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) for injection, for subcutaneous use

CIMZIA (certolizumab pegol) injection, for subcutaneous use

Initial U.S. Approval: 2008

CIMZIA is administered by subcutaneous injection. The initial dose of CIMZIA is 400 mg (given as two subcutaneous injections of 200 mg) (2).

Crohn’s Disease (2.1)

• 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks
• Treatment of adult patients with active 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 (1.1)
• Treatment of adults with moderately to severely active rheumatoid arthritis (1.2)
• Treatment of adult patients with active psoriatic arthritis. (1.3)
• Treatment of adults with active ankylosing spondylitis (1.4)

Dosage and Administration (2.6) 03/2018

Recent Major Changes

03/2018

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 (1.1)
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• 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks
• Rheumatoid Arthritis (2.2)

• 400 mg initially and at Weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.

Psoriatic Arthritis (2.3)

• 400 mg initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.

FULL PRESCRIBING INFORMATION: CONTENTS*

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).
• CIMZIA should be discontinued if a patient develops a serious infection or sepsis (5.1).
• Perform test for latent TB; if positive, start treatment for TB prior to starting CIMZIA (5.1).
• 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 TNF blockers, of which CIMZIA is a member (5.2). CIMZIA is not indicated for use in pediatric patients (8.4).

Recent Major Changes

03/2018

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 (1.1)
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• 400 mg initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.

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To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 1-866-922-0068 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions

• Use with Biological DMARDs – increased risk of serious infections (5.8, 7.1)

• Live vaccines – avoid use with CIMZIA (5.10, 7.2)

• Laboratory tests – may interfere with aPTT tests (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2018
**INDICATIONS AND USAGE**

1. **Crohn’s Disease**
   - CIMZIA is indicated for the treatment of adults with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy.

2. **Rheumatoid Arthritis**
   - CIMZIA is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA).

3. **Psoriatic Arthritis**
   - CIMZIA is indicated for the treatment of adult patients with psoriatic arthritis (PsA).

4. **Ankylosing Spondylitis**
   - CIMZIA is indicated for the treatment of adults with active ankylosing spondylitis (AS). [see Clinical Studies (14.4)]

**DOSEAGE AND ADMINISTRATION**

CIMZIA is administered by subcutaneous injection. Injection sites should be rotated and should not be located in areas where the skin is tender, bruised, red or hard. When a 400 mg dose is needed (given as two subcutaneous injections of 200 mg each), injections should occur at separate sites in the thigh or abdomen.

The solution should be carefully inspected visually for particulate matter and discoloration prior to administration. The solution should be a clear colorless to yellow liquid, essentially free from preservatives and should not be used if cloudy or foreign particulate matter is present. CIMZIA does not contain preservatives; therefore, unused portions of drug remaining in the syringe or vial should be discarded.

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

2.2 **Rheumatoid Arthritis**
   - The recommended dose of CIMZIA for adult patients with rheumatoid arthritis is 400 mg (given as two subcutaneous injections of 200 mg each) initially and at Weeks 2 and 4, followed by 200 mg every other week. For maintenance dosing, CIMZIA 400 mg every 4 weeks can be considered [see Clinical Studies (14.2)].

2.3 **Psoriatic Arthritis**
   - The recommended dose of CIMZIA for adult patients with psoriatic arthritis is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week. For maintenance dosing, CIMZIA 400 mg every 4 weeks can be considered [see Clinical Studies (14.3)].

2.4 **Ankylosing Spondylitis**
   - The recommended dose of CIMZIA for adult patients with ankylosing spondylitis is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks.

2.5 **Preparation and Administration of CIMZIA Using the Lyophilized Powder for Injection**
   - CIMZIA lyophilized powder should be prepared and administered by a health care professional. CIMZIA is provided in a package that contains everything required to reconstitute and inject the drug [see How Supplied/Storage and Handling (16)]. Step-by-step preparation and administration instructions are provided below.

**Preparation and Storage**

a. Remove CIMZIA from the refrigerator and allow the vial(s) to sit at room temperature for 30 minutes before reconstituting. Do not warm the vial in any other way. Use appropriate aseptic technique when preparing and administering CIMZIA.

b. Reconstitute the vial(s) of CIMZIA with 1 mL of Sterile Water for Injection, USP using the 20-gauge needle provided. The sterile water for injection should be directed at the vial wall rather than directly on CIMZIA.

c. Gently swirl each vial of CIMZIA for about one minute without shaking, assuring that all of the powder comes in contact with the Sterile Water for Injection. The swirling should be as gentle as possible in order to avoid creating a foaming effect.

d. Continue swirling every 5 minutes as long as non-dissolved particles are observed. Full reconstitution may take as long as 30 minutes. The final reconstituted solution contains 200 mg/mL and should be clear to opalescent, colorless to pale yellow essentially free from particulates.

e. Once reconstituted, CIMZIA can be stored in the vials for up to 24 hours between 2°C to 8°C (36°F to 46°F) prior to injection. Do not freeze.

**Administration**

a. Prior to injecting, reconstituted CIMZIA should be at room temperature but do not leave reconstituted CIMZIA at room temperature for more than two hours prior to administration.

b. Withdraw the reconstituted solution into a separate syringe for each vial using a new 20-gauge needle for each vial so that each syringe contains 1 mL of CIMZIA (200 mg of certolizumab pegol).

c. Replace the 20-gauge needle(s) on the syringes with a 23-gauge(s) for administration.

d. Inject the full contents of the syringe(s) subcutaneously, by pinching the skin of the thigh or abdomen. Where a 400 mg dose is required, two injections are required, therefore, separate sites should be used for each 200 mg injection.

2.6 **Preparation and Administration of CIMZIA Using the Prefilled Syringe**

After proper training in subcutaneous injection technique, a patient may self-inject with the CIMZIA Prefilled Syringe if a physician determines that it is appropriate.

Patients using the CIMZIA Prefilled Syringe should be instructed to inject the full amount in the syringe (1 mL), according to the directions provided in the Instructions for Use booklet.

The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of natural rubber latex and should be handled with caution by latex-sensitive individuals [see Warnings and Precautions (5.4)].

2.7 **Monitoring to Assess Safety**

Before initiation of therapy with CIMZIA, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. The possibility of undetected latent tuberculosis should be considered 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. Appropriate screening tests (e.g., tuberculin skin test and chest x-ray) should be performed in all patients.

2.8 **Concomitant Medications**

CIMZIA may be used as monotherapy or concomitantly with non-biological disease modifying anti-rheumatic drugs (DMARDs).

The use of CIMZIA in combination with biological DMARDs or other tumor necrosis factor (TNF) blocker therapy is not recommended.

**DOSEAGE FORMS AND STRENGTHS**

For injection: 200 mg of lyophilized powder in a single-dose vial for reconstitution

Injection: 200 mg/mL clear to opalescent, colorless to pale yellow solution in a single-dose prefilled syringe

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

5.1 **Risk of Serious Infections**

[see Boxed Warning]

Patients treated with CIMZIA are at an 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, parasitic, or other opportunistic pathogens including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis and tuberculosis have been reported with TNF blockers. Patients have frequently presented with disseminated rather than localized disease.

Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions, and/or patients taking concomitant immunosuppressants (e.g., corticosteroids or methotrexate) may be at a 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
- 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 CIMZIA, including patients who have previously or concomitantly received treatment for latent or active tuberculosis. Reports included cases of pulmonary and extrapulmonary (i.e., disseminated) tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating CIMZIA and periodically during therapy.
Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating CIMZIA assessment if treatment for latent tuberculosis is needed; and consider an induction of 5 mm or greater a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG).

Consider anti-tuberculosis therapy prior to initiation of CIMZIA in patients with a past history of latent or active tuberculosis in whom an alternative form of treatment cannot be confirmed; and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Despite previous or concomitant treatment for latent tuberculosis, cases of active tuberculosis have occurred in patients treated with CIMZIA. Some patients who have been successfully treated for active tuberculosis have developed tuberculosis while being treated with CIMZIA. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision of whether initiating anti-tuberculosis therapy is 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 the specific fungus may be negative in some patients. In situations where empirical treatment is being administered, ensure that the patient is being monitored and that the drug is being appropriately used.

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 concomitant or non-concomitant portions of CIMZIA studies of Crohn’s disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.5 (0.4, 0.7) per 100 patient-years among 4,650 CIMZIA-treated patients versus a rate of 0.6 (0.1, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of some of the controlled portions of the studies precludes the ability to draw firm conclusions.

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), of which CIMZIA is a member. Approximately half the cases were lymphomas, including Hodgkin’s and non-Hodgkin’s lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressors. These cases were reported post-marketing and are derived from a variety of sources, including case reports, registries and spontaneous post-marketing reports. CIMZIA is not indicated for use in pediatric patients.

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. Patients were monitored for malignancies in controlled portions of CIMZIA studies of Crohn’s disease and other diseases.

In the CIMZIA RA clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

Rates in clinical studies for CIMZIA for Crohn’s disease and other investigational uses, there was one case of lymphoma among 2,657 CIMZIA patients and one case of a lymphoma among 1,319 placebo-treated patients.

In the CIMZIA RA clinical trials (placebo-controlled and open label) a total of three cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

For patients with rheumatoid arthritis who discontinued treatment due to adverse reactions leading to discontinuation of CIMZIA, in these patients caution is needed [see Adverse Reactions (6.1)]. The needle shield inside the removable cap of the CIMZIA prefilled syringe contains 7% of a plastic derived from natural rubber latex which may cause an allergic reaction in individuals sensitive to latex.

5.5 Hepatitis B Virus Reactivation

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

Test patients for HBV infection before initiating treatment with CIMZIA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with 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 not known. Exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

5.6 Neurologic Reactions

Use of TNF blockers, of which CIMZIA is a member, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders (including multiple sclerosis) and with peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central or peripheral 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 [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 cytopenias (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 a history of, or are at increased risk for, 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 who confirmed significant hematologic abnormalities.

5.8 Use with Biological Disease-Modifying Antirheumatic Drugs (Biological DMARDs)

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and TNF blockers. The use of these agents together has resulted in severe and potentially life-threatening infections. Use of TNF blockers, of which CIMZIA is a member, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders (including multiple sclerosis) and with peripheral demyelinating disease, including Guillain-Barré syndrome. Exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central or peripheral 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 [see Adverse Reactions (6.1)].

5.9 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)].

5.10 Immunizations

Patients treated with CIMZIA may receive vaccinations, except for live or live attenuated vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA.

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in antibody response to vaccine between CIMZIA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CIMZIA. Similar proportions of patients in both treatment groups developed protective antibody levels to pneumococcal polysaccharide vaccine and influenza vaccine when treated with CIMZIA. However, patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared to patients receiving CIMZIA alone. The clinical significance of this is unknown.

5.11 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 CIMZIA on these other immune functions has not been studied, and therefore patients on CIMZIA should be monitored for the development of new infections or reactivation of pre-existing latent infections.

In prem市场control trials of all patient populations combined the most common adverse reactions (≥8%) were upper respiratory infections (18%), rash (9%) and urinary tract infections (8%).

Adverse Reactions Most Commonly Leading to Discontinuation of Treatment in Premarketstripable Trials

1. The proportion of patients with rheumatoid arthritis who discontinued treatment due to adverse reactions in the controlled clinical studies was 5% for CIMZIA and 2.5% for placebo. The most common adverse reactions leading to discontinuation of CIMZIA were tuberculosis infections (0.5%), and pyrexia, urticaria, pneumonia, and rash (0.3%).
Psoriatic Arthritis Clinical Study

In the active group were between the ages of 18 and 64.

Concurrent use of 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 Crohn’s disease patients who were antibody-positive (N = 100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,424), abdominal pain, arthritis, axillary lymphadenopathy, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection.

Immunogenicity

No association was seen between antibody development and the development of adverse events.

The incidence of new cases of infections in controlled clinical studies in rheumatoid arthritis was 0.91 per patient-year for all CIMZIA-treated patients and 0.72 per patient-year for placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, herpes infections, urinary tract infections, and lower respiratory tract infections. In the controlled rheumatoid arthritis studies, there were more new cases of serious infections in the placebo groups, compared to the placebo groups (0.06 per patient-year for all CIMZIA doses, 0.02 per patient-year for placebo). Rates of serious infections in the 200 mg every other week dose group were 0.06 per patient-year and in the 400 mg every 4 weeks dose group were 0.04 per patient-year. Serious infections included tuberculosis, pneumonia, cellulitis, and pyelonephritis. In the placebo group, no serious infection occurred in more than one subject. There is no evidence of an increased risk of infections with continued exposure over time [see Warnings and Precautions (5.1)].

Tuberculosis and Opportunistic Infections

In controlled and ongoing global clinical studies in all indications including 5,118 CIMZIA-treated patients, the overall rate of tuberculosis is approximately 0.61 per 100 patient-years across all indications. The majority of cases occurred in countries with high endemic rates of TB. Reports include cases of miliary, lymphatic, pericardial, as well as pulmonary TB. The median time to onset of TB for all patients exposed to CIMZIA was 10.4 months (95% CI: 10.0, 10.8) in the active group compared to placebo at 7.5 months (95% CI: 7.0, 8.0) in the placebo group. There were 36 cases of TB among 2,367 exposed patients, including some fatal cases. Rare cases of opportunistic infections have also been reported in these clinical trials [see Warnings and Precautions (5.1)].

Malignancies

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, occurring in patients receiving CIMZIA at doses of 400 mg or other doses include:

- Myocardial infarction
- Myocardial ischemia
- Pericardial effusion
- Pericarditis
- Stroke
- Transient ischemic attack

Blood and lymphatic system disorders:

- Anemia
- Leukopenia
- Lymphadenopathy
- Pancreatitis
- Thrombophlebitis

Cardiac disorders:

- Angina pectoris
- Arrhythmias
- Atrial fibrillation
- Cardiac failure
- Hypertensive heart disease
- Myocardial infarction
- Myocardial ischemia
- Pericardial effusion
- Pericarditis
- Stroke
- Transient ischemic attack

Eye disorders:

- Optic neuritis
- Retinal hemorrhage
- Uvei

General disorders and administration site conditions:

- Bleeding
- Injection site reactions

Hepatobiliary disorders:

- Elevated liver enzymes
- Hepatitis

Immune system disorders:

- Alopeica totalis

Psychiatric disorders:

- Anxiety
- Bipolar disorder
- Suicide attempt

Renal and urinary disorders:

- Nephrotic syndrome
- Renal failure

Reproductive system and breast disorders:

- Menstrual disorder

Skin and subcutaneous tissue disorders:

- Dermatitis
- Erythema nodosum
- Urticaria

Vascular disorders:

- Thrombophlebitis
- Vasculitis

Controlled Studies with Rheumatoid Arthritis

CIMZIA was studied primarily in placebo-controlled trials and in long-term follow-up studies. The data described below reflect the exposure to CIMZIA in 2,367 RA patients, including 2,030 exposed for at least 6 months, 1,663 exposed for at least one year, and 282 exposed for at least 2 years; and 1,774 in adequate long-term follow-up studies. The overall percentage of patients who were antibody positive to CIMZIA on at least one occasion was 8%; approximately 4% were neutralizing in vitro. In Study RA-IV (long-term monotherapy) the antibody positivity in RA was 28%. In Study RA-III there were 36 cases of TB among 2,367 exposed patients, including some fatal cases. Rare cases of opportunistic infections have also been reported in these clinical trials [see Warnings and Precautions (5.1)].

Malignancies

In clinical studies of CIMZIA, the overall incidence 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 (5.8)].

Heart Failure

In placebo-controlled and open-label rheumatoid arthritis studies, cases of new or worsening heart failure have been reported for CIMZIA-treated patients. The majority of these cases were mild to moderate and occurred during the first year of exposure [see Warnings and Precautions (5.3)].

Autoimmunity

Autoimmune diseases is unknown [see Warnings and Precautions (5.9)].

Immunogenicity

Patients with Crohn’s disease were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. In patients continuously exposed to CIMZIA, the overall percentage of patients who were antibody positive to CIMZIA on at least one occasion was 8%; approximately 4% were neutralizing in vitro. In Study RA-III, 28% of patients treated with CIMZIA and 19% 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.

In clinical trials of TNF blockers, including CIMZIA, in patients with RA, some patients have developed ANA. Four patients out of 2,367 patients treated with CIMZIA in RA clinical studies developed clinical signs suggestive 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 (5.9)].

Tuberculosis and Opportunistic Infections

The overall percentage of patients with antibodies to certolizumab pegol detectable on at least one occasion was 7% (105 of 1,509) in the rheumatoid arthritis placebo-controlled trials. Approximately one third (3%, 39 of 1,509) of these patients had antibodies with neutralizing activity in vitro. 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 patients treated with concomitant immunosuppressants. Patients not taking 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 patients treated with concomitant immunosuppressants. Patients not taking 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 patients treated with concomitant immunosuppressants. Patients not taking 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 patients treated with concomitant immunosuppressants. Patients not taking 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 patients treated with concomitant immunosuppressants.
Adults. Concentrations were lower (by at least 75%) in the infants than in mothers, suggesting low placental transfer of certolizumab pegol. Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.58 mcg/mL in maternal blood. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg/mL in infant blood; and ranged from 1.87 to 59.57 mcg/mL in maternal blood. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in mothers, suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg/mL over 4 weeks suggesting that certolizumab pegol may be eliminated at a slower rate in infants than adults.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy. For more information, healthcare providers or patients can contact:

MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS). The OTIS Autoimmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/

Risk Summary

Limited data from the ongoing pregnancy registry on use of CIMZIA in pregnant women are not sufficient to inform a risk of major birth defects or other adverse pregnancy outcomes. However, certolizumab pegol plasma concentrations obtained from two studies of CIMZIA use during the third trimester of pregnancy demonstrated that placental transfer of certolizumab pegol is negligible in most infants and low in other infants at birth. There are risks to the mother and fetus associated with active rheumatoid arthritis or Crohn's disease. The theoretical risks of administration of live or live-attenuated vaccines to the infants exposed in utero should be weighed against the benefits of vaccinations (see Clinical Considerations). No adverse developmental effects were observed in animal reproduction studies during which pregnant rats were administered intravenously a rodent anti-murine TNFα pegylated Fab' fragment (cTNF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mcg every 4 weeks.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively.

8.2 Lactation

Risk Summary

In a multicenter clinical study of 17 lactating women treated with CIMZIA at 200 mg every 2 weeks or 400 mg every 4 weeks, minimal certolizumab pegol concentrations were observed in breast milk. No serious adverse reactions were noted in the infants in this study. There are no data on the effects of milk production on the infant or on possible adverse effects on breastfed infants at 4 weeks post-partum (see Data). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CIMZIA and any potential adverse effects on the breastfed infant from CIMZIA or from the underlying maternal condition.

Data

A multicenter clinical study designed to evaluate breast milk was conducted in 17 lactating women who were at least 6 weeks post-partum and had received at least 3 consecutive doses of CIMZIA 200 mg every 2 weeks or 400 mg every 4 weeks for rheumatoid arthritis or Crohn’s disease. The effects of certolizumab pegol on milk production were not studied. The concentration of certolizumab pegol in breast milk was not measurable in 77 (96%) of the 137 samples taken over the dosing periods using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. The median of the estimated average daily infant doses was 0.0035 mg/kg/day (range: 0 to 0.01 mg/kg/day). The percentage of the maternal dose (200 mg CIMZIA dosed once every 2 weeks), that reaches an infant from 0.55% to 4.25% based on samples with measurable certolizumab pegol concentration. No serious adverse reactions were noted in the 17 breastfed infants in this study.

In a separate study, plasma certolizumab pegol concentrations were collected 4 weeks after birth in 9 breastfed infants whose mothers had been taking CIMZIA (regardless of whether C IM ZIA was being breastfed or not). Certolizumab pegol in infant plasma was not measurable i.e., below 0.032 mcg/mL.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect immune responses in the in utero-exposed newborn and infant (see Use in Specific Populations (8.1)).

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 patients. In one clinical study conducted in 10 pregnant women with Crohn’s disease treated with CIMZIA, the last dose of CIMZIA was given on average 11 days prior to delivery (range 5 to 42 days). The safety of administering live or live-attenuated vaccines to the infants exposed in utero should be weighed against the benefits of vaccinations (see Clinical Considerations). No adverse developmental effects were observed in animal reproduction studies during which pregnant rats were administered intravenously a rodent anti-murine TNFα pegylated Fab’ fragment (cTNF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mcg every 4 weeks.

Due to the small number of CIMZIA-exposed pregnancies with known outcomes (n=54), no meaningful comparisons between the exposed group and control groups may be conducted to determine an association with CIMZIA and major birth defects or adverse pregnancy outcomes.

12.1 Mechanism of Action

Certolizumab pegol is a TNFα blocker. CIMZIA is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα), 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 kDa.

CIMZIA (certolizumab pegol) for injection is supplied as a sterile white, lyophilized powder in a single-dose vial for subcutaneous use. After reconstitution of the lyophilized powder with 1 mL sterile Water for Injection, the final concentration is 200 mg/mL, with a volume of 1 mL (200 mcg) and a pH of approximately 6.2. Each single-dose vial provides 200 mg certolizumab pegol, lactic acid (0.9 mg), polysorbate (0.1 mg), and sucrose (100 mcg).

CIMZIA (certolizumab pegol) injection is supplied as a sterile, clear to opalescent, colorless to pale yellow solution that may contain particulates in a single-dose prefilled syringe for subcutaneous use. Each prefilled syringe delivers 1 mL of sterile Water for Injection containing 200 mg certolizumab pegol, sodium chloride (1.35 g), sodium hydroxide (7.31 mg), and Water for Injection, USP.

12.2 PHARMACOLOGY

Animal Data

Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab' fragment (cTNF) similar to certolizumab pegol. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on body surface area) and have revealed no evidence of harm to the fetus due to cTNF3 PF.

Drug Interactions

Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab' fragment (cTNF) similar to certolizumab pegol. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on body surface area) and have revealed no evidence of harm to the fetus due to cTNF3 PF.

12.3 CLINICAL PHARMACOLOGY

12.3.1 Pharmacokinetics

Pharmacokinetic properties of certolizumab pegol have been characterized in healthy volunteers treated with certolizumab pegol. Plasma certolizumab pegol concentrations were lower (by at least 75%) in the infants than in mothers, suggesting low placental transfer of certolizumab pegol. In one infant, the plasma certolizumab pegol concentration declined from 1.02 to 0.84 mcg/mL over 4 weeks suggesting that certolizumab pegol may be eliminated at a slower rate in infants than adults.

Because certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab' fragment (cTNF) similar to certolizumab pegol. Animal reproduction studies have been performed in rats during organogenesis at intravenous doses up to 100 mg/kg (about 2.4 times the recommended human dose of 400 mg, based on body surface area) and have revealed no evidence of harm to the fetus due to cTNF3 PF.
Compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower. Statistically significantly greater for CIMZIA-treated patients compared to controls. The difference in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

### Table 2 Study CD1 - Clinical Response and Remission, Overall Study Population

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>% Response or Remission (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 6</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Response*</td>
<td>27% (22%, 32%)</td>
</tr>
<tr>
<td><strong>Clinical Remission</strong></td>
<td>35% (30%, 40%)</td>
</tr>
<tr>
<td><strong>Week 26</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Response*</td>
<td>27% (22%, 31%)</td>
</tr>
<tr>
<td><strong>Clinical Remission</strong></td>
<td>37% (32%, 42%)</td>
</tr>
<tr>
<td>Both Weeks 6 &amp; 26</td>
<td></td>
</tr>
<tr>
<td>Clinical Response*</td>
<td>18% (14%, 22%)</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>29% (25%, 34%)</td>
</tr>
</tbody>
</table>
| 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 426 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 3. 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 3 Study CD2 - Clinical Response and Clinical Remission

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>% Response or Remission (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 26</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Response*</td>
<td>36% (30%, 43%)</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>63% (56%, 69%)</td>
</tr>
</tbody>
</table>
| * 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.

### 14.2 Rheumatoid Arthritis

The efficacy and safety of CIMZIA were assessed in four randomized, placebo-controlled, double-blind studies (RA-I, RA-II, RA-III, and RA-IV) in patients ≥ 18 years of age with moderately to severely active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had ≥ 5 swollen joints and ≥ 5 tender joints and had active RA for at least 6 months prior to baseline. CIMZIA was administered subcutaneously in combination with MTX at stable doses of at least 10 mg weekly in Studies RA-I, RA-II, and RA-III. CIMZIA was administered as monotherapy in Study RA-IV.

Study RA-I and Study RA-II evaluated patients who had received MTX for at least 6 months prior to study medication, but had an incomplete response to MTX alone. Patients were treated with a loading dose of 400 mg at Weeks 0, 2, and 4 (for both treatment arms) or placebo followed by either 200 mg or 400 mg of CIMZIA or placebo every other week, in combination with MTX for 52 weeks in Study RA-I and for 24 weeks in Study RA-II. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 24 (RA-I and RA-II) and modified Total Sharp Score (mTSS) at Week 52 (RA-II). The open-label extension follow-up study enrolled 846 patients who received 400 mg of CIMZIA every other week.

Study RA-III evaluated 247 patients who had active disease despite receiving MTX for at least 6 months prior to study enrollment. Patients received 400 mg of CIMZIA every 4 weeks for 24 weeks without a prior loading dose. Patients were evaluated for signs and symptoms of RA using the ACR20 at Week 24.

Study RA-IV (monotherapy) evaluated 220 patients who had failed at least one DMARD use prior to receiving CIMZIA. Patients were treated with CIMZIA 400 mg or placebo every 4 weeks for 24 weeks. Patients were evaluated for signs and symptoms of active RA using the ACR20 at Week 24.

#### Clinical Response

The percent of CIMZIA-treated patients achieving ACR20, 50, and 70 responses in Studies RA-I and RA-IV are shown in Table 4. CIMZIA-treated patients had higher ACR20, 50, and 70 response rates at 6 months compared to placebo-treated patients. The results in study RA-III (619 patients) were similar to the results in RA-I at Week 24. The results in study RA-III (247 patients) were similar to those seen in study RA-IV. Over the one-year Study RA-I, 13% of CIMZIA-treated patients achieved an ACR20 response compared to 6% of placebo-treated patients.
Table 4: ACR Responses in Studies RA-I, and RA-IV (Percent of Patients)

<table>
<thead>
<tr>
<th>Response</th>
<th>Study RA-I Methotrexate Combination (24 and 52 weeks)</th>
<th>Study RA-IV Monotherapy (24 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + CIMZIA^a 200 mg + MTX</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=199</td>
<td>g 2 weeks</td>
<td>N=109</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>CIMZIA^b 400 mg + MTX</td>
</tr>
<tr>
<td>N=393</td>
<td></td>
<td>g 4 weeks</td>
</tr>
<tr>
<td></td>
<td>- Placebo</td>
<td>- Placebo</td>
</tr>
<tr>
<td></td>
<td>(95% CI)^d</td>
<td>(95% CI)^d</td>
</tr>
<tr>
<td>ACR20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>14% 59% 45% (38%, 52%)</td>
<td>9% 46% 36% (25%, 47%)</td>
</tr>
<tr>
<td>Week 52</td>
<td>13% 53% 40% (33%, 47%)</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>ACR50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>8% 37% 30% (24%, 36%)</td>
<td>4% 23% 19% (10%, 28%)</td>
</tr>
<tr>
<td>Week 52</td>
<td>8% 38% 30% (24%, 37%)</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>ACR70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>3% 21% 18% (14%, 23%)</td>
<td>0% 6% 6% (1%, 10%)</td>
</tr>
<tr>
<td>Week 52</td>
<td>4% 21% 18% (13%, 22%)</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>Major Clinical Response^e</td>
<td>1% 13% 12% (8%, 15%)</td>
<td></td>
</tr>
</tbody>
</table>

^a CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
^b CIMZIA administered every 4 weeks not preceded by a loading dose regimen
^c Major clinical response is defined as achieving ACR70 response over a continuous 6-month period
^d 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution.
^e Health Assessment Questionnaire Disability Index; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

Table 5: Components of ACR Response in Studies RA-I and RA-IV

<table>
<thead>
<tr>
<th>Parameter^f</th>
<th>Study RA-I</th>
<th>Study RA-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + MTX</td>
<td>Placebo</td>
</tr>
<tr>
<td>N=199</td>
<td>200 mg + MTX</td>
<td>N=393</td>
</tr>
<tr>
<td>Number of tender joints (0-68)</td>
<td>28 27 29 9</td>
<td>28 (12.5) 24 (15.4)</td>
</tr>
<tr>
<td>Number of swollen joints (0-68)</td>
<td>20 19 20 4</td>
<td>20 (8.3) 16 (12.5)</td>
</tr>
<tr>
<td>Physician global assessment^g</td>
<td>66 56 65 25</td>
<td>4 (0.6) 3 (1.0)</td>
</tr>
<tr>
<td>Patient global assessment^g</td>
<td>67 60 64 32</td>
<td>3 (0.8) 3 (1.0)</td>
</tr>
<tr>
<td>Pain^h</td>
<td>65 60 65 32</td>
<td>55 (20.8) 60 (26.7)</td>
</tr>
<tr>
<td>Disability index (HAQ)^i</td>
<td>1.75 1.63 1.75 1.00</td>
<td>1.55 (0.65) 1.62 (0.68) 1.43 (0.63) 1.04 (0.74)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>16.0 14.0 16.0 4.0</td>
<td>11.3 13.5 11.6 6.4</td>
</tr>
</tbody>
</table>

^f CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
^g CIMZIA administered every 4 weeks not preceded by a loading dose regimen
^h Study RA-I - Visual Analog Scale: 0 = best, 100 = worst. Study RA-IV - Five Point Scale: 1 = best, 5 = worst
^i Patient Assessment of Arthritis Pain; Visual Analog Scale: 0 = best, 100 = worst
^j Health Assessment Questionnaire Disability Index: 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.
^k All values are last observation carried forward.
^l For Study RA-I, median is presented. For Study RA-IV, mean (SD) is presented except for CRP which presents geometric mean

14.3 Psoriatic Arthritis

The efficacy and safety of CIMZIA were assessed in a multi-center, randomized, double-blind, placebo-controlled trial (PA4001) in 409 patients aged 18 years and older with active psoriatic arthritis despite DMARD therapy. Patients in this study had ≥ 3 swollen and tender joints and adult-onset PsA of at least 6 months’ duration as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria, and increased acute phase reactants. Patients had failed one or more DMARDs. Previous treatment with one anti-TNF biologic therapy was allowed, and 20% of patients had prior anti-TNF biologic exposure. Patients receiving concomitant NSAIDs and conventional DMARDs were 73% and 79%, respectively.

Patients received a loading dose of CIMZIA 400 mg at Weeks 0 and 4 (for both treatment arms) or placebo followed by either CIMZIA 200 mg every other week or CIMZIA 400 mg every 4 weeks or placebo every other week. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 12 and modified Total Sharp Score (mTSS) at Week 24.

Clinical Response

The percentage of CIMZIA-treated patients achieving ACR20, 50 and 70 responses in study PA4001 are shown in Table 7. ACR20 response rates at weeks 12 and 24 were higher for each CIMZIA dose group relative to placebo (95% confidence intervals for CIMZIA 200 mg minus placebo at weeks 12 and 24 of (25%, 45%) and (30%, 51%), respectively and 95% confidence intervals for CIMZIA 400 mg minus placebo at weeks 12 and 24 of (17%, 39%) and (22%, 44%), respectively). The results of the components of the ACR response criteria are shown in Table 8.

Patients with enthesitis at baseline were evaluated for mean improvement in Leeds Enthesitis Index (LEI). CIMZIA-treated patients receiving either 200 mg every 2 weeks or 400 mg every 4 weeks showed a reduction in enthesitis of 1.8 and 1.7, respectively as compared with a reduction in placebo-treated patients of 0.9 at week 12. Similar results were observed for this endpoint at week 24. Treatment with CIMZIA resulted in improvement in skin manifestations in patients with PsA. However, the safety and efficacy of CIMZIA in the treatment of patients with plaque psoriasis has not been established.
Table 7: ACR Responses in Study PsA001 (Percent of Patients)

<table>
<thead>
<tr>
<th>Response</th>
<th>Placebo</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 200 mg Q2W</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 400 mg Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=136</td>
<td>N=138</td>
<td>N=135</td>
</tr>
<tr>
<td>ACR20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>24%</td>
<td>58%</td>
<td>52%</td>
</tr>
<tr>
<td>Week 24</td>
<td>24%</td>
<td>64%</td>
<td>56%</td>
</tr>
<tr>
<td>ACR50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>11%</td>
<td>36%</td>
<td>33%</td>
</tr>
<tr>
<td>Week 24</td>
<td>13%</td>
<td>44%</td>
<td>40%</td>
</tr>
<tr>
<td>ACR70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>3%</td>
<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>Week 12</td>
<td>4%</td>
<td>28%</td>
<td>24%</td>
</tr>
</tbody>
</table>

<sup>a</sup> CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>b</sup> CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>c</sup> Results are from the randomized set
<sup>d</sup> Non-responder imputation (NRI) is used for patients who escaped therapy or had missing data.

Table 8: Components of ACR Response in Study PsA001

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 200 mg Q2W</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 400 mg Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=136</td>
<td>N=138</td>
<td>N=135</td>
</tr>
<tr>
<td>Number of tender joints (0-68)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>20 17</td>
<td>22 11</td>
<td>20 11</td>
</tr>
<tr>
<td>Number of swollen joints (0-68)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>10 9</td>
<td>11 4</td>
<td>11 5</td>
</tr>
<tr>
<td>Physician global assessment&lt;sup&gt;e&lt;/sup&gt;</td>
<td>59 44</td>
<td>57 25</td>
<td>58 29</td>
</tr>
<tr>
<td>Patient global assessment&lt;sup&gt;e&lt;/sup&gt;</td>
<td>57 50</td>
<td>60 33</td>
<td>60 40</td>
</tr>
<tr>
<td>Pain&lt;sup&gt;e&lt;/sup&gt;</td>
<td>60 50</td>
<td>60 33</td>
<td>61 39</td>
</tr>
<tr>
<td>Disability index (HAQ)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.30 1.15</td>
<td>1.33 0.87</td>
<td>1.29 0.90</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>18.56 14.75</td>
<td>15.36 5.67</td>
<td>13.71 6.34</td>
</tr>
</tbody>
</table>

<sup>a</sup> CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>b</sup> CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>c</sup> Results are from the randomized set
<sup>d</sup> Non-responder imputation (NRI) is used for patients who escaped therapy or had missing data.

Table 9: ASAS Responses in AS patients at Weeks 12 and 24 in study AS-1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 200 mg every 2 weeks</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 400 mg every 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=57</td>
<td>N=65</td>
<td>N=56</td>
</tr>
<tr>
<td>ASAS20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>37%</td>
<td>57%</td>
<td>64%</td>
</tr>
<tr>
<td>Week 24</td>
<td>33%</td>
<td>68%</td>
<td>70%</td>
</tr>
<tr>
<td>ASAS40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>19%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Week 24</td>
<td>16%</td>
<td>48%</td>
<td>59%</td>
</tr>
</tbody>
</table>

<sup>a</sup> CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>b</sup> CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>c</sup> All percents reflect the proportion of patients who responded in the full analysis set

Table 10: Components of the ASAS response criteria and other measures of disease activity in AS patients at baseline and Week 12 in study AS-1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo&lt;sup&gt;b&lt;/sup&gt;</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 200 mg every 2 weeks</th>
<th>CIMZIA&lt;sup&gt;a&lt;/sup&gt; 400 mg every 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=57</td>
<td>N=65</td>
<td>N=56</td>
</tr>
<tr>
<td>ASAS20 response criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Patient Global Assessment (0-10)</td>
<td>6.9 5.6</td>
<td>7.3 4.2</td>
<td>6.8 3.8</td>
</tr>
<tr>
<td>- Total spinal pain (0-10)</td>
<td>7.3 5.8</td>
<td>7.0 4.3</td>
<td>6.9 4.0</td>
</tr>
<tr>
<td>- BASFI (0-10)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6.0 5.2</td>
<td>5.6 3.8</td>
<td>5.7 3.8</td>
</tr>
<tr>
<td>- Inflammation (0-10)</td>
<td>6.7 5.5</td>
<td>6.7 3.8</td>
<td>6.4 3.4</td>
</tr>
<tr>
<td>BASDAI (0-10)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>6.4 5.4</td>
<td>6.5 3.6</td>
<td>6.2 3.7</td>
</tr>
<tr>
<td>BASMI&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.8 4.4</td>
<td>4.2 3.6</td>
<td>4.3 3.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>b</sup> CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
<sup>c</sup> BASFI is Bath Ankylosing Spondylitis Functional Index
<sup>d</sup> BASDAI is Bath Ankylosing Spondylitis Disease Activity Index
<sup>e</sup> BASMI is Bath Ankylosing Spondylitis Metabolic Index

All values presented represent the mean in the full analysis set.

The percent of AS patients achieving ASAS20 responses by visit for Study AS001 is shown in Figure 3. Among patients receiving CIMZIA, clinical responses were seen in some AS patients within one to two weeks after initiation of therapy.
of the importance of informing their health care providers about all aspects of their health. Should be exercised in prescribing CIMZIA to patients with clinically important active infections, advise patients of the importance of contacting their doctor if they develop any symptoms of infection, including 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 Pregnancy
Advis patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to CIMZIA during pregnancy, patients can call 1-877-311-8972. [see Use in Specific Populations 8.1].

17.3 Instruction on Prefilled Syringe Self-Injection Technique
After proper training by a qualified healthcare professional in subcutaneous injection technique, a patient may self inject with CIMZIA using the Prefilled Syringe if a healthcare provider determines that it is appropriate. A patent's ability to administer CIMZIA subcutaneous injections should be checked to ensure correct administration. Suitable sites for injection include the thigh or abdomen. CIMZIA should be injected when the liquid is at room temperature.

Full injection instructions are provided in the Instructions for Use booklet for the Prefilled Syringe, packaged in each CIMZIA Prefilled Syringe kit.

To avoid needle-stick injury, patients and healthcare providers should not attempt to place the needle cap back on the syringe or otherwise recap the needle. Be sure to properly dispose of needles and syringes in a puncture-proof container, and instruct patients and caregivers in proper syringe and needle disposal technique. Actively discourage any reuse of the injection materials.

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Medication Guide
CIMZIA® (CIM-zee-uh)
certolizumab pegol
lyophilized powder or solution for subcutaneous use

Read the Medication Guide that comes with CIMZIA before you start using it, and before each injection of CIMZIA. This Medication Guide does not take the place of talking with your healthcare provider 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 have happened in patients taking CIMZIA. 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 healthcare provider should test you for TB before starting CIMZIA.
• Your healthcare provider should monitor you closely for signs and symptoms of TB during treatment with CIMZIA.

You should not start receiving CIMZIA if you have any kind of infection unless your healthcare provider says it is okay.

Before you receive CIMZIA, tell your healthcare provider if you:

• Think you have an infection, flu-like symptoms, or have any other symptoms of an infection such as:
  • fever, sweat, or chills
  • muscle aches
  • cough
  • shortness of breath
  • blood in phlegm
  • weight loss
  • are being treated for an infection

• get a lot of infections or have infections that keep coming back
• have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
• have tuberculosis (TB), or have been in close contact with someone with TB
• were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your healthcare provider if you are not sure.
• 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, blastomycosis). These infections may develop or become more severe if you take CIMZIA. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your healthcare provider.
• have or have had hepatitis B
• use the medicine Kineret® (anakinra), Ocrevus® (abatacept), Rituxan® (rituximab), or Tyzabri® (natalizumab)

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 healthcare provider right away. CIMZIA can make you more likely to get infections or make any infection that you may have worse.

Cancer
• For people taking TNF-blocker medicines, including CIMZIA, the chances of getting lymphoma or other cancers may increase.
• There have been cases of cancers in children, teenagers, and young adults who received TNF-blocker medicine that do not usually happen in people this age.
• People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
• Some people receiving TNF-blocker medicines, including CIMZIA, have 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 and young adult males with Crohn’s disease or ulcerative colitis. Also, most of these people had been treated with both a TNF-blocker medicine and another medicine called IMURAN® (azathioprine) or PURINETHOL® (6-mercaptopurine, 6-MP).

• If you use TNF-blocker medicine, including CIMZIA, your chance of developing certain kinds of skin cancer may increase. Tell your healthcare provider if any changes in the appearance of your skin, including growths on your skin, happen during or after your treatment.

What is CIMZIA?

CIMZIA is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker. CIMZIA is used in adult patients to:

• Lessen the signs and symptoms of moderately to severely active Crohn’s disease (CD) in patients who have not been helped enough by usual treatments

• Treat moderately to severely active rheumatoid arthritis (RA)

• Treat active psoriatic arthritis

• Treat active ankylosing spondylitis

What should I tell my healthcare provider before starting treatment with CIMZIA?

CIMZIA may not be right for you. Before starting CIMZIA, tell your healthcare provider 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 congestive heart failure.

• have seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis.

• are scheduled to receive a vaccine. Do not receive a live vaccine while taking CIMZIA.

• are allergic to any of the ingredients in CIMZIA. See the end of this Medication Guide for a list of the ingredients in CIMZIA.

• are allergic to rubber or latex. 7% of the plastic needle shield inside the removable cap is derived from natural rubber latex.

• are pregnant or planning to become pregnant. Tell your healthcare provider right away if you become pregnant while receiving CIMZIA.

Pregnancy Registry: If you become pregnant while taking CIMZIA, talk to your healthcare provider about registering in the pregnancy exposure registry for CIMZIA. You can enroll in this registry by calling 1-877-311-8972. The purpose of this registry is to collect information about the safety of CIMZIA during pregnancy.

• are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will receive CIMZIA or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Especially tell your healthcare provider if you take the following medicines due to a higher chance for serious infections:

• Kinetro® (anakinra), Orencia® (abatacept), Rituxan® (rituximab), or Tyasbri® (natalizumab).

• medicines called Tumor Necrosis Factor (TNF) blockers such as Remicade® (infliximab), Humira® (adalimumab), Enbrel® (etanercept), or Simponi® (golimumab).

Ask your healthcare provider if you are not sure.

You should not take CIMZIA while you take any of these medicines.

How should I receive CIMZIA?

• CIMZIA comes as lyophilized powder or as a solution in a prefilled syringe for injection.

• If your healthcare provider prescribes the CIMZIA powder, your CIMZIA should be injected by a healthcare provider. Each dose of CIMZIA will be given as 1 or 2 separate injections under the skin in your stomach area or upper thighs. If you are not sure how to inject CIMZIA, your healthcare provider can show you.

• You will receive a CIMZIA Prefilled Syringe Kit including a complete “Instructions for Use” booklet for the right way to inject CIMZIA.

• Read the detailed Instructions for Use booklet for instructions about how to prepare and inject your dose of CIMZIA, and how to properly throw away used syringes containing the needle.

• Do not give yourself an injection of CIMZIA unless you have been shown by your healthcare provider. A family member or friend can also be trained to help you give your injection. Talk to your healthcare provider if you have questions.

• CIMZIA is given by an injection under the skin. Your healthcare provider will tell you how much and how often to inject CIMZIA. Do not use more CIMZIA or inject more often than prescribed.

• You may need more than 1 injection at a time depending on your prescribed dose of CIMZIA.

• CIMZIA may be injected into your stomach or upper thighs. If you are prescribed more than 1 injection, each injection should be given at a different site in your stomach or upper thighs.

• Make sure the solution in the prefilled syringe is clear and colorless to yellow and free from particles. Do not use the CIMZIA prefilled syringe if the medicine is cloudy, discolored, or contains particles.

• Do not mix any doses of CIMZIA. If you miss a dose, call your healthcare provider or pharmacist for instructions.

• Make sure to keep all follow-up appointments with your healthcare provider.

What are the possible side effects of CIMZIA?

CIMZIA can cause serious side effects including:

• See “What is the most important information I should know about CIMZIA?”

• Heart Failure including new heart failure or worsening of heart failure you already have. Symptoms include shortness of breath, swelling of your ankles or feet, or sudden weight gain.

• Allergic Reactions. Signs of an allergic reaction include a skin rash, swelling or itching of the face, tongue, lips, or throat, or trouble breathing.

• Hepatitis B virus reactivation in patients who carry the virus in their blood. In some cases patients have died as a result of hepatitis B virus being reactivated. Your healthcare provider should monitor you carefully before and during treatment with CIMZIA to see if you carry the hepatitis B virus in your blood. Tell your healthcare provider if you have any of the following symptoms:

• feel unwell

• skin or eyes look yellow

• tiredness (fatigue)

• poor appetite or vomiting

• pain on the right side of your stomach (abdomen)

• New or worsening nervous system problems, such as multiple sclerosis (MS), Guillain-Barre syndrome, seizures, or inflammation of the nerves of the eyes. Symptoms may include:

• dizziness

• numbness or tingling

• problems with your vision

• weakness in your arms or legs

• 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 does not go away, bruising or bleeding very easily, or looking very pale.

• 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 healthcare provider right away if you have any serious side effects listed above. The most common side effects of CIMZIA include:

• upper respiratory infections (flu, cold)

• rash

• urinary tract infections (bladder infections)

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

These are not all of the possible side effects of CIMZIA. For more information, ask your healthcare provider or pharmacist.

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

How should I store CIMZIA?

• Keep CIMZIA in the refrigerator between 36°F to 46°F (2°C to 8°C).

• Do not freeze CIMZIA.

• Protect CIMZIA from light. Store CIMZIA in the carton it came in.

• Do not use CIMZIA if the medicine is expired. Check the expiration date on the prefilled syringe or carton.

• The CIMZIA prefilled syringe is made of glass. Do not drop or crush the syringe.

Keep CIMZIA and all medicines out of the reach of children.

General information about the safe and effective use of CIMZIA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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 symptoms that you have. It may harm them.

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

For more information, go to www.CIMZIA.com or call 1-866-424-6942.

What are the ingredients in CIMZIA?

CIMZIA lyophilized powder:

Active ingredient: certolizumab pegol

Inactive ingredients: lactic acid, polysorbate, sucrose

CIMZIA lyophilized powder is mixed with sterile Water for Injection.

CIMZIA prefilled syringe:

Active ingredient: certolizumab pegol

Inactive ingredients: sodium acetate, sodium chloride, Water for Injection

CIMZIA has no preservatives.

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

Product manufactured by: UCB, Inc. • 1950 Lake Park Drive • Smyrna, GA 30080

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