

## 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

### 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

Indications and Usage (1.5)	03/2019
Indications and Usage (1.6)	05/2018
Dosage and Administration (2.5)	03/2019
Dosage and Administration (2.6)	05/2018
Dosage and Administration (2.7)	02/2019
Contraindications (4)	05/2018
Warnings and Precautions (5.4)	02/2019

### 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)
- 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)
- Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation (1.5)
- Treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (1.6)

### DOSAGE AND ADMINISTRATION

CIMZIA is administered by subcutaneous injection. The recommended 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

#### 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.

#### Ankylosing Spondylitis (2.4)

- 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 or 400 mg every 4 weeks.

#### Non-radiographic Axial Spondyloarthritis (2.5)

- 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 or 400 mg every 4 weeks.

#### Plaque Psoriasis (2.6, 14.6)

- 400 mg (given as 2 subcutaneous injections of 200 mg each) every other week. For some patients (with body weight ≤ 90 kg), a dose of 400 mg (given as 2 subcutaneous injections of 200 mg each) initially and

Weeks 2 and 4, followed by 200 mg every other week may be considered.

### DOSAGE FORMS AND STRENGTHS

- For injection: 200 mg lyophilized powder in a single-dose vial (3)
- Injection: 200 mg/mL solution in a single-dose prefilled syringe (3)

### CONTRAINDICATIONS

Serious hypersensitivity reaction to certolizumab pegol or to any of the excipients. (4)

### WARNINGS AND PRECAUTIONS

- **Serious Infections:** CIMZIA should not be initiated in patients with an active infection. Monitor for infection during and after treatment; discontinue if a serious infection develops. If invasive fungal infection develops in patients who reside or travel to regions where mycoses are endemic, consider empiric antifungal therapy. (5.1)
- **Malignancies:** Cases of lymphoma and other malignancies have been observed among patients receiving TNF blockers, including CIMZIA. (5.2)
- **Heart Failure:** Monitor patients for new onset or worsening congestive heart failure. (5.3)
- **Hypersensitivity Reactions:** Discontinue CIMZIA and institute appropriate therapy if anaphylaxis or other serious hypersensitivity reactions occur. (5.4)
- **Hepatitis B Virus Reactivation:** Test for HBV infection before starting CIMZIA. Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop CIMZIA and begin anti-viral therapy (5.5)
- **Neurologic Reactions:** Exacerbation or new onset demyelinating disease may occur; use caution in patients with pre-existing or recent-onset demyelinating disorders. (5.6)
- **Hematological Reactions (including leukopenia, pancytopenia and thrombocytopenia):** Use with caution in patients who have ongoing, or a history of, significant hematologic abnormalities. Advise patients to seek immediate medical attention if symptoms develop; consider discontinuing CIMZIA in patients with confirmed abnormalities. (5.7)
- **Use with Anakinra, Abatacept, Rituximab and Natalizumab:** Increased risk of serious infections; concomitant use is not recommended. (5.8, 7.1)
- **Autoimmunity:** Discontinue CIMZIA if lupus-like syndrome develops. (5.9)
- **Live vaccines:** Avoid use with CIMZIA (5.10, 7.2)

### ADVERSE REACTIONS

Most common adverse reactions (≥7%): upper respiratory tract infection, rash, and urinary tract infection (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](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- **Laboratory Tests:** May cause erroneously elevated aPTT results. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2019

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## FULL PRESCRIBING INFORMATION

### WARNING: SERIOUS INFECTIONS AND MALIGNANCY

#### SERIOUS INFECTIONS

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

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

#### Reported infections include:

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

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

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*].

#### MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which CIMZIA is a member [see *Warnings and Precautions (5.2)*]. CIMZIA is not indicated for use in pediatric patients.

## 1 INDICATIONS AND USAGE

### 1.1 Crohn's Disease

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.

### 1.2 Rheumatoid Arthritis

CIMZIA is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA).

### **1.3 Psoriatic Arthritis**

CIMZIA is indicated for the treatment of adult patients with active psoriatic arthritis (PsA).

### **1.4 Ankylosing Spondylitis**

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

### **1.5 Non-radiographic Axial Spondyloarthritis**

CIMZIA is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation [see *Clinical Studies (14.5)*].

### **1.6 Plaque Psoriasis**

CIMZIA is indicated for the treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy [see *Clinical Studies (14.6)*]

## **2 DOSAGE AND ADMINISTRATION**

CIMZIA is administered by subcutaneous injection. Injection sites should be rotated and injections should not be given into 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), 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 particulates and should not be used if cloudy or if 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) 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 Rheumatoid Arthritis**

The recommended dose of CIMZIA for adult patients with rheumatoid arthritis is 400 mg (given as two subcutaneous injections of 200 mg) 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 week 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 Non-radiographic Axial Spondyloarthritis**

The recommended dose of CIMZIA for adult patients with non-radiographic axial spondyloarthritis 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.

## 2.6 Plaque Psoriasis

The recommended dose of CIMZIA for adults with moderate-to-severe plaque psoriasis is 400 mg (given as 2 subcutaneous injections of 200 mg each) every other week.

For some patients (with body weight  $\leq$  90 kg), CIMZIA 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 can be considered [see *Clinical Studies (14.6)*].

## 2.7 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

- If refrigerated, 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.
- 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.
- 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.
- 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 liquid essentially free from particulates.
- Once reconstituted, CIMZIA can be stored in the vials for up to 24 hours between 2° to 8° C (36° to 46° F) prior to injection. Do not freeze.

### Administration

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

## 2.8 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.

- If refrigerated, remove the prefilled syringe from the carton and let it warm to room temperature.
- Inspect the liquid in the prefilled syringe. It should be clear and colorless to yellow and free from particulates. Discard the syringe if cloudy, discolored or contains particulates.
- Suitable sites for injection include the thigh or abdomen at least 2 inches away from the navel.

- Inject at least 1 inch from the previous site.
- Do not inject into areas where the skin is tender, bruised, red or hard, or where there are scars or stretch marks.

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

## **2.9 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.

## **2.10 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.

## **3 DOSAGE FORMS AND STRENGTHS**

For Injection: 200 mg of white to off-white 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

## **4 CONTRAINDICATIONS**

CIMZIA is contraindicated in patients with a history of hypersensitivity reaction to certolizumab pegol or to any of the excipients. Reactions have included angioedema, anaphylaxis, serum sickness, and urticaria [see *Warnings and Precautions (5.4)*].

## **5 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, assess if treatment for latent tuberculosis is needed; and consider an induration of 5 mm or greater a positive tuberculin skin test result, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

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, 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 redeveloped 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 individual patient.

Strongly consider tuberculosis in patients who develop a new infection during CIMZIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

### Monitoring

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with CIMZIA, including the development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy. Tests for latent tuberculosis infection may also be falsely negative while on therapy with CIMZIA.

CIMZIA should be discontinued if a patient develops a serious infection or sepsis. A patient who develops a new infection during treatment with CIMZIA should be closely monitored, undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated.

### Invasive Fungal Infections

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

## 5.2 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 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. During CIMZIA studies of psoriasis, malignancies (excluding non-melanoma skin cancer) were observed corresponding to an incidence rate of 0.5 (0.2, 1.0) per 100 subject-years among a total of 995 subjects who received CIMZIA. The size of the control group and limited duration 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  $\leq$  18 years of age), of which CIMZIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. 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 immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including 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. 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's 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. In the CIMZIA PsO clinical trials (placebo-controlled and open label) there was one case of Hodgkin's lymphoma.

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 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 [see *Adverse Reactions (6.1)*]. The potential role of TNF blocker therapy in the development of malignancies in adults is not known.

Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma that has a very aggressive disease course and is usually fatal, have been reported in patients treated with TNF blockers, including CIMZIA. The majority of reported TNF blocker cases occurred in adolescent and young adult males with Crohn's disease or ulcerative colitis. Almost all of these patients had received treatment with the immunosuppressants azathioprine and/or 6-mercaptopurine (6-MP) concomitantly with a TNF blocker at or prior to diagnosis. It is uncertain whether the occurrence of HSTCL is related to use of a TNF blocker or a TNF blocker in combination with these other



immunosuppressants. The potential risk of using a TNF blocker in combination with azathioprine or 6-MP should be carefully considered.

Cases of acute and chronic leukemia have been reported in association with post-marketing TNF-blocker use in RA and other indications. Even in the absence of TNF-blocker therapy, patients with RA may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blockers, including CIMZIA. Periodic skin examinations are recommended for all patients, particularly those with risk factors for skin cancer.

### **5.3 Heart Failure**

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including CIMZIA. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in patients with CHF with another TNF blocker, worsening congestive heart failure (CHF) and increased mortality due to CHF were observed. Exercise caution in patients with heart failure and monitor them carefully [see *Adverse Reactions (6.1)*].

### **5.4 Hypersensitivity Reactions**

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, anaphylaxis, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. 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)*].

The needle shield inside the removable cap of the CIMZIA prefilled syringe contains a derivative of 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 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.

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 controlled is not known. Therefore, 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 disease, 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 cytopenia (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 Biological Disease-Modifying Antirheumatic Drugs (Biological DMARDs)**

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) and another TNF blocker, etanercept, with no added benefit compared to etanercept alone. A higher risk of serious infections was also observed in combination use of TNF blockers with abatacept and rituximab. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the use of CIMZIA in this combination. Therefore, the use of CIMZIA in combination with other biological DMARDs is not recommended [see *Drug Interactions (7.1)*].

### **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 developed protective levels of anti-vaccine antibodies between CIMZIA and placebo treatment groups; however patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared with 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 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, 5.5)* and *Adverse Reactions (6.1)*]. The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

## **6 ADVERSE REACTIONS**

The most serious adverse reactions were:

- Serious Infections [see *Warnings and Precautions (5.1)*]

- Malignancies [see Warnings and Precautions (5.2)]
- Heart Failure [see Warnings and Precautions (5.3)]

## 6.1 Clinical Trials Experience

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.

In premarketing controlled trials of all patient populations combined the most common adverse reactions ( $\geq 8\%$ ) were upper respiratory infections (18%), rash (9%) and urinary tract infections (8%).

### Adverse Reactions Most Commonly Leading to Discontinuation of Treatment in Premarketing Controlled Trials

The proportion of patients with Crohn's disease 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).

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%).

### Controlled Studies with Crohn's Disease

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 patients 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 Weeks 0, 2, 4). In controlled and uncontrolled studies, 1,564 patients received CIMZIA at some dose level, of whom 1,350 patients 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 were upper respiratory infections (e.g. nasopharyngitis, laryngitis, viral infection) in 20% of CIMZIA-treated patients and 13% of placebo-treated patients, urinary tract infections (e.g. bladder infection, bacteriuria, cystitis) in 7% of CIMZIA-treated patients and in 6% of placebo-treated patients, and arthralgia (6% CIMZIA, 4% placebo).

### 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, 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, atrial fibrillation, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, pericarditis, stroke and transient ischemic attack.

*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:* 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 for at least 2 years; and 1,774 in adequate and well-controlled studies. In placebo-controlled studies, the population had a median age of 53 years at entry; approximately 80% were females, 93% were Caucasian and all patients were suffering from active rheumatoid arthritis, with a median disease duration of 6.2 years. Most patients received the recommended dose of CIMZIA or higher.

Table 1 summarizes the reactions reported at a rate of at least 3% in patients treated with CIMZIA 200 mg every other week compared to placebo (saline formulation), given concomitantly with methotrexate.

**Table 1: Adverse Reactions Reported by  $\geq 3\%$  of Patients Treated with CIMZIA Dosed Every Other Week during Placebo-Controlled Period of Rheumatoid Arthritis Studies, with Concomitant Methotrexate.**

Adverse Reaction (Preferred Term)	Placebo+ MTX <sup>#</sup> (%) N =324	CIMZIA 200 mg EOW + MTX(%) N =640
Upper respiratory tract infection	2	6
Headache	4	5
Hypertension	2	5
Nasopharyngitis	1	5
Back pain	1	4
Pyrexia	2	3
Pharyngitis	1	3
Rash	1	3
Acute bronchitis	1	3
Fatigue	2	3

<sup>#</sup>EOW = Every other Week, MTX = Methotrexate.

Hypertensive adverse reactions were observed more frequently in patients receiving CIMZIA than in controls. These adverse reactions occurred more frequently among patients with a baseline history of hypertension and among patients receiving concomitant corticosteroids and non-steroidal anti-inflammatory drugs.

Patients receiving CIMZIA 400 mg as monotherapy every 4 weeks in rheumatoid arthritis controlled clinical trials had similar adverse reactions to those patients receiving CIMZIA 200 mg every other week.

#### Other Adverse Reactions

Other infrequent adverse reactions (occurring in less than 3% of RA patients) were similar to those seen in Crohn's disease patients.

#### Psoriatic Arthritis Clinical Study

CIMZIA has been studied in 409 patients with psoriatic arthritis (PsA) in a placebo-controlled trial. The safety profile for patients with PsA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

#### Ankylosing Spondylitis Clinical Study

CIMZIA has been studied in 325 patients with axial spondyloarthritis of whom the majority had ankylosing spondylitis (AS) in a placebo-controlled study (AS-1). The safety profile for patients in study AS-1 treated with CIMZIA was similar to the safety profile seen in patients with RA.

#### Non-radiographic Axial Spondyloarthritis Clinical Study

CIMZIA has been studied in 317 patients with non-radiographic axial spondyloarthritis (nr-axSpA-1). The safety profile for patients with nr-axSpA treated with CIMZIA was similar to the safety profile seen in patients with RA and previous experience with CIMZIA.

#### Plaque Psoriasis Clinical Studies

In clinical studies, a total of 1112 subjects with plaque psoriasis were treated with CIMZIA. Of these, 779 subjects were exposed for at least 12 months, 551 for 18 months, and 66 for 24 months.

Data from three placebo-controlled studies (Studies PS-1, PS-2, and PS-3) in 1020 subjects (mean age 46 years, 66% males, 94% white) were pooled to evaluate the safety of CIMZIA [see Clinical Studies (14)].

*Placebo-Controlled Period (Week 0-16)*

In the placebo-controlled period of Studies PS-1, PS-2 and PS-3 in the 400 mg group, adverse events occurred in 63.5% of subjects in the CIMZIA group compared to 61.8% of subjects in the placebo group. The rates of serious adverse events were 4.7% in the CIMZIA group and 4.5% in the placebo group. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the CIMZIA group than in the placebo group.

**Table 2: Adverse Reactions Occurring in  $\geq 1\%$  of Subjects in the CIMZIA Group and More Frequently than in the Placebo Group in the Plaque Psoriasis Studies PS-1, PS-2, and PS-3.**

<b>Adverse Reactions</b>	<b>Cimzia 400 mg every other week n (%) N=342</b>	<b>Cimzia 200 mg<sup>5</sup> every other week n (%) N=350</b>	<b>Placebo n (%) N=157</b>
Upper respiratory tract infections <sup>1</sup>	75 (21.9)	68 (19.4)	33 (21.0)
Headache <sup>2</sup>	13 (3.8)	10 (2.9)	4 (2.5)
Injection site reactions <sup>3</sup>	11 (3.2)	6 (1.7)	1 (0.6)
Cough	11 (3.2)	4 (1.1)	3 (1.9)
Herpes infections <sup>4</sup>	5 (1.5)	5 (1.4)	2 (1.3)

1: Upper respiratory tract infection cluster includes upper respiratory tract infection, pharyngitis bacterial, pharyngitis streptococcal, upper respiratory tract infection bacterial, viral upper respiratory tract infection, viral pharyngitis, viral sinusitis, and nasopharyngitis.

2: Headache includes headache and tension headache.

3: Injection site reactions cluster includes injection site reaction, injection site erythema, injection site bruising, injection site discoloration, injection site pain, and injection site swelling.

4: Herpes infections cluster includes oral herpes, herpes dermatitis, herpes zoster, and herpes simplex.

5: Subjects received 400 mg of CIMZIA at Weeks 0, 2, and 4, followed by 200 mg every other week.

*Elevated Liver Enzymes*

Elevated liver enzymes were reported more frequently in the CIMZIA-treated subjects (4.3% in the 200 mg group and 2.3% in the 400 mg group) than in the placebo-treated subjects (2.5%). Of CIMZIA-treated subjects who had elevation of liver enzymes, two subjects were discontinued from the trial. In controlled Phase 3 studies of CIMZIA in adults with PsO with a controlled period duration ranging from 0 to 16 weeks, AST and/or ALT elevations  $\geq 5 \times$  ULN occurred in 0.9% of CIMZIA 200 mg or CIMZIA 400 mg arms and none in placebo arm.

*Psoriasis-Related Adverse Events*

In controlled clinical studies in psoriasis, change of plaque psoriasis into a different psoriasis sub-types (including erythrodermic, pustular and guttate), was observed in <1% of Cimzia treated subjects.

Adverse Reactions of Special Interest Across Indications

Infections

The incidence of infections in controlled studies in Crohn’s disease was 38% for CIMZIA-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infections (20% for CIMZIA, 13% for placebo). The incidence of serious infections during the controlled

clinical studies was 3% per patient-year for CIMZIA-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis.

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 infection adverse reactions in the CIMZIA treatment groups, compared to the placebo groups (0.06 per patient-year for all CIMZIA doses vs. 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 increased risk of infections with continued exposure over time [*see Warnings and Precautions (5.1)*].

In controlled clinical studies in psoriasis, the incidence rates of infections were similar in the CIMZIA and placebo groups. The infections consisted primarily of upper respiratory tract infections and viral infections (including herpes infections). Serious adverse events of infection occurred in CIMZIA-treated patients during the placebo-controlled periods of the pivotal studies (pneumonia, abdominal abscess, and hematoma infection) and Phase 2 study (urinary tract infection, gastroenteritis, and disseminated tuberculosis).

#### Tuberculosis and Opportunistic Infections

In completed 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 disseminated (miliary, lymphatic, and peritoneal) as well as pulmonary TB. The median time to onset of TB for all patients exposed to CIMZIA across all indications was 345 days. In the studies with CIMZIA in RA, 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. In Phase 2 and Phase 3 studies with CIMZIA in plaque psoriasis, there were 2 cases of TB among 1112 exposed patients [*see Warnings and Precautions (5.1)*].

#### 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 (5.2)*].

#### Heart Failure

In placebo-controlled and open-label 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)*].

#### Hypersensitivity Reactions

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

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)*].

## 6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including 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 in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

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 6% 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 Crohn's disease patients who were antibody-positive (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.

In two long-term (up to 7 years of exposure), open-label Crohn's disease studies, overall 23% (207/903) of patients developed antibodies against certolizumab pegol on at least one occasion. Of the 207 patients who were antibody positive, 152 (73%) had a persistent reduction of drug plasma concentration, which represents 17% (152/903) of the study population. The data from these two studies do not suggest an association between the development of antibodies and adverse events.

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 (MTX) had a lower rate of antibody development than patients not taking immunosuppressants at baseline. Patients treated with concomitant immunosuppressant therapy (MTX) in RA-I, RA-II, RA-III had a lower rate of neutralizing antibody formation overall than patients treated with CIMZIA monotherapy in RA-IV (2% vs. 8%). Both the loading dose of 400 mg every other week at Weeks 0, 2 and 4 and concomitant use of MTX were associated with reduced immunogenicity.

Antibody formation was associated with lowered drug plasma concentration and reduced efficacy. In patients receiving the recommended CIMZIA dosage of 200 mg every other week with concomitant MTX, the ACR20 response was lower among antibody positive patients than among antibody-negative patients (Study RA-I, 48% versus 60%; Study RA-II 35% versus 59%, respectively). In Study RA-III, too few patients developed antibodies to allow for meaningful analysis of ACR20 response by antibody status. In Study RA-IV (monotherapy), the ACR20 response was 33% versus 56%, antibody-positive versus antibody-negative status, respectively [see *Clinical Pharmacology (12.3)*]. No association was seen between antibody development and the development of adverse events.



Approximately 8 % (22/265) and 19% (54/281) of subjects with psoriasis who received CIMZIA 400 mg every 2 weeks and CIMZIA 200 mg every 2 weeks for 48 weeks, respectively, developed antibodies to certolizumab pegol. Of the subjects who developed antibodies to certolizumab pegol, 45% (27/60) had antibodies that were classified as neutralizing. Antibody formation was associated with lowered drug plasma concentration and reduced efficacy.

A more sensitive and drug tolerant electrochemiluminescence (ECL)-based bridging assay was used for the first time in the nr-axSpA-1 study, resulting in a greater proportion of samples having measurable antibodies to certolizumab pegol and thus a greater incidence of patients being classed as antibody positive. In the placebo-controlled trial in patients with non-radiographic axial spondyloarthritis, after up to 52 weeks of treatment, the overall incidence of patients who were antibody positive to certolizumab pegol was 97% (248/255 patients). Of these antibody positive patients, higher titers were associated with reduced certolizumab pegol plasma levels.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to certolizumab pegol in an ELISA or ECL-based bridging assay, and are highly dependent on the sensitivity and specificity of the assay.

### **6.3 Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of CIMZIA. 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.

*Vascular disorder:* systemic vasculitis has been identified during post-approval use of TNF blockers.

*Skin:* case of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, new or worsening psoriasis (all sub-types including pustular and palmoplantar), and lichenoid skin reaction have been identified during post-approval use of TNF blockers.

*Immune System Disorders:* sarcoidosis

*Neoplasms benign, malignant and unspecified (including cysts and polyps):* Melanoma, Merkel cell carcinoma (neuroendocrine carcinoma of the skin) [*see Warnings and Precautions (5.2)*].

## **7 DRUG INTERACTIONS**

### **7.1 Use with Anakinra, Abatacept, Rituximab, and Natalizumab**

An increased risk of serious infections has been seen in clinical studies of other TNF-blocking agents used in combination with anakinra or abatacept, with no added benefit. Formal drug interaction studies have not been performed with rituximab or natalizumab. Because of the nature of the adverse events seen with these combinations with TNF blocker therapy, similar toxicities may also result from the use of CIMZIA in these combinations. There is not enough information to assess the safety and efficacy of such combination therapy. Therefore, the use of CIMZIA in combination with anakinra, abatacept, rituximab, or natalizumab is not recommended [*see Warnings and Precautions (5.8)*].

### **7.2 Live Vaccines**

Avoid use of live (including attenuated) vaccines concurrently with CIMZIA [*see Warnings and Precautions (5.10)*].

### 7.3 Laboratory Tests

Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated activated partial thromboplastin time (aPTT) assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-Lupus Anticoagulant (LA) test and Standard Target Activated Partial Thromboplastin time (STA-PTT) Automate tests 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 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 was negligible in most infants at birth, and low in other infants at birth (*see Data*). 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* to CIMZIA 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 TNF $\alpha$  pegylated Fab' fragment (cTN3 PF) similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mg every four 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.

#### Clinical Considerations

##### *Disease-Associated Maternal and/or Embryo/Fetal Risk*

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis or Crohn's disease is correlated with maternal disease activity and that active disease increases the risk of adverse pregnancy outcomes, including fetal loss, preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) and small for gestational age birth.

##### *Fetal/Neonatal Adverse Reactions*

Due to its inhibition of TNF $\alpha$ , CIMZIA administered during pregnancy could affect immune responses in the *in utero*-exposed newborn and infant. The clinical significance of BLQ or low levels is unknown for *in utero*-exposed infants. Additional data available from one exposed infant suggest that CIMZIA may be

eliminated at a slower rate in infants than in adults (*see Data*). The safety of administering live or live-attenuated vaccines in exposed infants is unknown.

## Data

### *Human Data*

A limited number of pregnancies have been reported in the ongoing pregnancy exposure registry. 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.

A multicenter clinical study was conducted in 16 women treated with CIMZIA at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks during the third trimester of pregnancy for rheumatological diseases or Crohn's disease. The last dose of CIMZIA was given on average 11 days prior to delivery (range 1 to 27 days). Certolizumab pegol plasma concentrations were measured in samples from mothers and infants using an assay that can measure certolizumab pegol concentrations at or above 0.032 mcg/mL. Certolizumab pegol plasma concentrations measured in the mothers at delivery (range: 4.96 to 49.4 mcg/mL) were consistent with non-pregnant women's plasma concentrations in Study RA-I [*see Clinical Studies (14.2)*]. Certolizumab pegol plasma concentrations were not measurable in 13 out of 15 infants at birth. The concentration of certolizumab pegol in one infant was 0.0422 mcg/mL at birth (infant/mother plasma ratio of 0.09%). In a second infant, delivered by emergency Caesarean section, the concentration was 0.485 mcg/mL (infant/mother plasma ratio of 4.49%). At Week 4 and Week 8, all 15 infants had no measurable concentrations. Among 16 exposed infants, one serious adverse reaction was reported in a neonate who was treated empirically with intravenous antibiotics due to an increased white blood cell count; blood cultures were negative. The certolizumab pegol plasma concentrations for this infant were not measurable at birth, Week 4, or Week 8.

In another clinical study conducted in 10 pregnant women with Crohn's disease treated with CIMZIA (400 mg every 4 weeks for every mother), certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood at the day of birth with an assay that can measure concentrations at or above 0.41 mcg/mL. The last dose of CIMZIA was given on average 19 days prior to delivery (range 5 to 42 days). Plasma certolizumab pegol concentrations ranged from not measurable to 1.66 mcg/mL in cord blood and 1.58 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.

### *Animal Data*

Because certolizumab pegol does not cross-react with mouse or rat TNF $\alpha$ , reproduction studies were performed in rats using a rodent anti-murine TNF $\alpha$  pegylated Fab' fragment (cTN3 PF) 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 the surface area) and have revealed no evidence of harm to the fetus due to cTN3 PF.

## **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 17 infants in the study. There are no data on the effects on milk production. In a separate study, certolizumab pegol concentrations were not detected in the plasma of 9 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 rheumatological disease 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 (56 %) 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 ranged from 0.56% to 4.25% based on samples with measurable certolizumab pegol concentration. No serious adverse reactions were noted in the 17 breastfed infants in the study.

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

#### **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established. Due to its inhibition of TNF $\alpha$ , 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 subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Population pharmacokinetic analyses of 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 with CIMZIA [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 evidence of dose-limiting toxicities. 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**

Certolizumab pegol is a TNF blocker. CIMZIA is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNF $\alpha$ ), 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 (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, USP, the final concentration is 200 mg/mL with a deliverable volume of 1 mL (200

























































period of up to 7 days. After your CIMZIA syringe has been stored at room temperature, do not place back in refrigerator.

- Write the date removed from the refrigerator in the space provided on the carton and throw away (discard) if not used within the 7-day period.

### Setting up for your CIMZIA injection:

#### Step 1.

If refrigerated, take the carton containing the prefilled syringes of CIMZIA out of the refrigerator. Check the expiration date on the syringe carton and label.

See Figure C.



Figure C

If the expiration date has passed, **do not** use the syringe. Call your pharmacist for questions about the expiration date. Do not use CIMZIA if the tamper evident seals are missing or broken on the top or bottom of the carton when you receive it. If the tamper evident seals are missing or broken, contact your pharmacist.

#### Step 2.

Remove the prefilled syringe from the carton and let it warm to room temperature. Do not warm the syringe in any other way. If you are not using the second syringe, put the carton containing the remaining prefilled syringe back in the refrigerator.

#### Step 3.

Find a clean, flat work surface, such as a table.

#### Step 4.

Make sure the liquid medicine in the prefilled syringe is clear and colorless to yellow and free from particles. **Do not** inject the medicine if it is cloudy, discolored, or contains particles. Call your healthcare provider or pharmacist if you have any questions about your CIMZIA prefilled syringe.

#### Step 5.

Gather all the supplies you will need for your injection.

#### Step 6.

Wash your hands with soap and warm water and dry with a clean towel.

## Selecting and preparing your injection site:

### Step 7.

Choose your injection site(s) on your stomach or upper thighs. **See Figure D.**

- Choose a new injection site each time you use CIMZIA.
- Each new injection should be given at least 1 inch from the site you used before. If you choose your stomach, avoid the 2 inches around your belly button (navel).
- Do not inject into areas where your skin is tender, bruised, red or hard, or where you have scars or stretch marks.
- Change injection sites between your stomach and upper thighs to reduce the chance of having a skin reaction.
- You may want to write down the site you use for your injection to help you remember to use a different site each time you inject.

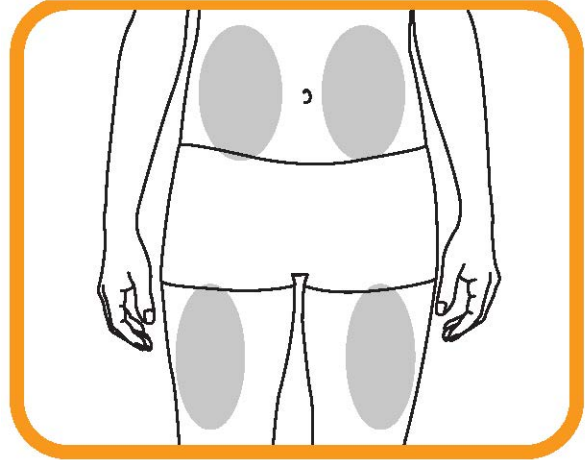


Figure D

### Step 8.

Clean your injection site with an alcohol swab. Let the area dry completely.

## Giving your CIMZIA injection:

### Step 9.

Pick up the prefilled syringe with 1 hand and hold it with the needle pointing up. You may see air bubbles. This is normal. There is no need to remove air bubbles before giving your injection. Injecting the solution with air bubbles will not harm you. With your other hand, remove the plastic ring needle cap by pulling straight up on the plastic ring. **See Figure E.**

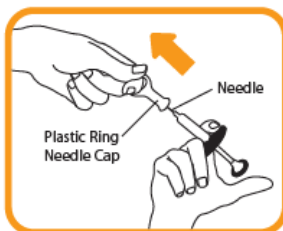


Figure E

**Do not** touch the needle and do not let the needle touch any surface. Do not bend the needle. Place the plastic ring needle cap to the side.

**Step 10.**

With your other hand, gently pinch a fold of skin at the cleaned injection site. **See Figure F.**

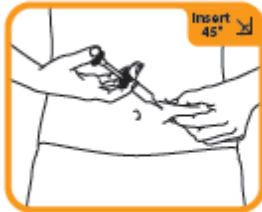


Figure F

**Step 11.**

With a quick, "dart-like" motion, insert the needle into your skin at about a 45 degree angle. Release the pinched skin, keeping the syringe in position. Slowly push on the plunger all the way down until the syringe is empty. **See Figure G.**

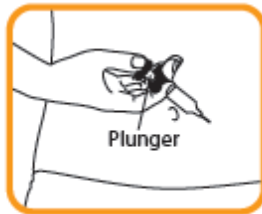


Figure G

**Step 12.**

When the syringe is empty, pull the needle out of your skin while carefully keeping the needle at the same angle as inserted. **See Figure H.**

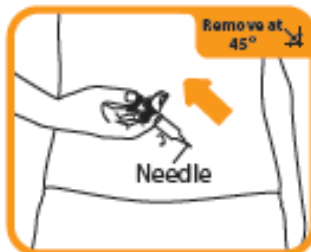


Figure H



**Step 13.**

Place a dry cotton ball or gauze pad over the injection site for several seconds. **See Figure I.**

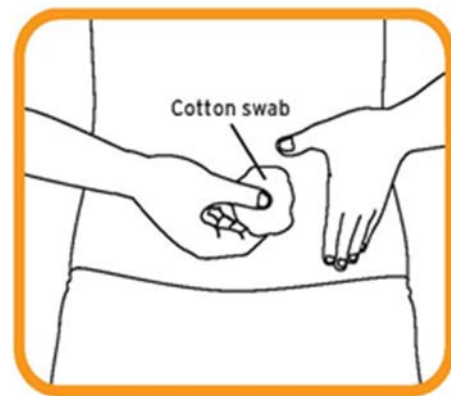


Figure I

Do not rub the injection site. Do not use an alcohol swab as it may cause stinging. If there is a little bleeding, cover the injection site with a small bandage.

**To avoid a needle-stick injury, do not try to recap the needle. Do not reuse any of your injection supplies.**

**Disposal of your syringes with needles attached:**

Put your used syringes with needle attached in a FDA-cleared sharps disposal container right away after use. **See Figure J.**

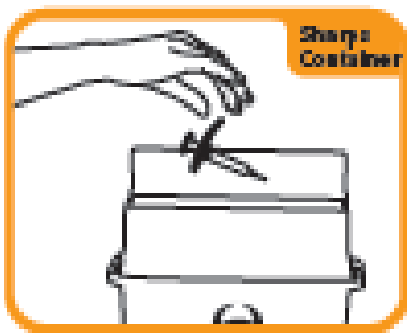


Figure J

**Do not throw away (dispose of) loose syringes and needles in your household trash.**

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
- upright and stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Product manufactured by:

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