CIMZIA (certolizumab pegol) for injection, for subcutaneous use
Initial U.S. Approval: 2008

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

- Treatment of adults with moderately to severely active rheumatoid arthritis (1.2)
- Reducing signs and symptoms of Crohn’s disease and maintaining clinical response in adult patients
  with active Crohn’s Disease (2.1)
- Treatment of adult patients with active ankylosing spondylitis (1.4)
- Treatment of adults with active psoriatic arthritis (1.3)
- Treatment of adults with active active rheumatoid arthritis who have had an inadequate response to conventional therapy (1.1)

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

CIMZIA (5.1).

- 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).

CONTRAINDICATIONS
None (4)

WARNINGS AND PRECAUTIONS
- Serious infections – do not start CIMZIA during an active infection. If an infection develops, monitor carefully, and stop CIMZIA if infection becomes serious (5.1).
- Invasive fungal infections – for patients who develop a systemic illness on CIMZIA, consider empiric antifungal therapy for those who reside or travel to regions where mycoses are endemic (5.1).
- Cases of lymphoma and other malignancies have been observed among patients receiving TNF blockers (5.2).
- Heart failure, worsening or new onset may occur (5.3).
- Anaphylaxis or serious allergic reactions may 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).
- Dermatitis, exacerbation or new onset, may occur (5.6).
- Cytopenias, pancytopenia – advise patients to seek immediate medical attention if symptoms develop, and consider stopping CIMZIA (5.7).
- Lupus-like syndrome – stop CIMZIA if syndrome develops (5.9).

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥7% and higher than placebo): 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.

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: 10/2015
For maintenance dosing, CIMIZIA 400 mg every 4 weeks can be considered. CIMIZIA is provided in a package that contains everything required to reconstitute and inject the drug. Two subcutaneous injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week.

2.3 Psoriatic Arthritis

2.2 Rheumatoid Arthritis

2.1 Crohn’s Disease

CIMIZIA is indicated for the treatment of adults with moderately to severely 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.

1.3 Psoriatic Arthritis

1.2 Rheumatoid Arthritis

1.1 Crohn’s Disease

CIMIZIA is indicated for the treatment of adults with active ankylosing spondylitis (AS).

CIMIZIA  is indicated for the treatment of adults with active psoriatic arthritis (PsA).

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

CIMIZIA 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 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. CIMIZIA does not contain preservatives; therefore, unused portions of drug remaining in the syringe or vial should be discarded.

The recommended initial adult dose of CIMIZIA 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.

The recommended dose of CIMIZIA 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, CIMIZIA 400 mg every 4 weeks can be considered [see Clinical Studies (14.2)].

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

The recommended dose of CIMIZIA for adult patients with ankylosing spondylitis is 400 mg (given as two 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.

Preparation and Administration of CIMIZIA Using the Lypohilized Powder for Injection

CIMIZIA Lypohilized powder should be prepared and administered by a health care professional. CIMIZIA 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. CIMIZIA should be brought to room temperature before reconstituting.
b. Use appropriate aseptic technique when preparing and administering CIMIZIA.
c. Reconstitute the vial(s) of CIMIZIA with 1 mL of Sterile Water for Injection, USP using the 20-gauge needle provided.
d. Gently swirl each vial of CIMIZIA without shaking, assuring that all of the powder comes in contact with the Sterile Water for Injection.
e. Leave the vial(s) undisturbed to fully reconstitute, which may take approximately 30 minutes.
f. The final reconstituted solution contains 200 mg/mL and should be clear to opalescent, colorless to pale yellow liquid essentially free from particulates.
g. Once reconstituted, CIMIZIA 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

a. Prior to injecting, reconstituted CIMIZIA should be at room temperature but do not leave reconstituted CIMIZIA 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 CIMIZIA (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 syringes subcutaneously into 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 CIMIZIA Using the Prefilled Syringe

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

Patients using the CIMIZIA 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.

2.7 Monitoring to Assess Safety

Before initiation of therapy with CIMIZIA, 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

CIMIZIA may be used as monotherapy or concomitantly with non-biological disease modifying anti-rheumatic drugs (DMARDs). The use of CIMIZIA in combination with biological DMARDs or other tumor necrosis factor (TNF) blocker therapy is not recommended.

3 DOSE FORMS AND STRENGTHS

- For Injection: Lyophilized Powder for Reconstitution
Sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. Each single-use vial provides approximately 200 mg of CIMIZIA.

- Injection: Prefilled Syringe
A single-use, 1 mL prefilled glass syringe with a fixed 25 gauge ½ inch thin wall needle, providing 200 mg per 1 mL of CIMIZIA.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Infections

[see Boxed Warning]

Patients treated with CIMIZIA 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.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMIZIA, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating CIMIZIA and periodically during therapy.
Treatment of latent tuberculosis infection prior to therapy with TNF-blocking agents has been shown to be effective in reducing the risk of infection reactivation during therapy. Induction of 5 mm or greater with tuberculin skin testing should be considered a positive test result when assessing if treatment for latent tuberculosis is needed prior to initiating CIMZIA, even for patients previously vaccinated with Bacille Calmette-Guérin (BCG).

Anti-tuberculosis therapy should also be considered 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. 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.

Tuberculosis should be strongly considered in patients who develop a new infection during CIMZIA treatment, especially in patients who have 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. Antibody and antigen 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 concurrent, and continuing, post-marketing studies of TNF blockers, cases of malignancies (excluding non-melanoma skin cancer) were observed at a rate of 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 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 at 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 occurrence of malignancies has been observed after a median of 30 months of treatment (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 patients with Crohn’s disease, malignancies of the lymphoma has been observed among patients receiving TNF blockers compared to controls. 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 place controlled-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.

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 who receive anti-TNF therapy have a higher risk of developing malignancies compared to patients with Crohn’s disease who are not treated with anti-TNF therapies.

Postmarketing cases of hematopoietic T-cell lymphoma (H-TCL) and rare 5 to 6 of T-cell lymphoma in patients who have ongoing, or a history of, significant hemato logic abnormalities. The malignancy 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.

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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 C02 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 ≥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, leucopenia, lymphadenopathy, pancytopenia, and thrombocytopenia.
- **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 totals.
- **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 treatment with CIMZIA or placebo betw een the ages of 18 and 64.

In placebo-controlled and open-label rheumatoid arthritis studies, cases of new or worsening 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 new more 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 group were 0.05 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)].

**Tuberculosis and Opportunistic Infections**

In completed and ongoing global clinical studies in all indications including 3,515 TNF-blocker treated patients, the overall rate of tuberculosis is approximately 0.01 per 100 patient-years across all indications.

The majority of cases occurred in countries with high endemic rates of TB. Reports include cases of military, lymphatic, 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 222,005 exposed patients including 11 fatal cases. Rare cases of opportunistic infections have also been reported in these clinical trials. [see Warnings and Precautions (5.1)].

**Autoimmune disorders**

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 patients treated with CIMZIA and 2 of the 2,367 patients treated with placebo developed antibodies to cyclic citrullinated peptides (anti-CCP). 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 disease is unknown.

**Adverse Reactions**

Table 1 summarizes the adverse effects reported in clinical studies of CIMZIA in patients treated with CIMZIA 200 mg every other week compared to placebo (placebo formulation), given concomitantly with methotrexate.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo + MTX (%)</th>
<th>CIMZIA 200 mg EOW + MTX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract infection</td>
<td>6</td>
<td>N = 234</td>
</tr>
<tr>
<td>Headache</td>
<td>5</td>
<td>N = 640</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>N = 51</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1</td>
<td>N = 51</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>N = 4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
<td>N = 3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>N = 3</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>N = 3</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>1</td>
<td>N = 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>N = 3</td>
</tr>
</tbody>
</table>

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 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 data 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 was similar to that observed in previous studies with CIMZIA. Patients received CIMZIA 200 mg subcutaneously every other week. In the evaluation of safety, patients continued to receive placebo or active treatment with etanercept and were monitored for a total of 52 weeks. 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.

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. Formuladrug interaction studies with other TNF-blocking agents have been negative. Simultaneous therapy with etanercept, adalimumab, or infliximab is not recommended. [see Warnings and Precautions (5.1)].

**7.2 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, and new or worsening psoriasis (all sub-types including palmar and palmopatellar) have been identified during post-approval use of TNF blockers.

**Immune System Disorders: sarcoidosis**

**7.3 DRUG INTERACTIONS**

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

**8.1 Anticancer Agents**

Avoid use of live (including attenuated) vaccines concurrently with CIMZIA. [see Warnings and Precautions (5.1)].
Certolizumab pegol does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause antibody-dependent cell-mediated cytotoxicity in vitro. It does not induce apoptosis in vitro in human peripheral blood mononuclear cells or lymphocytes, nor does certolizumab pegol induce neutrophil degranulation.

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

12.2 Pharmacodynamics

Biological activities ascribed to TNFα include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNFα also stimulates the production of downstream inflammatory mediators, including interleukins-1, -2, -6, -8, -17, interleukin-12, lymphotoxin βα, and tumor necrosis factor αβ.

TNFα is strongly expressed in the bowel wall in areas involved by Crohn’s disease and focal concentrations of TNFα in patients with Crohn’s disease have been shown to reflect clinical severity of the disease. After treatment with certolizumab pegol, patients with Crohn’s disease demonstrated a decrease in the levels of C-reactive protein (CRP). Increased TNFα levels are found in the sytovial fluid of rheumatoid arthritis patients and play an important role in the joint destruction that is a hallmark of this disease.

12.3 Pharmacokinetics

Absorption
A total of 126 healthy subjects received doses of up to 800 mg certolizumab pegol subcutaneously (sc) and up to 10 mg/kg intravenously (iv) in four pharmacokinetic studies. In these studies, subjects that was conducted in elderly patients and their outcomes were

Population pharmacokinetic analyses of these studies demonstrate that single intravenous and subcutaneous doses of certolizumab pegol have predictable pharmacokinetic profiles. The terminal elimination phase half-life of certolizumab pegol is dose-related and is approximately 2.2 days for doses up to 400 mg sc and 1.2 days for doses above 400 mg sc. The clearance of certolizumab pegol is not influenced by age, sex, smoking status, or body weight.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies of CMZ2A have not been conducted to assess the carcinogenic potential of certolizumab pegol. Certolizumab pegol was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay, or the mouse bone marrow micronucleus assay.

Since certolizumab pegol does not cross-react with mouse or rat TNFα, research studies were performed on rats and mice that were not conducted in a cytokine-neutralizing agent, certolizumab pegol. The results of these studies showed that certolizumab pegol had no effect on the fertility and general reproductive performance of male and female rats at dosages as high as 100 mg/kg/day. However, in studies conducted in rats, no increased incidence of tumors was observed in male or female rats treated with doses up to 100 mg/kg/day.

Normal murine drug-drug interaction studies have not been conducted with certolizumab pegol.
Clinical Studies

14.1 Crohn’s Disease

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

Study CD1

Study CD1 was a randomized placebo-controlled study in 682 patients with active Crohn’s disease. CIMZIA or placebo was administered at Weeks 0, 2, 4 and 4 then every four weeks to Week 24. Assessments were done at Weeks 6 and 26. Clinical response was defined as at least a 100-point reduction in CDAI score compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower.

The results for Study CD1 are provided in Table 2. At Week 6, the proportion of clinical responders was statistically significantly greater for CIMZIA-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at Week 6. The difference in the proportion of patients who were in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

Table 2 - 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></td>
<td>Placebo (N = 328)</td>
</tr>
<tr>
<td>Week 6</td>
<td>Clinical Response*</td>
</tr>
<tr>
<td></td>
<td>Clinical Remission*</td>
</tr>
<tr>
<td>Week 26</td>
<td>Clinical Response</td>
</tr>
<tr>
<td></td>
<td>Clinical Remission</td>
</tr>
<tr>
<td>Both Weeks 6 &amp; 26</td>
<td>Clinical Response</td>
</tr>
<tr>
<td></td>
<td>Clinical Remission</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 428 clinical responders was randomized to receive either CIMZIA 400 mg or placebo, every four weeks starting at Week 6, 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 24. 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></td>
<td>CIMZIA 400 mg x3 + Placebo (N = 210)</td>
</tr>
<tr>
<td>Week 26</td>
<td>Clinical Response*</td>
</tr>
<tr>
<td></td>
<td>Clinical Remission*</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 (RA) criteria. Patients had ≤ 5 swollen and 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 of MTX 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 CIMZIA for 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.
The percent of patients achieving ACR20 responses by visit for Study RA-I is shown in Figure 1. Among patients receiving CIMZIA, clinical responses were seen in some patients within one to two weeks after initiation of therapy.

![Figure 1 Study RA-I ACR20 Response Over 52 Weeks*](image)

### Radiographic Response

In Study RA-I, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified Total Sharp Score (mTSS) and its components, the Erosion Score (ES) and Joint Space Narrowing (JSN) score, at Week 52, compared to baseline. CIMZIA inhibited the progression of structural damage compared to placebo plus MTX after 12 months of treatment as shown in Table 6. In the placebo group, 52% of patients experienced no radiographic progression (mTSS 0.0) at Week 52 compared to 69% in the CIMZIA 200 mg every other week treatment group. Study RA-II showed similar results at Week 24.

### Clinical Response

The percentage of CIMZIA-treated patients achieving ACR20, 50 and 70 responses in study PsA001 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 (23%, 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.

### Physical Function Response

In studies RA-I, RA-II, RA-III, and RA-IV, CIMZIA-treated patients achieved greater improvements from baseline to placebo-treated patients in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 52 (RA-II, RA-III and RA-N) and at Week 52 (RA-I).

### 14.3 Psoriatic Arthritis

The efficacy and safety of CIMZIA were assessed in a multi-center, randomized, double-blind, placebo controlled trial (PsA001) 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 70% respectively.

Patients received a loading dose of CIMZIA 400 mg at Weeks 0, 2 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.

### Table 7: Components of ACR Response in Study PsA001

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>CIMZIA^a 200 mg Q2W</th>
<th>CIMZIA^a 400 mg Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tender joints (0-66)^b</td>
<td>20 17 22 11</td>
<td>20 11</td>
<td></td>
</tr>
<tr>
<td>Number of swollen joints (0-66)^b</td>
<td>10 9 11 4</td>
<td>11 5</td>
<td></td>
</tr>
<tr>
<td>Physician global assessment^e</td>
<td>59 44 57 25</td>
<td>58 29</td>
<td></td>
</tr>
<tr>
<td>Patient global assessment^e</td>
<td>57 50 60 33</td>
<td>60 40</td>
<td></td>
</tr>
<tr>
<td>Patient A 100= best 0= worst</td>
<td>1.3 1.1 1.3 0.87</td>
<td>1.29 0.90</td>
<td></td>
</tr>
<tr>
<td>Disability index (HAQ)^c,d</td>
<td>18.56 14.75 15.36 5.67</td>
<td>13.71 6.34</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 preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
^c Results are from the randomized set. Non-responder Imputation (NRI) is used for patients who escaped therapy or had missing data.
^d The Patient Assessment of Arthritis Pain, VA S 0= no pain and 100= most severe pain
^e Patient and Physician Global Assessment of Disease Activity, VAS 0= best 100= worst
^f The Patient Assessment of Arthritis Pain, VAS 0= no pain and 100= most severe pain
^g The HAQ-DI, 4 point scale 0=without difficulty and 3=unable to do
^h All values presented represent the mean

### Table 8: Radiographic Changes at 6 and 12 months in Study RA-I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + MTX Mean (SD)</th>
<th>CIMZIA 200 mg + MTX Mean (SD)</th>
<th>CIMZIA 200 mg + MTX – Placebo + MTX Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTSS Baseline</td>
<td>40 (45)</td>
<td>38 (49)</td>
<td>—</td>
</tr>
<tr>
<td>Week 24</td>
<td>1.3 (3.8)</td>
<td>0.2 (3.2)</td>
<td>-1.1</td>
</tr>
<tr>
<td>Week 52</td>
<td>2.8 (7.8)</td>
<td>0.4 (5.7)</td>
<td>-2.4</td>
</tr>
<tr>
<td>Erosion Score Baseline</td>
<td>14 (21)</td>
<td>15 (24)</td>
<td>—</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.7 (2.1)</td>
<td>0.0 (1.5)</td>
<td>-0.7</td>
</tr>
<tr>
<td>Week 52</td>
<td>1.5 (4.3)</td>
<td>0.1 (2.5)</td>
<td>-1.4</td>
</tr>
<tr>
<td>JSN Score Baseline</td>
<td>25 (27)</td>
<td>24 (28)</td>
<td>—</td>
</tr>
<tr>
<td>Week 24</td>
<td>0.7 (2.4)</td>
<td>0.2 (2.5)</td>
<td>-0.5</td>
</tr>
<tr>
<td>Week 52</td>
<td>1.4 (5.0)</td>
<td>0.4 (4.2)</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

* The same patients may not have responded at each time point.

An ANCOVA was fitted to the ranked change from baseline for each measure with region and treatment as factors and rank baseline as a covariate.

**Radiographic Changes at 6 and 12 months in Study RA-I**

<table>
<thead>
<tr>
<th>Paramet er</th>
<th>Placebo</th>
<th>CIMZIA^a 200 mg Q2W</th>
<th>CIMZIA^a 400 mg Q4W</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20 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 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 Week 12</td>
<td>3%</td>
<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>Week 24</td>
<td>4%</td>
<td>28%</td>
<td>24%</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 preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
^c Results are from the randomized set. Non-responder Imputation (NRI) is used for patients who escaped therapy or had missing data.

### Table 7: ACR Responses in Study PsA001 (Percent of Patients)

- The same patients may have not responded at each time point.
In study PsA001, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp score (mTSS) and its components, the Erosion Score (ES) and Joint Space Narrowing score (JSN) at week 24, compared to baseline. The mTSS score was modified for psoriatic arthritis by addition of hand distal interphalangeal (DIP) joints.

Patients treated with CIMZIA 200 mg every other week demonstrated greater reduction in radiographic progression compared with placebo-treated patients at Week 24 as measured by change from baseline in total modified mTSS Score (estimated mean change was -0.16 in the placebo group compared with -0.02 in the CIMZIA 200 mg group; 95% CI for the difference was (-0.39, -0.04)). Patients treated with CIMZIA 400 mg every four weeks did not demonstrate greater inhibition of radiographic progression compared with placebo-treated patients at Week 24.

Physical Function Response

In Study PsA001, CIMZIA-treated patients showed improvement in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24 as compared to placebo (estimated mean change from baseline was 0.19 in the placebo group compared with 0.54 in the CIMZIA 200 mg group; 95% CI for the difference was (-0.39, -0.14)).

14.4 Ankylosing Spondylitis

The efficacy and safety of CIMZIA were assessed in one multicenter, randomized, double-blind, placebo-controlled study (AS-1) in 325 patients ≥18 years of age with adult-onset active axial spondyloarthritis for at least 3 months. The majority of patients in the study had active AS.

Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4, and spinal pain ≥4 on a 0 to 10 Numerical Rating Scale (NRS). Patients must have been intolerant to or had an inadequate response to at least one NSAID. Patients were treated with a loading dose of CIMZIA 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg of CIMZIA every 2 weeks or 400 mg of CIMZIA every 4 weeks or placebo. Concomitant NSAIDs were received by 91% of the AS patients. The primary efficacy variable was the proportion of patients achieving an ASAS20 response at Week 12.

Clinical Response

In study AS-1, at Week 12, a greater proportion of AS patients treated with CIMZIA 200 mg every 2 weeks or 400 mg every 4 weeks achieved ASAS20 response compared to AS patients treated with placebo (Table 9). Responses were similar in patients receiving CIMZIA 200 mg every 2 weeks and CIMZIA 400 mg every 4 weeks. The results of the components of the ASAS response criteria and other measures of disease activity are shown in Table 10.

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

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo</th>
<th>CIMZIA 200 mg every 2 weeks</th>
<th>CIMZIA 400 mg every 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 57</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>N = 56</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>

ASAS20 = ASAS20 response criteria

All percents reflect the proportion of patients who responded in the full analysis set.

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

Storage and Stability

Refrigerate intact carton between 2 to 8°C (36 to 46°F). Do not freeze. Do not separate contents of carton prior to use. Do not use beyond expiration date, which is located on the drug label and carton. Protect solution from light.

- Lyophilized Powder for Reconstitution:
  NDC 50474-700-62
  Pack Content
  Qty    Item
  2     Type 1 glass vials with rubber stopper and overseals each containing 200 mg of lyophilized CIMZIA for reconstitution.
  2     2 mL Type 1 glass vials containing 1 mL sterile Water for Injection
  2     3 mL plastic syringes
  4     20 gauge luer-lock needles (1 inch)
  2     23 gauge luer-lock needles (1 inch)
  8     Alcohol swabs

-Prefilled Syringe
  NDC 50474-710-79
  2 alcohol swabs and 2 single use prefilled glass syringes with a fixed 25 ½ gauge thin-wall needle, each containing 200 mg (1 mL) of CIMZIA.

- Prefilled Syringe Starter Kit
  NDC 50474-710-81
  6 alcohol swabs and 6 single use prefilled glass syringes with a fixed 25 ½ gauge thin-wall needle. The Starter Kit contains 3 sets of 2 prefilled syringes to provide sufficient drug supply for the initial 3 induction doses at the start of treatment. Each prefilled syringe contains 200 mg (1 mL) of CIMZIA.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Patient Counseling

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

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

- Allergic Reactions
  Advise patients to seek immediate medical attention if they experience any symptoms of severe allergic reactions. The prefilled syringe components do not contain any latex or dry natural rubber.

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

17.2 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...
Medication Guide

CIMZIA® (CIM-zee-uh)
(certolizumab pegol)
yyophilized 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, cold, 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), Orencia® (abatacept), Rituxan® (rituximab), or Tysabri® (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.

Certain types of Cancer

- There have been cases of unusual cancers in children and teenage patients using TNF-blocking agents.
- For people taking TNF-blocker medicines, including CIMZIA, the chances of getting lymphoma or other cancers may increase.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.

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 pregnant or planning to become pregnant. It is not known if CIMZIA will harm your unborn baby. 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 planning to breastfeed. It is not known if CIMZIA passes into your breast milk. 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:

- Kineret® (anakinra), Orencia® (abatacept), Rituxan® (rituximab), or Tysabri® (natalizumab).
- medicines called Tumor Necrosis Factor (TNF) blockers such as Remicade® (infliximab), Humira® (adalimumab), Enbrel® (etanercept), 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 your healthcare provider prescribes the CIMZIA prefilled syringe, you will be trained on how to inject CIMZIA.
- 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 on 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 to colorless to light yellow. The solution should be mostly free from particles. Do not use the CIMZIA prefilled syringe if the medicine looks cloudy or if there are large or colored particles.
- Do not miss 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 doctor should monitor you carefully before and during treatment with CIMZIA to see if you carry the hepatitis B virus in your blood. Tell your doctor 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 doesn’t 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 36ºF to 46ºF (2ºC to 8ºC)
  • 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.

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