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RESEARCH**

APPLICATION NUMBER:

BLA 125160/0

LABELING

Cimzia®
(certolizumab pegol)

UCB Version 18 April 2008

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CIMZIA (certolizumab pegol)

Lyophilized powder for solution for subcutaneous injection

Initial U.S. Approval: 2008

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

Tuberculosis (TB), invasive fungal, and other opportunistic infections, some fatal, have occurred. Perform test for latent TB; if positive, start treatment for TB prior to starting CIMZIA. Monitor all patients for active TB during CIMZIA treatment, even if initial tuberculin skin test is negative (5.1, 5.2).

INDICATIONS AND USAGE

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

- Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy (1)

DOSAGE AND ADMINISTRATION

- 400 mg subcutaneously initially and at Weeks 2 and 4 (2.1)
- If response occurs, follow with 400 mg subcutaneously every four weeks (2.1)

DOSAGE FORMS AND STRENGTHS

- 200 mg lyophilized powder for reconstitution with 1 mL of sterile Water for Injection, USP (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Serious infections – do not start CIMZIA during an active infection. If an infection develops, monitor carefully, and stop CIMZIA if infection becomes serious (5.1)
- Hepatitis B virus reactivation – monitor HBV carriers during and several months after therapy. If reactivation occurs, stop CIMZIA and begin anti-viral therapy (5.3)
- Cases of lymphoma and other malignancies have been observed among patients receiving TNF blockers (5.4)
- Anaphylaxis or serious allergic reactions may occur (5.5)
- Demyelinating disease, exacerbation or new onset, may occur (5.6)
- Cytopenias, pancytopenia – advise patients to seek immediate medical attention if symptoms develop, and consider stopping CIMZIA (5.7)
- Heart failure, worsening or new onset may occur (5.9)
- Lupus-like syndrome – stop CIMZIA if syndrome develops (5.10)

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥5% and higher than placebo): upper respiratory tract infection, urinary tract infection, and arthralgia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 1-866-822-0068 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Anakinra – increased risk of serious infections (5.8, 7.1)
- Live vaccines – do not give with CIMZIA (5.11, 7.2)
- Laboratory tests – may interfere with aPTT tests (7.3)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE.

Revised: 4/2008

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FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving CIMZIA. Some of these infections have been fatal. Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with TNF blockers such as CIMZIA. However, active tuberculosis has developed in patients receiving CIMZIA whose tuberculin test was negative.

Evaluate patients for tuberculosis risk factors and test for latent tuberculosis infection prior to initiating CIMZIA and during therapy. Initiate treatment of latent tuberculosis infection prior to therapy with CIMZIA. Monitor patients receiving CIMZIA for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis infection [see *Warnings and Precautions (5.1, 5.2) and Adverse Reactions (6.1)*].

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The recommended initial adult dose of CIMZIA is 400 mg (given as two subcutaneous injections of 200 mg) initially, and at Weeks 2 and 4. In patients who obtain a clinical response, the recommended maintenance regimen is 400 mg every four weeks.

2.2 Preparation Instructions

CIMZIA should be prepared by a health care professional.

CIMZIA is provided in a package that contains everything required to reconstitute and inject the drug as described below. CIMZIA should be brought to room temperature before reconstituting to facilitate dissolution.

Reconstitute two 200 mg vials of CIMZIA for each dose. Using appropriate aseptic technique, reconstitute each lyophilized vial of CIMZIA with 1 mL of sterile Water for Injection, USP, using a syringe with a 20 gauge needle. Gently swirl each vial of CIMZIA without shaking so that all of the lyophilized powder comes into contact with the sterile Water for Injection. Leave the vials undisturbed to fully reconstitute (this may take as long as 30 minutes). Reconstituted CIMZIA has a concentration of approximately 200 mg/mL.

Do not leave reconstituted CIMZIA at room temperature for more than 2 hours prior to administration. Once reconstituted, CIMZIA can be stored in the vials for up to 24 hours at 2 to 8 °C (36 to 46 °F) prior to injection. Do not freeze.

2.3 Administration Instructions

CIMZIA should be administered by a health care professional.

Once reconstituted, CIMZIA is a clear to opalescent, colorless to pale yellow liquid with no visible particulates or gels in solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstituted CIMZIA with obvious particulate matter or discoloration should be discarded.

Prior to injecting, reconstituted CIMZIA should be at room temperature. Using a new 20 gauge needle for each vial, withdraw the reconstituted solution into a separate syringe for each vial, resulting in two syringes each containing 1 mL of CIMZIA (200 mg). Switch each 20 gauge needle to a 23 gauge needle and inject the full contents of each syringe subcutaneously into separate sites on the abdomen or thigh.

3 DOSAGE FORMS AND STRENGTHS

CIMZIA is supplied as a sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. Each single-use vial provides approximately 200 mg certolizumab pegol.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious infections, sepsis, and cases of opportunistic infections, including fatalities, have been reported in patients receiving TNF blockers, including CIMZIA. Many of the serious infections reported have occurred in patients on concomitant immunosuppressive therapy that, in addition to their Crohn's disease, could predispose them to infections. In postmarketing experience with TNF blockers, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms, and infections have been noted in all organ systems. Infections have been reported in patients receiving CIMZIA alone or in conjunction with immunosuppressive agents.

Do not initiate treatment with CIMZIA in patients with active infections, including chronic or localized infections. Monitor patients for signs and symptoms of infection while on and after treatment with CIMZIA. Patients who develop a new infection while undergoing treatment with CIMZIA should be monitored closely. Discontinue administration of CIMZIA if a patient develops a serious infection. Exercise caution when considering the use of CIMZIA in patients with a history of recurrent infection, concomitant immunosuppressive therapy, or underlying conditions that may predispose them to infections, or patients who have resided in regions where tuberculosis and histoplasmosis are endemic. The benefits and risks of CIMZIA

treatment should be carefully considered before initiation of CIMZIA therapy [*see Adverse Reactions (6.1)*].

5.2 Tuberculosis

As observed with other TNF blockers, tuberculosis associated with the administration of CIMZIA in clinical studies has been reported, including fatalities.

Before initiation of therapy with CIMZIA, evaluate patients for tuberculosis risk factors and test for latent tuberculosis infection. Initiate treatment of latent tuberculosis infections prior to therapy with CIMZIA. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guerin (BCG). If latent infection is diagnosed, institute appropriate prophylaxis in accordance with the current guidelines from the Centers for Disease Control and Prevention.

Consider the possibility of undetected latent tuberculosis, especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or had close contact with a person with active tuberculosis. All patients treated with CIMZIA should have a thorough history taken prior to initiating therapy. Some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF blockers.

Consider anti-tuberculosis therapy prior to initiation of CIMZIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Anti-tuberculosis therapy prior to initiating CIMZIA should also be considered in patients who have several, or highly significant, risk factors for tuberculosis infection and have a negative test for latent tuberculosis, but the decision to initiate anti-tuberculosis therapy in the patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consult a physician with experience in the treatment of tuberculosis.

Monitor patients receiving CIMZIA for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. Instruct patients to seek medical advice if signs/symptoms (e.g., persistent cough, wasting, weight loss, low grade fever) suggestive of a tuberculosis infection occur.

5.3 Hepatitis B Virus Reactivation

Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Evaluate patients at risk for HBV infection for prior evidence of HBV infection before initiating CIMZIA therapy. Exercise caution in prescribing CIMZIA for patients identified as carriers of HBV. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with CIMZIA 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, discontinue CIMZIA and initiate effective anti-viral therapy with appropriate supportive treatment. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. Therefore, exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

5.4 Malignancies

In the controlled portions of clinical studies of some TNF blockers, more cases of malignancies have been observed among patients receiving TNF blockers compared to control patients. During controlled and open-labeled portions of CIMZIA studies of Crohn's disease and other investigational uses, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.6 (0.4, 0.8) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.2, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

In the controlled portions of clinical trials of all the TNF blockers, more cases of lymphoma have been observed among patients receiving TNF blockers compared to control patients. In controlled studies of CIMZIA for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 Cimzia-treated patients and one case of Hodgkin lymphoma among 1,319 placebo-treated patients.

Rates in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. Patients with Crohn's disease or other diseases that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF blocker therapy. The potential role of TNF blocker therapy in the development of malignancies is not known.

5.5 Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed [*see Adverse Reactions (6.1)*].

5.6 Neurologic Reactions

Use of TNF blockers, including CIMZIA, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA; the causal relationship to CIMZIA remains unclear [*see Adverse Reactions (6.1)*].

5.7 Hematological Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blockers. Adverse reactions of the hematologic system, including medically significant cytopenia

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(e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with CIMZIA [see *Adverse Reactions (6.1)*]. The causal relationship of these events to CIMZIA remains unclear.

Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. Advise all patients to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA. Consider discontinuation of CIMZIA therapy in patients with confirmed significant hematologic abnormalities.

5.8 Use with Anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, with no added benefit. Because of the nature of the adverse reactions seen with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blockers. Therefore, the combination of CIMZIA and anakinra is not recommended [see *Drug Interactions (7.1)*].

5.9 Heart Failure

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in CHF of another TNF blocker, a higher rate of serious CHF-related adverse reactions was observed. Exercise caution when using CIMZIA in patients who have heart failure and monitor them carefully.

5.10 Autoimmunity

Treatment with CIMZIA 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 CIMZIA, discontinue treatment [see *Adverse Reactions (6.1)*].

5.11 Immunizations

No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA. Do not administer live vaccines or attenuated vaccines concurrently with CIMZIA.

5.12 Immunosuppression

Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blockers, including CIMZIA, to affect host defenses against infections and malignancies. The impact of treatment with CIMZIA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood [see *Warnings and Precautions (5.1, 5.2, 5.3, 5.4) and Adverse Reactions (6.1)*]. The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most serious adverse reactions were:

- Serious Infections [*see Warnings and Precautions (5.1, 5.2)*]
- Malignancies [*see Warnings and Precautions (5.4)*]

The data described below reflect exposure to CIMZIA at 400 mg subcutaneous dosing in studies of patients with Crohn's disease. In the safety population in controlled studies, a total of 620 subjects with Crohn's disease received CIMZIA at a dose of 400 mg, and 614 subjects received placebo (including subjects randomized to placebo in Study CD2 following open label dosing of CIMZIA at Week 0, 2, 4). In controlled and uncontrolled studies, 1,564 subjects received CIMZIA at some dose level, of whom 1,350 subjects received 400 mg CIMZIA. Approximately 55% of subjects were female, 45% were male, and 94% were Caucasian. The majority of patients in the active group were between the ages of 18 and 64.

During controlled clinical studies, the proportion of patients with serious adverse reactions was 10% for CIMZIA and 9% for placebo. The most common adverse reactions (occurring in $\geq 5\%$ of Cimzia-treated patients, and with a higher incidence compared to placebo) in controlled clinical studies with CIMZIA was upper respiratory infection (20% CIMZIA, 13% placebo), urinary tract infection (7% CIMZIA, 6% placebo), and arthralgia (6% CIMZIA, 4% placebo).

The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for CIMZIA and 7% for placebo. The most common adverse reactions leading to the discontinuation of CIMZIA (for at least 2 patients and with a higher incidence than placebo) were abdominal pain (0.4% CIMZIA, 0.2% placebo), diarrhea (0.4% CIMZIA, 0% placebo), and intestinal obstruction (0.4% CIMZIA, 0% placebo).

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

Infections

The incidence of infections in controlled clinical studies was 38% for CIMZIA-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infection (20% CIMZIA, 13% placebo). The incidence of serious infections during the controlled clinical studies was 3% for CIMZIA-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis [*see Warnings and Precautions (5.1, 5.2)*].

Tuberculosis and Opportunistic Infections

In completed and ongoing clinical studies that include over 4,650 patients, the overall rate of tuberculosis is approximately 0.5 per 100 patient-years. The rate in Crohn's disease studies was 0.3 cases per 100 patient-years. The reports include cases of pulmonary and disseminated tuberculosis. Cases of opportunistic infection have also been reported in clinical trials. Some cases of opportunistic infections and tuberculosis have been fatal [*see Warnings and Precautions (5.2)*].

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Malignancies

In clinical studies of CIMZIA, the overall incidence rate of malignancies was similar for CIMZIA-treated and control patients. For some TNF blockers, more cases of malignancies have been observed among patients receiving those TNF blockers compared to control patients [see *Warnings and Precautions (5.4)*].

Autoantibodies

In clinical studies in Crohn's disease, 4% of patients treated with CIMZIA and 2% of patients treated with placebo that had negative baseline ANA titers developed positive titers during the studies. One of the 1,564 Crohn's disease patients treated with CIMZIA developed symptoms of a lupus-like syndrome. The impact of long-term treatment with CIMZIA on the development of autoimmune diseases is unknown [see *Warnings and Precautions (5.10)*].

Immunogenicity

Patients were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. The overall percentage of antibody positive patients was 8% in patients continuously exposed to CIMZIA, of which approximately 80% were neutralizing *in vitro*. No apparent correlation of antibody development to adverse events or efficacy was observed. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients not taking immunosuppressants at baseline (3% and 11%, respectively).

The following adverse events were reported in antibody-positive patients (N = 100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,242): abdominal pain, arthralgia, edema peripheral, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection.

The data reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to certolizumab pegol with the incidence of antibodies to other products may be misleading.

Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dermatitis allergic, dizziness (postural), dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, serum sickness, and (vasovagal) syncope [see *Warnings and Precautions (5.5)*].

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Other Adverse Reactions

The most commonly occurring adverse reactions in controlled trials of Crohn's disease were described above. Other serious or significant adverse reactions reported in controlled and uncontrolled studies in Crohn's disease and other diseases under investigation, occurring in patients receiving CIMZIA at doses of 400 mg or other doses include:

Blood and lymphatic system disorders: Anemia, leukopenia, lymphadenopathy, pancytopenia, and thrombophilia.

Cardiac disorders: Angina pectoris, arrhythmias, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, and pericarditis.

Eye disorders: Optic neuritis, retinal hemorrhage, and uveitis.

General disorders and administration site conditions: Bleeding and injection site reactions.

Hepatobiliary disorders: Elevated liver enzymes and hepatitis.

Immune system disorders: Alopecia totalis.

Psychiatric disorders: Anxiety, bipolar disorder, and suicide attempt.

Renal and urinary disorders: Nephrotic syndrome and renal failure.

Reproductive system and breast disorders: Menstrual disorder.

Skin and subcutaneous tissue disorders: Dermatitis, erythema nodosum, and urticaria.

Vascular disorders: Vasculitis.

6.2 Adverse Reaction Information from Other Sources

Cases of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme, have been identified during post-approval use of other TNF blockers. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

7.1 Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF blocker has shown an increased risk of serious infections, an increased risk of neutropenia, and no added benefit compared to these medicinal products alone. Therefore, the combination of

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anakinra with other TNF blockers, including CIMZIA, may also result in similar toxicities [see *Warnings and Precautions (5.8)*].

7.2 Live Vaccines

Do not give live (including attenuated) vaccines concurrently with CIMZIA [see *Warnings and Precautions (5.11)*].

7.3 Laboratory Tests

Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-LA test from Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilized silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. Interference with thrombin time (TT) and prothrombin time (PT) assays has not been observed. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – Because certolizumab pegol does not cross-react with mouse or rat TNF α , reproduction studies were performed in rats using a rodent anti-murine TNF α pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Reproduction studies have been performed in rats at doses up to 100 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF. There are, however, no adequate and well-controlled studies of CIMZIA in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CIMZIA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of CIMZIA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. A population pharmacokinetic analysis of all patients enrolled in CIMZIA clinical studies concluded that there was no apparent difference in drug concentration regardless of age. Because there is a higher incidence of infections in the elderly population in general, use caution when treating the elderly [see *Warnings and Precautions (5.1)*].

10 OVERDOSAGE

The maximum tolerated dose of certolizumab pegol has not been established. Doses of up to 800 mg subcutaneous and 20 mg/kg intravenous have been administered without serious adverse reactions. In cases of overdosage, it is recommended that patients be monitored closely for any adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

CIMZIA (certolizumab pegol) is a TNF blocker. CIMZIA is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNF α), conjugated to an approximately 40kDa polyethylene glycol (PEG2MAL40K). The Fab' fragment is manufactured in *E. coli* and is subsequently subjected to purification and conjugation to PEG2MAL40K, to generate certolizumab pegol. The Fab' fragment is composed of a light chain with 214 amino acids and a heavy chain with 229 amino acids. The molecular weight of certolizumab pegol is approximately 91 kilodaltons.

CIMZIA is supplied as a sterile, white, lyophilized powder for solution for subcutaneous injection. Reconstituted CIMZIA is a clear to opalescent solution that is colorless to pale yellow without particulates or gels. After reconstitution with 1 mL sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial provides approximately 200 mg certolizumab pegol, 100 mg sucrose, 0.9 mg lactic acid, and 0.1 mg polysorbate. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Certolizumab pegol binds to human TNF α with a KD of 90pM. TNF α is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNF α (IC₉₀ of 4 ng/mL for inhibition of human TNF α in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralize lymphotoxin α (TNF β). Certolizumab pegol cross-reacts poorly with TNF from rodents and rabbits, therefore *in vivo* efficacy was evaluated using animal models in which human TNF α was the physiologically active molecule.

Certolizumab pegol was shown to neutralize membrane-associated and soluble human TNF α in a dose-dependent manner. Incubation of monocytes with certolizumab pegol resulted in a dose-dependent inhibition of LPS-induced TNF α and IL-1 β production in human monocytes.

Certolizumab pegol does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody-dependent cell-mediated cytotoxicity *in vitro*. It does not induce apoptosis *in vitro* in human peripheral blood-derived monocytes or lymphocytes, nor does certolizumab pegol induce neutrophil degranulation.

A tissue reactivity study was carried out *ex vivo* to evaluate potential cross-reactivity of certolizumab pegol with cryosections of normal human tissues. Certolizumab pegol showed no reactivity with a designated standard panel of normal human tissues.

12.2 Pharmacodynamics

Biological activities ascribed to TNF α include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNF α stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNF α have been implicated in the pathology of Crohn's disease. TNF α is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal concentrations of TNF α in patients with Crohn's disease have been shown to reflect clinical severity of the disease. After treatment with certolizumab pegol, patients with Crohn's disease demonstrated a decrease in the levels of C-reactive protein (CRP).

12.3 Pharmacokinetics

A total of 78 healthy subjects received doses of up to 800 mg certolizumab pegol subcutaneously and up to 10 mg/kg intravenously in three pharmacokinetic studies. Data from these studies demonstrate that single intravenous and subcutaneous doses of certolizumab pegol have predictable dose-related plasma concentrations with a linear relationship between the dose administered and the maximum serum concentration (C_{max}), and the Area Under the certolizumab pegol plasma concentration versus time Curve (AUC). Patients with Crohn's disease were dosed subcutaneously every four weeks with certolizumab pegol at 100, 200, or 400 mg and at 400 mg every two weeks for three doses, followed by a maintenance dose of 400 mg every four weeks. Certolizumab pegol plasma concentrations were broadly dose-proportional and pharmacokinetics observed in patients with Crohn's disease were consistent with those seen in healthy subjects.

The pharmacokinetics of certolizumab pegol were evaluated in a cross-study population pharmacokinetic analysis of data from 1580 subjects, of whom 1268 were patients with Crohn's disease. The population pharmacokinetic analysis concluded that age, gender, creatinine clearance, and white blood cell count did not influence the pharmacokinetics of certolizumab pegol. The population pharmacokinetic analysis did not allow any conclusion to be drawn on the effect of hepatic impairment because of the small number of patients with significant liver dysfunction included in the analysis.

Anti-certolizumab pegol antibodies, repeated administration, weight, and immunosuppressant use were covariates that had a statistically significant effect on the pharmacokinetics of certolizumab pegol. Only the presence of antibodies had more than a 30% effect on C_{max} and/or AUC.

None of the subject-dependant covariates identified in the population pharmacokinetic analysis had an effect that would require dose adjustment.

Pharmacokinetic parameters in Japanese subjects were similar to those in Caucasian subjects following subcutaneous dosing at three dose levels in a biocomparability study.

- **Absorption**

Following subcutaneous administration, peak plasma concentrations of certolizumab pegol were attained between 54 and 171 hours post-injection. Certolizumab pegol has bioavailability (F) of approximately 80% (ranging from 76% to 88%) following subcutaneous administration

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compared to intravenous administration. Steady-state concentrations range from 0.5 to 90 mcg/mL for a fixed dose of 400 mg of certolizumab pegol. For patients developing anti-certolizumab pegol antibodies, the steady state concentrations range from 0.5 to 75 mcg/mL.

- **Distribution**

The steady state volume of distribution (V_{ss}) was estimated as 6.4 L in the population pharmacokinetic analysis.

- **Metabolism and Elimination**

Pegylation, the covalent attachment of PEG polymers to peptides, delays the elimination of these entities from the circulation by a variety of mechanisms, including decreased renal clearance, proteolysis, and immunogenicity. Accordingly, certolizumab pegol is an antibody Fab' fragment conjugated with PEG in order to extend the terminal plasma elimination half-life of the Fab' to a value comparable with a whole antibody product. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all doses tested. The clearance following subcutaneous dosing was estimated as 17 mL/h in the population pharmacokinetic analysis, with an inter-subject variability of 38% (CV) and an inter-occasion variability of 16%. The route of elimination of certolizumab pegol has not been studied in human subjects.

- **Drug Interaction Studies**

Formal drug-drug interaction studies have not been conducted with CIMZIA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of CIMZIA have not been conducted to assess its carcinogenic potential. Certolizumab pegol was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay, or the mouse bone marrow micronucleus assay.

Since certolizumab pegol does not cross-react with mouse or rat TNF α , reproduction studies were performed in rats using a rodent anti-murine TNF α pegylated Fab fragment (cTNF PF), similar to certolizumab pegol. cTNF PF had no effects on the fertility and general reproductive performance of male and female rats at intravenous doses up to 100 mg/kg, administered twice weekly.

14 CLINICAL STUDIES

14.1 Crohn's Disease

The efficacy and safety of CIMZIA were assessed in two double-blind, randomized, placebo-controlled studies in patients aged 18 years and older with moderately to severely active Crohn's disease, as defined by a Crohn's Disease Activity Index (CDAI¹) of 220 to 450 points, inclusive. CIMZIA was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn's disease were permitted.

Study CD1

Study CD1 was a randomized placebo-controlled study in 662 patients with active Crohn's disease. CIMZIA or placebo was administered at Weeks 0, 2, and 4 and then every four weeks to Week 24. Assessments were done at Weeks 6 and 26. Clinical response was defined as at least a 100-point reduction in CDAI score compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower.

The results for Study CD1 are provided in Table 1. At Week 6, the proportion of clinical responders was statistically significantly greater for CIMZIA-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at Week 6. The difference in the proportion of patients who were in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

Table 1 Study CD1 – Clinical Response and Remission, Overall Study Population

Timepoint	% Response or Remission (95% CI)	
	Placebo (N = 328)	CIMZIA 400 mg (N = 331)
Week 6		
Clinical Response [#]	27% (22%, 32%)	35% (30%, 40%)*
Clinical Remission [#]	17% (13%, 22%)	22% (17%, 26%)
Week 26		
Clinical Response	27% (22%, 31%)	37% (32%, 42%)*
Clinical Remission	18% (14%, 22%)	29% (25%, 34%)*
Both Weeks 6 & 26		
Clinical Response	16% (12%, 20%)	23% (18%, 28%)*
Clinical Remission	10% (7%, 13%)	14% (11%, 18%)
* p-value < 0.05 logistic regression test		
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points		

Study CD2

Study CD2 was a randomized treatment-withdrawal study in patients with active Crohn's disease. All patients who entered the study were dosed initially with CIMZIA 400 mg at Weeks 0, 2, and 4 and then assessed for clinical response at Week 6 (as defined by at least a 100-point reduction in CDAI score). At Week 6, a group of 428 clinical responders was randomized to receive either CIMZIA 400 mg or placebo, every four weeks starting at Week 8, as maintenance therapy through Week 24. Non-responders at Week 6 were withdrawn from the study. Final evaluation was based on the CDAI score at Week 26. Patients who withdrew or who received rescue therapy were considered not to be in clinical response. Three randomized responders received no study injections, and were excluded from the ITT analysis.

The results for clinical response and remission are shown in Table 2. At Week 26, a statistically significantly greater proportion of Week 6 responders were in clinical response and in clinical remission in the CIMZIA-treated group compared to the group treated with placebo.

Table 2 Study CD2 - Clinical Response and Clinical Remission

	% Response or Remission (95% CI)	
	CIMZIA 400 mg x3 + Placebo N = 210	CIMZIA 400 mg N = 215
Week 26		
Clinical Response [#]	36% (30%, 43%)	63% (56%, 69%)*
Clinical Remission [#]	29% (22%, 35%)	48% (41%, 55%)*
* p < 0.05 # Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points		

Baseline use of immunosuppressants or corticosteroids had no impact on the clinical response to CIMZIA.

15 REFERENCES

1. Best WR, Beckett JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; 70(3): 439-444

16 HOW SUPPLIED/STORAGE AND HANDLING

• Pack Content

Qty.	Item
2	Type I glass vials with rubber stopper and overseals each containing 200 mg of lyophilized CIMZIA for reconstitution.
2	2 mL Type I glass vials containing 1 mL sterile Water for Injection
2	3 mL plastic syringes
4	20 gauge luer-lock needles (1 inch)
2	23 gauge luer-lock needles (1 inch)
8	Alcohol swabs

NDC 50474-700-62

• Storage and Stability

Refrigerate intact carton at 2 to 8 °C (36 to 46 °F). Do not freeze. Do not separate contents of carton prior to use. Do not use beyond expiration date on container.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 Patient Counseling

Advise patients of the potential risks and benefits of CIMZIA therapy. Give patients the Medication Guide and allow them time to read it prior to starting CIMZIA therapy and to review it periodically. Any questions resulting from the patient's reading of the Medication Guide should be discussed. Because caution should be exercised in administering CIMZIA to patients with clinically important active infections, advise patients of the importance of informing their health care providers about all aspects of their health at each treatment visit.

- **Immunosuppression**

Inform patients that CIMZIA may lower the ability of the immune system to fight infections. Instruct patients of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis and reactivation of hepatitis B virus infections.

Counsel patients about the possible risk of lymphoma and other malignancies while receiving CIMZIA.

- **Allergic Reactions**

Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions.

- **Other Medical Conditions**

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

17.2 Medication Guide

MEDICATION GUIDE
CIMZIA® (CIM-zee-uh)
(certolizumab pegol)

Read the Medication Guide that comes with CIMZIA before you receive the first treatment, and before each time you get a treatment of CIMZIA. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment.

What is the most important information I should know about CIMZIA?

CIMZIA is a medicine that affects your immune system. CIMZIA can lower the ability of the immune system to fight infections. Serious infections, including tuberculosis (TB) have happened in patients taking CIMZIA. Some patients have died from these infections.

- Your doctor should test you for TB before starting CIMZIA.

Cimzia®
(certolizumab pegol)

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- Your doctor should monitor you closely for signs and symptoms of TB during treatment with CIMZIA.

Before starting CIMZIA, tell your doctor if you:

- think you have an 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
- have HIV
- have tuberculosis (TB), or have been in close contact with someone with TB
- have or have had hepatitis B
- use the medicine Kineret® (anakinra)

After starting CIMZIA, if you get 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. CIMZIA can make you more likely to get infections or make any infection that you may have worse.

What is CIMZIA?

CIMZIA is a medicine called a Tumor Necrosis Factor (TNF) blocker. CIMZIA is used to reduce the signs and symptoms of moderately to severely active Crohn's disease in adult patients who have not been helped enough by usual treatments.

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

CIMZIA may not be right for you. Before starting CIMZIA, 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 CIMZIA?')
- **have or have had any type of cancer.**
- **have seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis**
- **have heart failure**
- **are scheduled to receive a vaccine.** Do not receive a live vaccine while taking CIMZIA.

Tell your doctor if you are pregnant, planning to become pregnant, or breastfeeding. CIMZIA has not been studied in pregnant or nursing women.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Your doctor will tell you if it is okay to take your other medicines while taking CIMZIA. Especially, tell your doctor if you take:

- Kineret® (anakinra). You have a higher chance for serious infections when taking CIMZIA with Kineret®.

How should I receive CIMZIA?

- CIMZIA should be injected by a healthcare provider. Each dose of CIMZIA will be given as two separate injections under the skin in your stomach area (abdomen) or upper leg (thigh).
- Make sure to keep all of your injection and follow-up appointments with your doctor.

What are the possible side effects of CIMZIA?

Serious side effects have happened in patients taking CIMZIA including:

- **Serious infections including tuberculosis (TB).** See “What is the most important information I should know about CIMZIA?”
- **Cancer including lymphoma.**
- **Nervous System Problems** such as Multiple Sclerosis, seizures, or inflammation of the nerves of the eyes. Symptoms include dizziness, numbness or tingling, problems with your vision, and weakness in your arms or legs.
- **Allergic Reactions.** Signs of an allergic reaction include a skin rash, swollen face, or trouble breathing.
- **Blood Problems.** Your body may not make enough of the blood cells that help fight infections or help stop bleeding. Symptoms include a fever that doesn't go away, bruising or bleeding very easily, or looking very pale.
- **Heart Failure** including new heart failure or worsening of heart failure you already have. Symptoms include shortness of breath, or swelling of your ankles or feet.
- **Immune reactions including a lupus-like syndrome.** Symptoms include shortness of breath, joint pain, or a rash on the cheeks or arms that worsens with sun exposure.

Call your doctor right away if you develop any of the above side effects or symptoms.

The most common side effects of CIMZIA are:

- upper respiratory infections (flu, cold)
- urinary tract infections (bladder infections)
- joint pain

Injection site reactions happen in some people.

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

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

General information about CIMZIA

Cimzia®
(certolizumab pegol)

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Medicines are sometimes prescribed for purposes that are not mentioned in Medication Guides. Do not use CIMZIA for a condition for which it was not prescribed. Do not give CIMZIA to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about CIMZIA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CIMZIA that is written for health professionals.

For more information go to www.CIMZIA.com or call 1-866-822-0068.

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 CIMZIA?

The active ingredient is certolizumab pegol.

The inactive ingredients in CIMZIA include: sucrose, lactic acid, polysorbate. No preservatives are present.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Product developed and manufactured for:

UCB, Inc.

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Smyrna, GA 30080

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