10 OVERDOSAGE

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

11 DESCRIPTION

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Certolizumab pegol binds to human TNFα with a KD of 90pM. TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNFα (IC_{90} of 4 ng/mL for inhibition of human TNFα in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralize lymphotoxin α (TNFβ). Certolizumab 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.

Certolizumab pegol 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.

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

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

12.2 Pharmacodynamics

Biological activities ascribed to 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 Crohn's disease. 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).

12.3 Pharmacokinetics

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

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

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

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

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

- **Absorption**

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

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

- **Distribution**

The steady state volume of distribution (Vss) was estimated as 6.4 L in the population pharmacokinetic analysis.

- **Metabolism and Elimination**

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

- **Drug Interaction Studies**

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

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

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

14 CLINICAL STUDIES

14.1 Crohn's Disease

The efficacy and safety of CIMZIA were assessed in two double-blind, randomized, placebo-controlled studies in patients aged 18 years and older with moderately to severely active Crohn's disease, as defined by a Crohn's Disease Activity Index (CDAI[1]) of 220 to 450 points, inclusive. CIMZIA was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn's disease were permitted.

Study CD1

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

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

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

Timepoint	% Response or Remission (95% CI)	
	Placebo (N = 328)	**CIMZIA 400 mg (N = 331)**
Week 6		
Clinical Response[#]	**27%** (22%, 32%)	**35%** (30%, 40%)*
Clinical Remission[#]	**17%** (13%, 22%)	**22%** (17%, 26%)
Week 26		
Clinical Response	**27%** (22%, 31%)	**37%** (32%, 42%)*
Clinical Remission	**18%** (14%, 22%)	**29%** (25%, 34%)*
Both Weeks 6 & 26		
Clinical Response	**16%** (12%, 20%)	**23%** (18%, 28%)*
Clinical Remission	**10%** (7%, 13%)	**14%** (11%, 18%)

* p-value < 0.05 logistic regression test
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Study CD2

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

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

Table 2 Study CD2 - Clinical Response and Clinical Remission

	% Response or Remission (95% CI)	
	CIMZIA 400 mg x3 + Placebo N = 210	**CIMZIA 400 mg N = 215**
Week 26		
Clinical Response[#]	**36%** (30%, 43%)	**63%** (56%, 69%)*
Clinical Remission[#]	**29%** (22%, 35%)	**48%** (41%, 55%)*

* $p < 0.05$
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

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

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

- **Pack Content**

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

NDC 50474-700-62

- **Storage and Stability**

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

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.2).

17.1 Patient Counseling

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

- **Immunosuppression**

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

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

- **Allergic Reactions**

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

- **Other Medical Conditions**

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

17.2 Medication Guide

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

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

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

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

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

Cimzia®
(certolizumab pegol)

Before starting CIMZIA, tell your doctor if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as a fever, cough, flu-like symptoms
- have any open cuts or sores on your body
- get a lot of infections or have infections that keep coming back
- have diabetes
- have HIV
- have tuberculosis (TB), or have been in close contact with someone with TB
- have or have had hepatitis B
- use the medicine Kineret® (anakinra)

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

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

What should I tell my doctor before starting treatment with CIMZIA?
CIMZIA may not be right for you. Before starting CIMZIA, tell your doctor about all of your medical conditions, including if you:

- **have an infection.** (See, 'What is the most important information I should know about CIMZIA?")
- **have or have had any type of cancer.**
- **have seizures, any numbness or tingling, or a disease that affects your nervous system such as multiple sclerosis**
- **have heart failure**
- **are scheduled to receive a vaccine.** Do not receive a live vaccine while taking CIMZIA.

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

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

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

How should I receive CIMZIA?

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

What are the possible side effects of CIMZIA?
Serious side effects have happened in patients taking CIMZIA including:

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

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

The most common side effects of CIMZIA are:

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

Injection site reactions happen in some people.

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

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

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

Cimzia®
(certolizumab pegol)

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

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

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

What are the ingredients in CIMZIA?

The active ingredient is certolizumab pegol.
The inactive ingredients in CIMZIA include: sucrose, lactic acid, polysorbate. No preservatives are present.

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

Product developed and manufactured for:
UCB, Inc.
1950 Lake Park Drive
Smyrna, GA 30080

US License No. 1736

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