CIMZIA® (certolizumab pegol) for injection, for subcutaneous use

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

INITIAL U.S. APPROVAL: 2008

CIMZIA® injection, for subcutaneous use

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

Crohn’s Disease (2.1)

• 400 mg initially and at Weeks 2 and 4. If response occurs, follow with 400 mg every four weeks

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.

2.4 Ankylosing Spondylitis

Dosage and Administration

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)

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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.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
**INDICATIONS AND USAGE**

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.

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

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

4. **Ankylosing Spondylitis**
   CIMZIA is indicated for the treatment of adult patients with ankylosing spondylitis (AS).

**DOSAGE AND ADMINISTRATION**

5. **Injection**
   CIMZIA is administered by subcutaneous injection. Injection sites should be rotated and 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 each), injections should occur at separate sites in the thigh or abdomen.

6. **Concomitant Medications**
   CIMZIA is indicated for the treatment of adult patients with active ankylosing spondylitis (AS). (see Clinical Studies (14.4)).

7. **Dosage Forms and Strengths**
   CIMZIA is provided in a package that contains everything required to reconstitute and inject the drug. Prepare each dose immediately before use. Do not freeze.

8. **Preparation and Administration**
   CIMZIA lyophilized powder should be prepared and administered by a healthcare professional. 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.

9. **Maintenance Dosing**
   CIMZIA is provided in a package that contains everything required to reconstitute and inject the drug. Prepare each dose immediately before use. Do not freeze.

10. **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 previously or concomitantly received treatment for 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 on all patients.

**WARNINGS AND PRECAUTIONS**

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

**CONTRAINDICATIONS**

12. **None.**

**REFERENCES**

13. **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 infection and tuberculosis disease. Prior to initiating therapy, patients are assessed if treatment for latent tuberculosis infection 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 positive tuberculin skin test result. The test should be performed prior to initiating therapy. Antigen and antibody tests for tuberculosis infection, although not diagnostic, may be negative in some patients with active infection. When feasible, the decision to administer antituberculosis therapy in these patients should be made in consultation with a physician. In patients treated with TNF blockers, including CIMZIA, the impact of therapy on the development of tuberculosis is not fully understood. The risk of active tuberculosis was increased in patients treated with TNF blockers, as compared to those treated with placebo. Treatment with TNF blockers, including CIMZIA, does not provide protection against tuberculosis.

CIMZIA should not be administered to patients with a history of tuberculosis disease, and the potential risk of using a TNF blocker in combination with azathioprine or 6-MP should be carefully considered.

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

The most serious adverse reactions were:

- Malignancies
- Serious infections
- Infections of the central nervous system
- Autoimmune conditions
- Uveitis

5.11 Immunosuppression

The safety and efficacy of CIMZIA in patients with immunosuppression has not been formally evaluated.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- Infusion reactions were:
  - Serious infections
  - Malignancies
  - Heart failure

Because clinical studies are conducted under widely varying and controlled conditions, adverse reactions observed in the 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 (≥5%) were upper respiratory infections (15%), rash (9%) and urinary tract infections (6%).

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

The proportion of patients with rheumatoid arthritis who discontinued treatment due to adverse reactions in the controlled clinical trials with CIMZIA was 5% for CIMZIA and 2.5% for placebo. The most common adverse reactions leading to discontinuation of CIMZIA were tuberculosis infections (0.5%), pyrexia, urticaria, and pneumonia, and rash (0.3%).
Controlled Studies with Crohn’s Disease

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 and approximately 80% were females. 95% 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>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo + MTX (%)</th>
<th>CIMZIA 200 mg EOW + MTX (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 640</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

EOW = Every Other Week, MTX = Methotrexate.

Hypersensitive 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.

Pyoderma Garni Clinical Study

CIMZIA was 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.

Anakinra Spondylitis Clinical Study

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

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 infections in CIMZIA-treated patients (0.09 cases per patient-year for CIMZIA 200 mg EOW vs. 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)].

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 lymphadenitis, miliary tuberculosis (in the absence of clinical or imaging evidence of pulmonary TB) and the median disease duration of 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 [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 rheumatoid arthritis studies, cases of new or worsening heart failure have been reported for CIMZIA-treated patients. The majority of these cases were mild to moderate and occurred during the first year of exposure [see Warnings and Precautions (5.3)].

Autoantibodies

In clinical studies of 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 with concomitant 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)].

Immunogenicity

Patients with Crohn’s disease were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. In patients continuously exposed to CIMZIA, the overall percentage of patients who were antibody positive to CIMZIA on at least one occasion was 8%; approximately 6% were neutralizing in vitro. No association was observed between 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 = 1,413): abdominal pain (N = 1,242), abdominal 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, 15% (32/207) 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 (3% , 39 of 1,509) of these patients had antibodies w ith neutralizing activity. No association was seen between antibody development and the development of adverse events.

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

Hypersensitivity Reactions

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dermatitis, dizziness (postural), dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, skin discoloration, and vasovagal syncope [see Warnings and Precautions (5.4)].

6.2 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 their causal relationship to the 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 pustular and palmoplantar) have been identified during post-approval use of TNF blockers.

Immune System Disorders: sarcoidosis

Neoplasms benign, malignant and unspecified (including cysts and polyposis): Melanoma, Merkel cell carcinoma, mesothelioma, carcinoma in situ of the skin [see Warnings and Precautions (5.2)].

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 w ith CIMZIA.
SAFETY AND EFFECTIVENESS IN PEDIATRIC PATIENTS HAVE NOT BEEN ESTABLISHED. DUE TO ITS INHIBITION OF TNF, THE UNDERLYING MATERNAL CONDITION, CLINICAL NEED FOR CIMZIA® AND ANY POTENTIAL ADVERSE EFFECTS ON THE BREASTFED CHILD FROM CIMZIA® OR FROM THE EXPOSURE IN THE GASTROINTESTINAL TRACT ARE UNKNOWNS.

DATA

7.3 Laboratory Tests

CIMZIA® administered during pregnancy could affect immune responses in the in utero-exposed newborn similar to certolizumab pegol during organogenesis at up to 2.4 times the recommended human dose of 400 mg per month.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, 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, preterm delivery (before 37 weeks of gestation), low birth weight (<2500 g) and small for gestational age birth.

Fetal/Neonatal Adverse Reactions

Due to its inhibition of TNF, CIMZIA® administered during pregnancy could affect immune responses in the in utero-exposed newborn. Although certolizumab pegol concentration levels were low in 12 infants exposed to CIMZIA® in utero, the clinical significance of these low levels is unknown. Additional data available from one exposed infant suggests that CMZIA 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 CMZIA-exposed pregnancies with known outcomes (n=23), 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.

In an independent clinical study conducted in 10 pregnant women with Crohn's disease treated with CIMZIA®, certolizumab pegol concentrations were measured in maternal blood as well as cord and infant blood (n=12) at the day of birth. The last dose of CIMZIA® (400 mg for each mother) was given on average 19 days prior to delivery (range 5-42 days). Plasma certolizumab pegol concentrations were <0.41–1.86 µg/mL in cord blood, <0.41–1.58 µg/mL in infant blood, and 1.87–59.57 µg/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 0.94 µg/mL in the first 48 hours suggesting that CMZIA may be eliminated at a slower rate in infants than adults.

Animal Data

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

8.2 Lactation

Risk Summary

No data are available regarding the presence of certolizumab pegol in human milk, the effects on the breastfed infant, or the effects on milk production. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because certolizumab pegol is a large molecule and is degraded in the gastrointestinal tract. However, if certolizumab pegol is transferred into human milk, effects of local exposure in the gastrointestinal tract are unknown.

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 breastfeeding child from CIMZIA® or from the underlying maternal condition.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of CIMZIA® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger 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 overdose, it is recommended that patients be monitored closely for any adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

CIMZIA® (certolizumab pegol) is a TNFα binder. CIMZIA® is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα), conjugated to an approximately 40kDa polyethylene glycol (PEG)2MAL40K. The Fab' fragment is manufactured in E. coli and is subsequently subjected to purification and conjugation to PEG2MAL40K, to generate certolizumab pegol. The Fab' fragment is composed of a light chain with 214 amino acids and a heavy chain with 229 amino acids. The molecular weight of certolizumab pegol is approximately 91 kDa.

CIMZIA® is supplied as either a sterile, white, lyophilized powder for solution or as a sterile, solution in a single-use prefilled 1 mL glass syringe for subcutaneous injection. After reconstitution of the lyophilized powder with 1 mL sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial provides approximately 230 mg certolizumab pegol, 0.9 mg lactic acid, 0.1 mg polysorbate, and 100 mg sucrose. The pH of certolizumab pegol delivered in 1 mL of solution is a pH of approximately 4.7 for subcutaneous use. Each 1 mL syringe of CIMZIA® contains certolizumab pegol (200 mg), sodium acetate (1.36 mg), sodium chloride (7.31 mg), and Water for Injection, USP.

CIMZIA® is a clear to opalescent solution that is colorless to pale yellow and essentially free from particulates. No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CIMZIA® binds to human TNFα with KD of 90mM. TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes. CIMZIA® selectively neutralizes TNFα (IC50 of 4 pg/mL) for inhibition of human TNFα in the in vitro L929 murine fibrosarcoma cytotoxicity assay but does not neutralize lymphotoxin α (TNFα).

CIMZIA® pegol cross-reacts poorly with TNF from rodents and rabbits, therefore in vivo efficacy was evaluated using animal models in which human TNFα was the physiologically active molecule. CIMZIA® was shown to neutralize membrane-associated and soluble human TNFα in a dose-dependent manner. Incubation of monocytes with certolizumab pegol resulted in a dose-dependent inhibition of LPS-induced TNFα and IL-1β production in human monocytes.

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

A tissue reactivity study was carried out ex vivo to evaluate potential cross-reactivity of certolizumab pegol with cryoprecipitates of normal human tissues. CIMZIA® 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 stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNFα have been implicated in the pathology of chronic inflammatory diseases. Certolizumab pegol binds to TNFα, inhibiting its role as a key mediator of inflammation. TNFα is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal 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 synovial 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. Data from these studies demonstrate that single intravenous and subcutaneous doses of certolizumab pegol have predictable dose-related plasma concentrations with a linear relationship between the dose administered and the maximum plasma concentration (Cmax), and the Area Under the certolizumab pegol plasma concentration versus time Curve (AUC). A mean Cmax of approximately 4 ng/mL occurred at Week 5 during the initial loading dose regimen. The recommended dose regimen for the treatment of patients with rheumatoid arthritis (400 mg sc at Weeks 0, 2 and 4 followed by 200 mg every other week).

Certolizumab pegol plasma concentrations were broadly dose-proportional and pharmacokinetic observed in patients with rheumatoid arthritis and Crohn's disease were consistent with those seen in healthy subjects.

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

Distribution

The steady state volume of distribution (Vss) was estimated as 6 to 8 L in the population pharmacokinetic analysis for patients with Crohn's disease and patients with rheumatoid arthritis.

Metabolism

The metabolism of certolizumab pegol has not been studied in human subjects. Data from animals indicate that once cleaved from the Fab' fragment the PEG moiety is mainly excreted in urine without further metabolism.

Elimination

PEGylation, the covalent attachment of PEG polymers to peptides, delays the metabolism and elimination of these entities from the circulation by a variety of mechanisms, including reduced renal clearance, proteolysis, and immunogeneity. Accordingly, certolizumab pegol is an antibody Fab' fragment conjugated with PEG in order to extend the terminal plasma elimination half-life (t1/2) of the Fab'. The terminal elimination phase half-life (t1/2) was approximately 14 days for all doses tested. The clearance following IV administration to healthy
subjects ranged from 9.21 mL/h to 14.38 mL/h. The clearance following sc dosing was estimated 17 mL/h in the Crohn's disease population PK analysis with an inter-subject variability of 38% (CV) and an inter-occasion variability of 16%. Similarly, the clearance following sc dosing was estimated as 21.0 mL/h in the RA population PK analysis, with an inter-subject variability of 30.8% (CV) and inter-occasion variability 22.0%. The route of elimination of certolizumab pegol has not been studied in human subjects. Studies in animals indicate that the major route of elimination of the PE component is via urinary excretion.

Special Populations

- Population pharmacokinetic analysis was conducted on data from patients with rheumatoid arthritis and patients with Crohn's disease, to evaluate the effect of age, race, gender, methotrexate use, concomitant medication, creatinine clearance and presence of anti-certolizumab antibodies on pharmacokinetics of certolizumab pegol.
- Only bodyweight and presence of anti-certolizumab antibodies significantly affected certolizumab pegol pharmacokinetics. Pharmacokinetic exposure was inversely related to body weight but pharmacodynamic exposure-response analysis showed that no additional therapeutic benefit would be expected from a weight-adjusted dose regimen. The presence of anti-certolizumab antibodies was associated with a 3.6-fold increase in clearance.
- Age: Pharmacokinetics of certolizumab pegol was not different in elderly compared to young adults.
- Gender: Pharmacokinetics of certolizumab pegol was similar in male and female subjects.
- Renal Impairment: Specific clinical studies have not been performed to assess the effect of renal impairment on the pharmacokinetics of CIMZIA. The pharmacokinetics of the PEG (polyethylene glycol) fraction of certolizumab pegol is expected to be dependent on renal function but has not been assessed in renal impairment. There are insufficient data to provide a dosing recommendation in moderate and severe renal impairment.
- Race: A specific clinical study showed no difference in pharmacokinetics between Caucasian and Japanese subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

- Long-term animal studies of CIMZIA have not been conducted to assess its carcinogenic potential. Certolizumab pegol was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay and the mouse micronucleus assay.
- Since certolizumab pegol does not cross-react with mouse or rat TNFα, reproduction studies were performed in rats using a rodent anti-murine TNFα pegylated Fab fragment (cTN3 PF), similar to certolizumab pegol. The cTN3 PF had no effects on the fertility and general reproductive performance of male and female rats at intravenous doses up to 100 mg/kg, administered twice weekly.

14 CLINICAL STUDIES

14.1 Crohn's Disease

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

Study CD1

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

- The results for Study CD1 are provided in Table 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  Study CD1 – Clinical Response and Remission, Overall Study Population

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Placebo (N = 328)</th>
<th>CIMZIA 400 mg (N = 331)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>Clinical Response</td>
<td>27% (22%, 32%)</td>
</tr>
<tr>
<td></td>
<td>Clinical Remission</td>
<td>17% (13%, 22%)</td>
</tr>
<tr>
<td>Week 26</td>
<td>Clinical Response</td>
<td>27% (22%, 31%)</td>
</tr>
<tr>
<td></td>
<td>Clinical Remission</td>
<td>18% (14%, 22%)</td>
</tr>
<tr>
<td>Both Weeks 6 &amp; 26</td>
<td>Clinical Response</td>
<td>16% (12%, 20%)</td>
</tr>
<tr>
<td></td>
<td>Clinical Remission</td>
<td>10% (7%, 13%)</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 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 26. Patients who withdrew or who received rescue therapy were considered not to be in clinical response. Three randomized responders received no study injections, and were excluded from the ITT analysis.

- The results for clinical response and remission are shown in Table 3. At Week 26, a statistically significantly greater proportion of Week 6 responders were in clinical response and in clinical remission in the CIMZIA-treated group compared to the group treated with placebo.

Table 3  Study CD2 – Clinical Response and Clinical Remission

<table>
<thead>
<tr>
<th>Week 26</th>
<th>% Response or Remission (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 210)</td>
</tr>
<tr>
<td>Clinical Response</td>
<td>36% (30%, 43%)</td>
</tr>
<tr>
<td>Clinical Remission</td>
<td>29% (22%, 35%)</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 immunosuppressors 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 moderate to severely active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had ≥ 9 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 at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg or 400 mg of CIMZIA or placebo every other week, in combination with MTX for 52 weeks in Study RA-I and for 24 weeks in Study RA-II. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 24 (RA-I and RA-II) and modified Total Sharp Score (mTSS) at Week 52 (RA-II). The open-label extension follow-up study enrolled 846 patients who received 400 mg of CIMZIA every other week.

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

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

Clinical Response

- The percent of CIMZIA-treated patients achieving ACR20, 50, and 70 responses in Studies RA-I and RA-IV are shown in Table 4. CIMZIA-treated patients had higher ACR20, 50 and 70 response rates at 6 months compared to placebo-treated patients. The results in study RA-II (619 patients) were similar to the results in RA-I at Week 24. The results in study RA-III (247 patients) were similar to those seen in study RA-IV. Over the one-year Study RA-I, 13% of CIMZIA-treated patients achieved a major clinical response, defined as achieving an ACR70 response over a continuous 6-month period, compared to 1% of placebo-treated patients.

Table 4  ACR Responses in Studies RA-I, and RA-IV (Percent of Patients)

<table>
<thead>
<tr>
<th>Study RA-I</th>
<th>Methylprednisolone Combination (24 and 52 weeks)</th>
<th>Study RA-IV</th>
<th>Monotherapy (24 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Placebo + MTX (N = 198)</td>
<td>CIMZIA 400 mg</td>
<td>Placebo (N = 111)</td>
</tr>
<tr>
<td></td>
<td>200 mg + MTX g 2 weeks</td>
<td>g 4 weeks + MTX (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>14% 59% 45% (38%, 52%) 9% 46% 36% (25%, 47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td>13% 53% 40% (33%, 47%)  N/A N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td>8% 37% 30% (24%, 36%)  4% 23% 19% (10%, 28%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR50</td>
<td>8% 38% 30% (24%, 37%)  N/A N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR70</td>
<td>3% 21% 18% (14%, 23%)  0% 6% 6% (1%, 10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td>4% 21% 18% (13%, 22%)  N/A N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Clinical Response (a)</td>
<td>1% 13% 12% (8%, 15%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
* CIMZIA administered every 4 weeks not preceded by a loading dose regimen
* Major clinical response is defined as achieving ACR70 response over a continuous 6-month period
* 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution.
Table 5: Components of ACR Response in Studies RA-I and RA-IV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study RA-I</th>
<th>Study RA-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + MTX N=199</td>
<td>Placebo + MTX N=109</td>
</tr>
<tr>
<td></td>
<td>Placebo + MTX 200 mg + MTX q 2 weeks N=303</td>
<td>Placebo + MTX 400 mg q 4 weeks Monotherapy N=111</td>
</tr>
<tr>
<td>Number of tender joints (0-68)</td>
<td>28 (12.5) 24 (15.4)</td>
<td>30 (13.7) 16 (15.8)</td>
</tr>
<tr>
<td>Number of swollen joints (0-68)</td>
<td>20 (9.3) 16 (12.5)</td>
<td>21 (10.1) 12 (11.2)</td>
</tr>
<tr>
<td>Physician global assessment**</td>
<td>66 (64) 65 (63)</td>
<td>65 (64) 65 (32)</td>
</tr>
<tr>
<td>Patient global assessment**</td>
<td>67 (66) 64 (32)</td>
<td>63 (1.0) 6 (1.0)</td>
</tr>
<tr>
<td>Pain**</td>
<td>65 (64) 65 (32)</td>
<td>55 (20.8) 60 (26.7)</td>
</tr>
<tr>
<td>Disability index (HAQ)**</td>
<td>1.75 (0.65) 1.62 (0.68)</td>
<td>1.55 (0.63) 1.04 (0.74)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>16.0 (4.0)</td>
<td>11.3 (3.5)</td>
</tr>
</tbody>
</table>

* CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
** CIMZIA administered every 4 weeks not preceded by a loading dose regimen

The percentage 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.

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-I showed similar results at Week 24.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + MTX N=199 Mean (SD)</th>
<th>CIMZIA 200 mg + MTX N=303 Mean (SD)</th>
<th>CIMZIA 200 mg + MTX N=111 Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTSS</td>
<td>38 (49)</td>
<td>0.2 (0.2)</td>
<td>-1.1</td>
</tr>
<tr>
<td>Erosion Score</td>
<td>15 (24)</td>
<td>0.1 (1.5)</td>
<td>-0.7</td>
</tr>
<tr>
<td>JSN Score</td>
<td>24 (28)</td>
<td>2.2 (5.3)</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Response**</th>
<th>Placebo N=136</th>
<th>CIMZIA 200 mg q 2W N=138</th>
<th>CIMZIA 400 mg q 4W N=135</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>24%</td>
<td>58%</td>
<td>52%</td>
</tr>
<tr>
<td>ACR50</td>
<td>11%</td>
<td>36%</td>
<td>33%</td>
</tr>
<tr>
<td>ACR70</td>
<td>3%</td>
<td>25%</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

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 79% 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.

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 (65% confidence intervals for CIMZIA 200 mg minus placebo at weeks 12 and 24 of 25%, 45% and 30%, 51% respectively and 95% confidence intervals for CIMZIA 400 mg minus placebo at weeks 12 and 24 of 17%, 39% and 22%, 44% respectively). The results of the components of the ACR response criteria are shown in Table 8.

Patients with enthesitis at baseline were evaluated for mean improvement in Leeds Enthesitis Index (LEI). CIMZIA-treated patients receiving either 200 mg every 2 weeks or 400 mg every 4 weeks showed a reduction in enthesitis of 1.8 and 1.7, respectively as compared with a reduction in placebo-treated patients of 0.7 at week 12. Similar results were observed for this endpoint at week 24. Treatment with CIMZIA resulted in improvement in skin manifestations in patients with PsA. However, the safety and efficacy of CIMZIA in the treatment of patients with plaque psoriasis has not been established.

Table 8: Components of ACR Response in Studies RA-I and RA-IV

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study RA-I</th>
<th>Study RA-IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + MTX N=199</td>
<td>Placebo + MTX N=109</td>
</tr>
<tr>
<td></td>
<td>Placebo + MTX 200 mg + MTX q 2 weeks N=303</td>
<td>Placebo + MTX 400 mg q 4 weeks Monotherapy N=111</td>
</tr>
<tr>
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<td>Physician global assessment**</td>
<td>66 (64) 65 (63)</td>
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<tr>
<td>Patient global assessment**</td>
<td>67 (66) 64 (32)</td>
<td>63 (1.0) 6 (1.0)</td>
</tr>
<tr>
<td>Pain**</td>
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<td>Disability index (HAQ)**</td>
<td>1.75 (0.65) 1.62 (0.68)</td>
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<tr>
<td>CRP (mg/L)</td>
<td>16.0 (4.0)</td>
<td>11.3 (3.5)</td>
</tr>
</tbody>
</table>

* CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
** CIMZIA administered every 4 weeks not preceded by a loading dose regimen

In studies RA-I, RA-II, RA-III, and RA-IV, CIMZIA-treated patients achieved greater improvements from baseline than placebo-treated patients in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 24 (RA-II, RA-III and RA-IV) and at Week 52 (RA-IV).
Randomized Set. Non-responder imputation used for patients with missing data or those who escaped therapy.

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

Radiographic Response

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 from baseline was 0.18 in the placebo group compared with -0.02 in the CIMZIA 200 mg group; 95% CI for the difference was (-0.38, -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 (-0.47, -0.22) and 0.46 in the CIMZIA 400 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 for 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 10: Components of the ASAS response criteria and other measures of disease activity in AS patients at baseline and Week 12 in study AS-1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (N=57)</th>
<th>CIMZIA** (N=65)</th>
<th>CIMZIA*** (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>6.9</td>
<td>7.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Total spinal pain (0-10)</td>
<td>7.3</td>
<td>7.0</td>
<td>6.9</td>
</tr>
<tr>
<td>BASFI (0-10)</td>
<td>6.0</td>
<td>5.6</td>
<td>5.7</td>
</tr>
<tr>
<td>BASDAI (0-40)</td>
<td>6.4</td>
<td>6.5</td>
<td>6.2</td>
</tr>
<tr>
<td>BASMI (0-10)</td>
<td>4.8</td>
<td>4.4</td>
<td>4.3</td>
</tr>
</tbody>
</table>

* CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
** CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4
*** BASFI is Bath Ankylosing Spondylitis Functional Index
**** BASDAI is Bath Ankylosing Spondylitis Disease Activity Index
***** BASMI is Bath Ankylosing Spondylitis Metropology Index

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

The percent of AS patients achieving ASAS20 responses by visit for Study AS001 is shown in Figure 3. Among patients receiving CIMZIA, clinical responses were seen in some AS patients within one to two weeks after initiation of therapy.
What is the most important information I should know about CIMZIA?

CIMZIA® (certolizumab pegol) is a medicine that affects your immune system. CIMZIA® can lower the ability of the immune system to fight infections. Serious infections have happened in patients taking CIMZIA®. These infections include tuberculosis (TB) and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some patients have died from these infections.

- Your healthcare provider should test you for TB before starting CIMZIA®.
- Your healthcare provider should monitor you closely for signs and symptoms of TB during treatment with CIMZIA®.

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

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

- Think you have an infection, flu-like symptoms, or have any other symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes, HIV or a weak immune system. People with these conditions have a higher chance for infections
- have tuberculosis (TB), or have been in close contact with someone with TB
- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your healthcare provider if you are not sure
- live or have lived in certain parts of the country (such as the Ohio and Mississippi River valleys) where there is an increased risk for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may develop or become more severe if you take CIMZIA®. If you do not know if you have lived in an area where histoplasmosis, coccidioidomycosis, or blastomycosis is common, ask your healthcare provider.
- have or have had hepatitis B
- use the medicine Kineret® (anakinra), Orencia® (abatacept), Ritukey® (rituximab), or Tyasmbri® (natalizumab)

After starting CIMZIA®, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have open cuts or sores on your body, call your healthcare provider right away. CIMZIA® can make you more likely to get infections or make any infection that you may have worse.

Cancer

- For people taking TNF-blocker medicines, including CIMZIA®, the chances of getting lymphoma or other cancers may increase.
- There have been cases of cancers in children, teenagers, and young adults who received TNF-blocker medicine that do not usually happen in people this age.
- People with RA, especially more serious RA, may have a higher chance for getting a kind of cancer called lymphoma.
- Some people receiving TNF-blocker medicines, including CIMZIA®, have developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers and young adult males with Crohn's disease or ulcerative colitis. Also, most of these people had been treated with both a TNF-blocker medicine and another medicine called IMURANO® (azathioprine) or PURINETHOL® (6-mercaptourine, 6-MP).
- If you use TNF-blocker medicine, including CIMZIA®, your chance of developing certain kinds of skin cancer may increase. Tell your healthcare provider if any changes in the appearance of your skin, including growths on your skin, happen during or after your treatment.

What is CIMZIA®?

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

- Lessen the signs and symptoms of moderately to severely active Crohn's disease (CD) in patients who have not been helped enough by usual treatments
- Treat moderately to severely active rheumatoid arthritis (RA)
- Treat active psoriatic arthritis
- Treat active ankylosing spondylitis

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

CIMZIA® may not be right for you. Before starting CIMZIA®, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. (See, “What is the most important information I should know about CIMZIA?”)
- have or have had any type of cancer
- have congestive heart failure
- have seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis.
- are scheduled to receive a vaccine. Do not receive a live vaccine while taking CIMZIA®,
- are allergic to any of the ingredients in CIMZIA®. See the end of this Medication Guide for a list of
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 about how to prepare and inject your dose of CIMZIA, and how to properly throw away used syringes containing the needle.
• Do not give yourself an injection of CIMZIA unless you have been shown by your healthcare provider. A family member or friend can also be trained to help you give your injection. Talk to your healthcare provider if you have questions.
• CIMZIA is given by an injection under the skin. Your healthcare provider will tell you how much and how often to inject CIMZIA. Do not use more CIMZIA or inject more often than prescribed.
• You may need more than 1 injection at a time depending on your prescribed dose of CIMZIA.
• CIMZIA may be injected into your stomach or upper thighs. If you are prescribed more than 1 injection, each injection should be given at a different site in your stomach or upper thighs.
• Make sure the solution in the prefilled syringe is clear and colorless to yellow and free from particles. Do not use the CIMZIA prefilled syringe if the medicine is cloudy, discolored, or contains particles.
• Do not 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 healthcare provider should monitor you carefully before and during treatment with CIMZIA to see if you carry the hepatitis B virus in your blood. Tell your healthcare provider if you have any of the following symptoms:
  • feel unwell
  • skin or eyes look yellow
  • tiredness (fatigue)
  • poor appetite or vomiting
  • pain on the right side of your stomach (abdomen)

• New or worsening nervous system problems, such as multiple sclerosis (MS), Guillain-Barre syndrome, seizures, or inflammation of the nerves of the eyes. Symptoms may include:
  • dizziness
  • numbness or tingling
  • problems with your vision
  • weakness in your arms or legs
• Blood Problems. Your body may not make enough of the blood cells that help fight infections or help stop bleeding. Symptoms include a fever that does not go away, bruising or bleeding very easily, or looking very pale.
• Immune reactions including a lupus-like syndrome. Symptoms include shortness of breath, joint pain, or a rash on the cheeks or arms that worsens with sun exposure.

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 8 ºC).
• 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.