECAUTIONS, Human Antichimeric Antibody Development and Drug Interactions).*

Infections

Among all placebo-controlled trials evaluating Infliximab, infections were reported by 21% of Infliximab-treated patients (average of 22 weeks of follow-up) and by 11% of placebo-treated patients (average of 12 weeks of follow-up). Fifteen Infliximab-treated patients (3%) reported serious infections, including: suspected pneumonia; cellulitis; and infection at a central venous catheter, sepsis, cholecystitis, endophthalmitis, and furunculosis. Two placebo-treated patients (2%) reported serious infections requiring antibiotic therapy. (See *PRECAUTIONS, Malignancy/Infection*).

Twelve percent of patients with fistulizing Crohn's disease, developed a new abscess 8 to 16 weeks after the last infusion with Infliximab (see *CLINICAL STUDIES, Fistulizing Crohn's Disease*).

Auto-Antibodies /Lupus-like Syndrome

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Of the Infliximab-treated patients evaluated for antinuclear antibodies (ANA), the percentage of patients positive for ANA increased from 24% (85/357) at screening to 36% (128/357) at the last evaluation. Anti-dsDNA antibodies developed in approximately 9% of patients treated with Infliximab. No association of total Infliximab exposure with the development of anti-dsDNA antibodies was noted. However, particularly in Crohn's disease patients, baseline therapy with an immunosuppressant of any type reduced development of anti-dsDNA antibodies [3% (4/115) of patients compared to 21% (10/48) of patients not receiving any immunosuppressant]. Crohn's disease patients were approximately 2 times more likely to develop anti-dsDNA antibodies if they were ANA-positive at study entry.

Two patients developed clinical signs consistent with a lupus-like syndrome. One of these, a non-Crohn's disease patient, developed dyspnea and pleuropericarditis with resolution of symptoms within 6 to 8 weeks of initiation of treatment with oral corticosteroids. The other, a Crohn's disease patient, developed lupus arthritis, also responsive to corticosteroids, with symptoms resolving within 6 months after the last Infliximab infusion (see *WARNINGS, Autoimmunity*).

No other autoimmune disorders were reported in patients followed for 6 months to 3 years after receiving their last infusion.

Lymphoproliferative Disorders

In 394 Infliximab-treated patients (from all studies) who were followed for 6 months to 3 years after receiving their last infusion, one case of lymphoma occurred in a Crohn's disease patient and 2 cases occurred in non-Crohn's patients. One case of myeloma occurred in a non-Crohn's disease patient. One additional case of lymphoma occurred in a non-Crohn's patient with HIV/AIDS during a shorter period of follow up. The data are insufficient to determine if an association exists between the occurrence of lymphomas and the dose or duration of exposure to Infliximab. The lymphomas reported occurred in patients with a long duration of disease and chronic exposure to immunosuppressant therapies, a population at greater risk for development of malignancy[15,16] (see *PRECAUTIONS, Malignancy/Infection*).

Other Adverse Reactions

Table 1 lists the adverse reactions occurring at a frequency of at least 5% in the Crohn's disease trials.

Table 1
ADVERSE REACTIONS IN CROHN'S DISEASE TRIALS

	Placebo (n =56)	Infliximab (n = 199)
Avg. wks of follow-up	14.7	27.0
Pts with ≥ 1 AE	35 (62.5%)	168 (84.4%)
WHOART preferred term		
Headache	12 (21.4%)	45 (22.6%)
Nausea	2 (3.6%)	33 (16.6%)
Upper Respiratory Tract Infection	5 (8.9%)	32 (16.1%)
Abdominal Pain	2 (3.6%)	24 (12.1%)
Fatigue	3 (5.4%)	21 (10.6%)
Fever	4 (7.1%)	20 (10.1%)

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Pharyngitis	3 (5.4%)	17 (8.5%)
Vomiting	0 (0.0%)	17 (8.5%)
Dizziness	5 (8.9%)	16 (8.0%)
Pain	3 (5.4%)	17 (8.5%)
Bronchitis	1 (1.8%)	14 (7.0%)
Rash	3 (5.4%)	12 (6.0%)
Rhinitis	2 (3.6%)	12 (6.0%)
Chest Pain	3 (5.4%)	11 (5.5%)
Coughing	0 (0.0%)	10 (5.0%)
Pruritus	1 (1.8%)	10 (5.0%)
Sinusitis	1 (1.8%)	10 (5.0%)
Myalgia	3 (5.4%)	10 (5.0%)
Back Pain	2 (3.6%)	10 (5.0%)
Moniliasis	0 (0.0%)	10 (5.0%)

In general, the adverse event rates in the combined data set (Crohn's disease and non-Crohn's disease) were similar to those observed in Crohn's disease trials.

Adverse events by WHOART body system that have occurred in all Infliximab-treated patients at frequencies less than 5% but more than 1% are as follows:

Body as a Whole: chills, edema peripheral, fall, hot flushes, malaise
Cardiovascular Disorders, General: hypertension, hypotension
Central & Peripheral Nervous System Disorders: muscle contractions involuntary, paresthesia, vertigo
Eye and Vision Disorders: conjunctivitis
Gastrointestinal System Disorders: constipation, dyspepsia, flatulence, intestinal obstruction, oral pain, stomatitis ulcerative, toothache
Heart Rate and Rhythm Disorders: tachycardia
Liver and Biliary System Disorders: hepatic enzymes increased
Musculoskeletal System Disorders: arthralgia, arthritis
Psychiatric Disorders: anxiety, depression, insomnia
Red and Blood Cell Disorders: anemia
Resistance Mechanism Disorders: abscess, flu syndrome, herpes simplex, herpes zoster
Skin and Appendages Disorders: acne, alopecia, dermatitis fungal, eczema, erythema, rash erythematous, rash maculopapular, rash papular, skin dry, sweating increased, urticaria
Urinary System Disorders: dysuria, micturition frequency
Vascular (Extracardiac) Disorders: ecchymosis, flushing, hematoma

Among Infliximab-treated patients with Crohn's disease, serious adverse events occurred at a frequency < 2% with the majority occurring at a frequency of ≤ 0.5%. These were abdominal pain, abdominal hernia, abscess, adult respiratory distress syndrome, back pain, chest pain, cholecystitis, Crohn's disease, dehydration, diarrhea, dyspnea, dysuria, fall, fever, furunculosis, hypertension, hypotension, infection bacterial, intestinal obstruction, intestinal perforation, intestinal stenosis, kidney infarction, lymphoma, lupus erythematosus syndrome, nausea, palpitation, pneumonia, proctalgia, sepsis, splenic infarction, splenomegaly, syncope, tendon injury, thrombocytopenia, ureteral obstruction and vomiting.

In the Infliximab-treated non-Crohn's disease patients, all serious events except fever (1.2%) occurred at a frequency of <1% with the majority at ≤ 0.4%. These were arthralgia, arthritis rheumatoid, bone fracture, breast neoplasm malignant, bronchitis, cardiac failure, cellulitis, coughing, depression, dizziness, dyspnea, endophthalmitis, fall, fever, headache, injection site inflammation, myalgia, nausea, pleurisy, pneumonia, rash erythematous, renal calculus, rheumatoid nodules, sepsis, somnolence, sweating increased, tachycardia and vomiting.

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OVERDOSAGE:

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

DOSAGE AND ADMINISTRATION:

The recommended dose of Infliximab is 5 mg/kg given as a single intravenous infusion for treatment of moderately to severely active Crohn's disease in patients who have had an inadequate response to conventional therapy. In patients with fistulizing disease, an initial 5 mg/kg dose should be followed with additional 5 mg/kg doses at 2 and 6 weeks after the first infusion.

There are insufficient safety and efficacy data for the use of Infliximab beyond the recommended duration (see *INDICATIONS AND USAGE).*

Preparation and administration instructions: Use aseptic technique.

Remicade vials do not contain antibacterial preservatives. Therefore, the vials after reconstitution should be used immediately, not re-entered or stored. The diluent to be used for reconstitution is 10 mL of Sterile Water for Injection, USP. The total dose of the reconstituted product must be further diluted to 250 mL with 0.9% Sodium Chloride Injection, USP. The infusion concentration should range between 0.4 mg/mL and 4 mg/mL The Remicade infusion should begin within 3 hours of preparation.

Studies have indicated that reconstituted Remicade and diluted Remicade infusion solution are incompatible with plasticized PVC (polyvinylchloride) equipment or devices. Diluted Remicade solutions should be prepared only in glass infusion bottles or polypropylene or polyolefin infusion bags and administered through polyethylene-lined administration sets.

1. Calculate the dose and the number of Remicade vials needed. Each Remicade vial contains 100 mg of Infliximab. Calculate the total volume of reconstituted Remicade solution required.

2. Reconstitute each Remicade vial with 10 mL of Sterile Water for Injection, USP, using a syringe equipped with a 21-gauge or smaller needle. 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. Do not use the vial if the vacuum is not present. Gently swirl the solution by rotating the vial to dissolve the lyophilized powder. Avoid prolonged or vigorous agitation. DO NOT SHAKE. Foaming of the solution on reconstitution is not unusual. Allow the reconstituted solution to stand for 5 minutes. The solution should be colorless to light yellow and opalescent, and the solution may develop a few translucent particles as Infliximab is a protein. Do not use if opaque particles, discoloration, or other foreign particles are present.

3. Dilute the total volume of the reconstituted Remicade solution dose to 250 mL with 0.9% Sodium Chloride Injection, USP, by withdrawing a volume of 0.9% Sodium Chloride Injection, USP, equal to the volume of reconstituted Remicade from the 0.9% Sodium Chloride Injection, USP, 250 mL glass bottle or polypropylene or polyolefin bag. Slowly add the total volume of

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reconstituted Remicade solution to the 250 mL infusion bottle or bag. Gently mix.

4. The infusion solution must be administered over a period of not less than 2 hours and must use a polyethylene-lined infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2-μm or less). Any unused portion of the infusion solution should not be stored for reuse.

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

6. Parenteral drug products should be inspected visually 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.

Storage

Store the lyophilized product under refrigeration at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use beyond the expiration date. This product contains no preservative.

HOW SUPPLIED:

Remicade (Infliximab) lyophilized concentrate for injection is supplied in individually-boxed single-use vials in the following strength:

NDC 57894-030-01 100 mg infliximab in a 20-mL vial

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