PRODUCT MONOGRAPH

CIMZIA®

certolizumab pegol

Solution for Injection in a Single-use Pre-filled Glass Syringe, 200 mg/mL

Biological Response Modifier

CIMZIA (certolizumab pegol) should be prescribed by physicians who have sufficient knowledge of rheumatoid arthritis and/or psoriatic arthritis and/or ankylosing spondylitis and who have fully familiarized themselves with the efficacy/safety profile of CIMZIA.

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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients*
Subcutaneous (SC) injection	Solution for injection in a single-use pre-filled glass syringe / 200 mg/mL	None

** For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

CIMZIA (certolizumab pegol) is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα). The Fab' fragment is manufactured in *Escherichia coli* and is subsequently purified and conjugated to polyethylene glycol (PEG).

INDICATIONS AND CLINICAL USE

Rheumatoid Arthritis (RA)

CIMZIA (certolizumab pegol) in combination with methotrexate (MTX) is indicated for:

- reducing signs and symptoms, inducing major clinical response, and reducing the progression of joint damage as assessed by X-ray, in adult patients with moderately to severely active rheumatoid arthritis (RA).

CIMZIA may be used alone for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) who do not tolerate MTX.

Psoriatic Arthritis (PsA)

CIMZIA alone or in combination with methotrexate (MTX) is indicated for:

- reducing signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray, in adult patients with moderately to severely active psoriatic arthritis (PsA) who

have failed one or more disease-modifying anti-rheumatic drugs (DMARDs).

Ankylosing Spondylitis (AS)

CIMZIA is indicated for:

- reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy.

Geriatrics (≥ 65 years of age): Specific clinical studies have not been performed in elderly subjects (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Pediatrics (< 18 years of age): Safety and efficacy of CIMZIA in pediatric patients have not been established.

CONTRAINDICATIONS

- Patients with known hypersensitivity to CIMZIA (certolizumab pegol) or any of its components. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

- Patients with active tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections. (see WARNINGS AND PRECAUTIONS, Serious Infections).

- Patients with moderate to severe heart failure (NYHA Class III/IV) (see WARNINGS AND PRECAUTIONS, Heart Failure).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

SERIOUS INFECTIONS
SERIOUS INFECTIONS, SEPSIS, TUBERCULOSIS (INCLUDING MILIARY, DISSEMINATED AND EXTRAPULMONARY DISEASE), INVASIVE FUNGAL INFECTIONS (SUCH AS HISTOPLASMOSIS) AND OTHER OPPORTUNISTIC INFECTIONS, SOME OF WHICH HAVE BEEN FATAL, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF BLOCKING AGENTS INCLUDING CIMZIA (CERTOLIZUMAB PEGOL). MANY OF THE SERIOUS INFECTIONS REPORTED HAVE OCCURRED IN PATIENTS ON CONCOMITANT IMMUNOSUPPRESSIVE THERAPY THAT, IN ADDITION TO THEIR UNDERLYING DISEASE, COULD PREDISPOSE THEM TO INFECTIONS. CIMZIA SHOULD NOT BE GIVEN TO PATIENTS WITH A CLINICALLY IMPORTANT INFECTION, INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF CIMZIA IN PATIENTS WITH A HISTORY OF RECURRING INFECTION. PATIENTS SHOULD BE MONITORED FOR SIGNS AND SYMPTOMS OF INFECTION WHILE ON AND AFTER TREATMENT WITH CIMZIA.

ANY NEW INFECTION THAT DEVELOPS WHILE ON CIMZIA, OR AFTER RECENT TREATMENT, SHOULD BE CLOSELY MONITORED. CIMZIA SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION (see WARNINGS AND PRECAUTIONS, Serious Infections).

MALIGNANCY
LYMPHOMA AND OTHER MALIGNANCIES, SOME FATAL, HAVE BEEN REPORTED IN CHILDREN AND ADOLESCENT PATIENTS TREATED WITH TNF BLOCKERS, OF WHICH CIMZIA IS A MEMBER (see WARNINGS AND PRECAUTIONS, Malignancies). CIMZIA IS NOT INDICATED FOR USE IN PEDIATRIC PATIENTS.

Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, parasitic or other opportunistic pathogens including tuberculosis (TB), histoplasmosis, aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, legionellosis, listeriosis, nocardiosis and pneumocystosis have been reported in patients receiving TNF blocking agents. Patients have frequently presented with disseminated rather than localized disease and are often taking concomitant immunosuppressants that, in addition to their underlying disease, could predispose them to infections.

Treatment with CIMZIA should not be initiated in patients with an active infection, including clinically important localized infections. The risks and benefits of treatment should be considered prior to initiating therapy in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis
- with underlying conditions that may predispose them to infection

Patients must be monitored closely for signs and symptoms of serious infections before, during and after treatment with CIMZIA. Because the elimination of CIMZIA may take up to 5 months, monitoring should be continued throughout this period.

Patients with rheumatoid arthritis may not manifest typical symptoms of infection, including fever, due to their disease and concomitant drug therapies. Therefore, early detection of any infection, particularly atypical clinical presentations of a serious infection, is critical to minimize delays in diagnosis and initiation of treatment.

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.

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

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving CIMZIA, including patients who have previously received treatment for latent or active tuberculosis. Before initiation of therapy with CIMZIA, all patients must be evaluated for both active and inactive (latent) tuberculosis infection. This evaluation should include a detailed medical history of tuberculosis or possible previous exposure to patients with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, e.g. tuberculin skin test and chest X -ray, should be performed in all patients and interpreted in accordance with the current Canadian Tuberculosis Standards guidelines. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised.

If active tuberculosis is diagnosed, CIMZIA therapy must not be initiated. If latent tuberculosis is diagnosed or suspected, appropriate anti-tuberculosis prophylaxis should be instituted in accordance with the current Canadian Tuberculosis Standards guidelines before starting treatment with CIMZIA. In this situation, the benefit/risk balance of therapy with CIMZIA should be very carefully considered. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur during or after initiation of therapy with CIMZIA (see ADVERSE REACTIONS, Adverse Drug Reaction Overview, Infections, Tuberculosis and Opportunistic Infections).

In completed and ongoing clinical trials including 5118 CIMZIA-treated patients, the overall rate of tuberculosis is approximately 0.61 per 100 patient-years. The majority of cases occurred in countries with high endemic rates of tuberculosis. Reports include cases of pulmonary and disseminated tuberculosis. Some cases of tuberculosis have been fatal.

Malignancies

In clinical studies with CIMZIA and other TNF blocking agents, more cases of malignancies have been observed among patients receiving active drug than in placebo patients.

In rheumatoid arthritis placebo-controlled and open-label studies combined, most observed malignancies included lung, breast and ovarian cancers, basal cell carcinoma, and lymphoma. Three cases of lymphoma were reported in patients treated with CIMZIA (1 case in the placebo-controlled studies and 2 in the open-label studies), corresponding to a rate of 0.09 (0.02-0.27)/100 patient-years among 2367 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. Malignancies other than lymphomas and non-melanoma skin cancers were observed at a rate (95% confidence interval) of 0.61 (0.37-0.94)/100 patient-years among 2367 CIMZIA-treated patients and 0.41 (0.01-2.27)/100 patient-years among 647 placebo-treated patients.

The size of the control groups and limited duration of the controlled portions of the studies preclude the ability to draw firm conclusions but the possible risk for the development of lymphomas or other malignancies in patients treated with a TNF blocker cannot be excluded. The potential role of TNF blocking therapy in the development of malignancies is not known.

Rates in clinical trials for CIMZIA cannot be compared to rates for other TNF blockers and may not predict the rates observed in a broader patient population. Patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk for development of lymphoma (see ADVERSE REACTIONS, Adverse Drug Reaction Overview, Malignancies).

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF blocking agents (initiation of therapy ≤ 18 years of age), of which CIMZIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports.

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

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

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

Heart Failure
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with

TNF blockers, including CIMZIA. CIMZIA has not been formally studied in patients with CHF; however, in clinical studies in patients with CHF with another TNF blocker, worsening CHF and increased mortality due to CHF were observed. Exercise caution in patients with heart failure and monitor them carefully (see ADVERSE REACTIONS, Adverse Drug Reaction Overview, Heart Failure). CIMZIA is contraindicated in moderate to severe heart failure (see CONTRAINDICATIONS).

Hepatitis B Virus Reactivation

Use of TNF blockers, including CIMZIA, has been associated with reactivation of Hepatitis B virus (HBV) in patients who are chronic carriers of this virus (i.e. surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation.

Patients should be tested for HBV infection before initiating treatment with CIMZIA. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of Hepatitis B is recommended. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with TNF blocker therapy, in conjunction with anti-viral therapy, to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy. In patients who develop HBV reactivation, CIMZIA should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF blocker therapy after HBV reactivation is controlled is not known. In this situation, prescribers should exercise caution when considering resumption of CIMZIA therapy and monitor patients closely.

Hematological Reactions

Rare reports of pancytopenia, including aplastic anemia, have been reported with TNF blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) have been infrequently reported with CIMZIA. The causal relationship of these reports to CIMZIA remains unclear. Prescribers should exercise caution in considering the use of CIMZIA in patients who have or have had significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on CIMZIA. Discontinuation of CIMZIA therapy should be considered in patients with confirmed significant hematologic abnormalities.

Neurologic Reactions

Use of TNF blocking agents, of which CIMZIA is a member, has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, and with peripheral

demyelinating disease, including Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders. Neurological disorders, including seizure disorder, optic neuritis, and peripheral neuropathy have been reported in patients treated with CIMZIA. Causal relationship to CIMZIA remains unclear.

Use with Other Biologic Medicines

The use of CIMZIA in combination with other biologic medicines has not been studied. 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. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of CIMZIA and other biologic disease modifying anti-rheumatic drugs (DMARDs). Therefore, the use of CIMZIA in combination with other biologic DMARDs is not recommended (see DRUG INTERACTIONS).

Switching between Biologic DMARDs

When switching from one biologic DMARD to another, patients should continue to be monitored for signs of infection.

Surgery

There is limited safety experience with surgical procedures in patients treated with CIMZIA. The 14 day half-life of certolizumab pegol should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on CIMZIA should be closely monitored for infections, and appropriate actions should be taken.

Hypersensitivity

The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following CIMZIA administration to patients: angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration of CIMZIA. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed.

Autoimmunity

Treatment with CIMZIA may result in the formation of autoantibodies. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with CIMZIA, treatment should be discontinued (see ADVERSE REACTIONS, Adverse Drug Reaction Overview, Autoantibodies).

Immunizations
Patients treated with CIMZIA may receive vaccinations, except for live or live-attenuated vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA. Do not administer live or live-attenuated vaccines concurrently with CIMZIA.

In a placebo-controlled clinical trial of patients with rheumatoid arthritis, no difference was detected in antibody response between CIMZIA and placebo treatment groups when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with CIMZIA. Similar proportions of patients developed protective levels of antibodies between CIMZIA and placebo treatment groups; however, patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared with patients receiving CIMZIA alone. The clinical significance of this is unknown. CIMZIA does not suppress the humoral immune response to the pneumococcal polysaccharide vaccine or influenza vaccine.

Immunosuppression
Since TNF mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blocking agents, including CIMZIA, to affect host defenses against infections and malignancies. The impact of treatment with CIMZIA on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood. The use of CIMZIA in patients with severe immunosuppression has not been formally evaluated (see ADVERSE REACTIONS, Adverse Drug Reaction Overview, Infections, Tuberculosis and Opportunistic Infections, Malignancies).

Laboratory Tests
Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated activated partial thromboplastin time (aPTT) assay results in patients without coagulation abnormalities. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation. After patients receive CIMZIA, careful attention should be used in selecting the type of method used to measure coagulation (see DRUG INTERACTIONS, Drug-Laboratory Interactions**)**

Carcinogenesis and Mutagenesis
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.

Special Populations

Women of Childbearing Potential: Women of childbearing potential should use adequate contraception to prevent pregnancy and continue its use for at least 5 months after the last CIMZIA administration.

Pregnant Women: There are no adequate and well-controlled studies of CIMZIA in pregnant women. Since certolizumab pegol does not cross-react with mouse or rat TNFα, reproductive studies were performed in rats using a rodent anti-murine TNFα PEGylated Fab' fragment (cTN3 PF) similar to certolizumab pegol. Doses up to and including 100 mg/kg revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF. Because animal reproduction and developmental studies are not always predictive of human response, CIMZIA should be used during pregnancy only if clearly needed.

Pre-clinical data suggest that active placental transfer of IgGs is mediated by the Fc part of an antibody binding to the neonatal Fc receptor (FcRn). Certolizumab pegol consists of just the Fab part of an antibody and does not contain an Fc part. In reproduction studies in rats cTN3 γ1 (a surrogate full antibody to certolizumab including an Fc part) was transferred to the fetus during gestation. However, there was little or no measurable transfer of cTN3 PF (surrogate Fab´fragment to certolizumab without an Fc) to the fetus when compared to maternal plasma concentrations, indicating that the Fc portion of the antibody appears to be an important factor for placental transfer.

Administration of live vaccines to infants exposed to CIMZIA *in utero* is not recommended for a minimum of 5 months following the mother's last CIMZIA administration during pregnancy.

Nursing Women: It is not known whether CIMZIA is excreted in human milk or absorbed systemically. Rodent studies have shown limited excretion of cTN3 PF (a rodent anti-murine TNFα PEGylated Fab' fragment similar to certolizumab pegol) in milk. Because many drugs and immunoglobulins are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CIMZIA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatrics (< 18 years of age): Safety and efficacy of CIMZIA in pediatric patients have not been established.

Geriatrics (≥ 65 years of age): Specific clinical studies have not been performed in elderly subjects. Because there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse reactions were (see WARNINGS AND PRECAUTIONS):

- Serious infections
- Malignancies
- Heart failure

Rheumatoid Arthritis

The data described below reflect the exposure to CIMZIA (certolizumab pegol) in 2367 RA patients, including 2030 exposed for at least 6 months, 1663 exposed for at least one year and 282 for at least 2 years and 1774 in adequate and well-controlled studies. CIMZIA was studied primarily in placebo-controlled trials and in long-term follow-up studies. In placebo-controlled studies, the population had a median age of 53 years at entry; approximately 80% were female, 93% were Caucasian and all patients were suffering from active RA, with a median disease duration of 6.2 years. Most patients received the recommended dose of CIMZIA or higher.

The most commonly occurring adverse reactions, reported in a greater percentage of CIMZIA-treated patients in all placebo-controlled trials (difference ≥2%) were upper respiratory tract infections (17.6% for CIMZIA, 9.4% for placebo), lower respiratory tract and lung infections (5.6% for CIMZIA, 3.4% for placebo), musculoskeletal and connective tissue signs and symptoms (6.7% for CIMZIA, 4.2% for placebo), herpes viral infections (3.6% for CIMZIA, 1.2% for placebo), rashes, eruptions and exanthems (4.0% for CIMZIA, 1.3% for placebo), and vascular hypertensive disorders (5.1% for CIMZIA, 1.2% for placebo).

The percentage of patients who discontinued treatment due to adverse reactions during the phase III RA placebo-controlled studies were 5% for CIMZIA-treated patients and 2.5% for placebo-treated patients. The most common adverse reactions leading to discontinuation of CIMZIA were tuberculosis infections (0.5%); and pyrexia, urticaria, pneumonia, and rash (0.3%).

Deaths

In the placebo-controlled studies, 9 of 1774 patients (0.51%) who received CIMZIA at any dose, compared with 1 of 647 patients (0.15%) who received placebo, died. The most common causes leading to death in patients who received CIMZIA were cardiovascular events and/or infections. All cardiovascular deaths were in patients with pre-existing history of cardiovascular conditions.

In the combined placebo-controlled and open-label studies in patients with RA, 28 deaths occurred in patients who received CIMZIA over 3218.0 patient-years of exposure (1 death per 115 patient-years) and 1 death occurred in a placebo-treated patient over 224.9 patient-years of exposure (1 death per 225 patient-years). Cardiovascular (primarily in predisposed patients)

and/or infectious events were the most common causes leading to death in patients who received CIMZIA.

Infections
The incidence of new cases of infections in placebo-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 placebo-controlled studies, there were more new cases of serious infection adverse reactions in the CIMZIA treatment groups, compared to the placebo groups (0.06 per patient-year for all CIMZIA doses vs. 0.02 per patient-year for placebo). Rates of serious infections in the 200 mg every other week dose group were 0.06 per patient-year and 0.04 in the 400 mg every 4 weeks dose group. Serious infections included tuberculosis, pneumonia, cellulitis, pyelonephritis, and erysipelas. 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, Serious Warnings and Precautions).

Tuberculosis and Opportunistic Infections
In placebo-controlled and open-label rheumatoid arthritis studies, there were 36 cases of TB reported which occurred with CIMZIA treatment and none on placebo. The majority of cases occurred in countries with high endemic rates of TB. Reports include cases of miliary, lymphatic, peritoneal, as well as pulmonary TB. In rare cases, tuberculosis has been fatal. Rare cases of opportunistic infections have also been reported in these clinical trials (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions, Serious Infections).

Malignancies
A total of 12 malignancies were identified during the placebo-controlled studies. Eleven patients (0.6%) among 1774 patients receiving CIMZIA and 1 patient (0.2%) among 647 patients receiving placebo experienced malignancies. In the controlled and uncontrolled studies, there were 30 malignancies among 2367 CIMZIA-treated patients.

Lymphoma
In rheumatoid arthritis placebo-controlled and open-label studies combined, 3 cases of lymphoma were reported in patients treated with CIMZIA (1 case in the placebo-controlled studies and 2 in the open-label studies), corresponding to a rate of 0.09 (0.02-0.27)/100 patient-years among 2367 patients. No lymphoma was reported among 647 placebo-treated patients.

Non-Lymphoma Malignancies
In the rheumatoid arthritis placebo-controlled studies, 8 patients (0.045%) treated with CIMZIA and 1 patient (0.2%) in the placebo group experienced malignancies other than lymphomas and non-melanoma skin cancers (NMSC).

In rheumatoid arthritis placebo-controlled and open-label studies combined, 20 malignancies other than lymphomas and non-melanoma skin cancers were observed at a rate (95% confidence interval) of 0.61 (0.37-0.94)/100 patient-years among 2367 CIMZIA-treated patients and 1 malignancy (bladder cancer) at a rate of 0.41 (0.01-2.27)/100 patient years among 647 placebo-treated patients. Observed malignancies included 1 endocrine, 5 gastrointestinal, 2 breast, 1 hepatobiliary, 7 reproductive, 2 renal and urinary tract, 1 respiratory tract and 1 metastases malignancies.

Non-Melanoma Skin Cancers

In the rheumatoid arthritis placebo-controlled studies, non-melanoma skin cancers occurred in 2 patients (0.1%) receiving CIMZIA and no patient in the placebo group. In the controlled and uncontrolled studies, there were a total of 5 (6 events) non-melanoma skin cancers reported (see WARNINGS AND PRECAUTIONS, Malignancies).

Cardiovascular Disorders

In the placebo-controlled studies, the percentage of patients with any event in the cardiac disorders System Organ Class (SOC) was 3.4% in the CIMZIA-treated group (1.60 events per 100 patient-years) and 2.0% in the placebo group (1.23 events per 100 patient-years). Sixteen patients in the CIMZIA-treated group (0.9%; 1.63 per 100 patient-years) versus 3 patients in the placebo group (0.5%; 1.69 per 100 patient-years) reported a serious event in the cardiac disorders SOC.

In the CIMZIA-treated group, the most common cardiovascular events at the high level term across SOCs, compared with placebo, were vascular hypertensive disorders (5.1% vs. 1.2%), rate and rhythm disorders (1.0% vs. 0.2%), ischaemic coronary artery disorders (0.7% vs. 0.3%), peripheral embolism and thrombosis (0.6% vs. 0), and supraventricular arrhythmias (0.6% vs. 0.5%). Four patients (0.2%) experienced cerebrovascular accidents (CVAs) and 4 patients (0.2%) experienced transient ischaemic attacks (TIAs) in the CIMZIA-treated group, compared with 1 patient (0.2%) who experienced a CVA in the placebo group. One patient, each, in the CIMZIA-treated and placebo groups experienced a pulmonary embolism. Three patients in the CIMZIA-treated group experienced hypertension events, including 2 vascular hypertension and 1 malignant hypertension events, compared with no patient in the placebo group.

Heart Failure

In placebo-controlled studies, 1 patient (0.1%) reported cardiac failure (0.11 per 100 patient-years) in the CIMZIA-treated patient group, compared to no patient in the placebo group. In the open-label rheumatoid arthritis studies, an additional 6 patients (0.3%) reported cardiac failure (where cardiac failure was the primary event), and of these, 3 died. All patients with cardiac failure events had other risk factors for cardiac disease.

The incidence rate per 100 patient years of cardiac failure in both placebo-controlled and open-label studies was 0.18 (see WARNINGS AND PRECAUTIONS, Heart Failure).

Hepatic

In placebo-controlled rheumatoid arthritis studies, the adverse events of ALT elevated occurred in 2.6% of CIMZIA-treated and 2.3% of placebo-treated patients, and AST elevated occurred in 1.9% of CIMZIA and placebo-treated patients. Hepatic adverse events occurred in 1.7% of CIMZIA-treated patients and 1.1% of placebo-treated patients. In placebo-controlled and open-label rheumatoid arthritis studies combined, the incidence of hepatic adverse events in CIMZIA-treated patients was 2.07 per 100 patient years, as compared to 2.87 per 100 patient years during the placebo-controlled rheumatoid arthritis studies.

Autoantibodies

In placebo-controlled rheumatoid arthritis studies, there was no clinically meaningful increase in ANA or double-stranded DNA conversion noted for CIMZIA-treated patients at any dose. For subjects who were ANA negative at baseline, 16.7% of those treated with CIMZIA developed positive ANA titers, compared with 12.0% of subjects in the placebo group. Taking into account the difference in exposure between the 2 groups, there is no increased risk of developing a positive ANA with CIMZIA treatment. In both placebo-controlled and long-term follow-up studies for rheumatoid arthritis there were 3 cases of lupus-like syndrome, including one patient who had manifestations of lupus prior to treatment with CIMZIA. There have been rare reports of other immune-mediated conditions; the causal relationship to CIMZIA is not known. The impact of long-term treatment with CIMZIA on the development of autoimmune diseases is unknown.

Immunogenicity

The overall percentage of patients with antibodies to CIMZIA detectable on at least one occasion was 7% in the phase III RA placebo-controlled trials. Approximately one third (3%) of these patients had antibodies with neutralizing activity *in vitro*. Patients treated with concomitant immunosuppressants (methotrexate) had a lower rate of antibody development than patients not taking immunosuppressants at baseline. Antibody formation was associated with lowered drug plasma concentration and reduced efficacy. 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 pegol in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to certolizumab pegol with the incidence of antibodies to other TNF blocking agents is not appropriate.

Psoriatic Arthritis

CIMZIA has been studied in 409 patients with psoriatic arthritis (PsA) in a 24 Week double-blind placebo-controlled trial that included a follow-up CIMZIA dose-blind treatment period (Week 24 to 48) and an open label treatment period (Week 48 to 158). The safety profile for patients with PsA treated with CIMZIA was consistent to the safety profile seen in patients with RA and previous experience with CIMZIA, except that more patients in the PsA trial reported neutropenia, cellulitis, pneumonia and hepatic enzyme elevations (see Clinical Trial Adverse Drug Reactions, Table 3).

In addition, there were two deaths (cardiac arrest, sudden death) reported during the 24 Week double-blind treatment period. Four additional deaths (breast cancer, myocardial infarction, sepsis, lymphoma) occurred after patients completed the 24 Week double-blind treatment period (during the follow-up CIMZIA dose-blind or open label treatment periods). Three of the deaths (sepsis [laboratory tests revealed the presence of *Klebsiella pneumoniae* and *Pseudomonas aeuriginosa*], lymphoma, sudden death) were considered at least possibly related.

During the 24 Week double-blind treatment period, serious adverse events occurring more often in patients receiving CIMZIA were infections, including bronchopneumonia, herpes zoster, pneumonia, and bronchitis, pleurisy, hepatic enzyme increased, and cutaneous lupus erythematosus.

There were two malignancies (cervix carcinoma [CIMZIA treatment group], breast cancer [placebo treatment group]), reported during the 24 Week double-blind treatment period. Four additional malignancies (breast cancer [2 events], lymphoma, thyroid neoplasm) were reported after patients completed the 24 Week double-blind treatment period (during the follow-up CIMZIA dose-blind or open label treatment periods).

During the 24 Week double-blind treatment period, the incidence of treatment emergent adverse events leading to permanent withdrawal was 3% in the all CIMZIA treatment group and 1.5 % in the placebo group.

Through the 24 Week double-blind treatment period and follow-up CIMZIA dose-blind or open label treatment periods, females reported almost double the number of adverse events.

Immunogenicity
The overall percentage of patients with antibodies to CIMZIA detectable on at least one occasion up to Week 24 was 11.7% in the Phase III placebo-controlled trial in patients with psoriatic arthritis. Antibody formation was associated with lowered drug plasma concentration. The incidence of trial discontinuation due to treatment emergent adverse events was similar regardless of patient anti-CIMZIA antibody status. The incidence of serious adverse events was higher in patients with antibodies to CIMZIA compared with antibody negative patients (11.1% vs. 6.1% respectively). However, the number of patients with antibodies to CIMZIA in this trial was insufficient to make valid conclusions on the effects of the antibody formation on efficacy and safety.

Ankylosing Spondylitis
CIMZIA has been studied in 325 patients with axial spondyloarthritis of whom the majority had ankylosing spondylitis (AS) in a 24 Week double-blind placebo-controlled trial (AS-1) that included a follow-up CIMZIA dose-blind treatment period (Week 24 to 48) and an open-label treatment period (Week 48 to Week 158). The safety profile for patients in study AS-1 treated with CIMZIA was consistent with the safety profile in patients with RA and previous experience with CIMZIA except that more patients reported creatine phosphokinase (CPK) elevations. The CPK elevations were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal.

No deaths were reported during the 24 Week double-blind treatment period nor after patients completed the 24 Week double-blind treatment period (during the follow-up CIMZIA dose-blind or open-label treatment periods).

During the 24 Week double-blind treatment period, serious adverse reactions occurring more often in patients receiving CIMZIA were infections, including appendicitis and esophageal candidiasis, retinal vein occlusion, and hypersensitivity.

There were no malignancies reported during the 24 Week double-blind treatment period. Two pulmonary nodules were reported during the follow-up CIMZIA dose-blind and open-label treatment periods. These non-neoplastic nodules were considered non-serious, unrelated to drug therapy and did not result in any change in drug therapy.

During the 24 Week double-blind treatment period, the incidence of treatment emergent adverse events leading to permanent withdrawal was 2.2% in the all CIMZIA treatment group and 1.9 % in the placebo group.

Immunogenicity
The overall percentage of patients with antibodies to CIMZIA detectable on at least one occasion up to Week 24 was 4.4% in study AS-1. 5.9% of the AS patients had antibodies to CIMZIA detectable on at least one occasion. Antibody formation was associated with lowered drug

plasma concentration. However, the number of patients with antibodies to CIMZIA in this trial was insufficient to make valid conclusions on the effects of the antibody formation on efficacy and safety.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 summarizes the adverse reactions reported at a rate of at least 1% in patients treated with CIMZIA 200 mg every other week compared to placebo, given concomitantly with methotrexate in the phase III RA placebo-controlled studies. Table 2 summarizes the adverse reactions reported at a rate of at least 1% in patients treated with CIMZIA 400 mg every 4 weeks, compared to placebo, given without concomitant methotrexate in the phase III RA placebo-controlled study. Table 3 summarizes the adverse reactions reported at a rate of at least 1% in patients treated with CIMZIA 200 mg every other week or 400 mg every 4 weeks and at a frequency higher than placebo in the phase III PsA placebo-controlled study. Table 4 summarizes the adverse reactions reported at a rate of at least 1% in patients treated with CIMZIA 200 mg every other week or 400 mg every 4 weeks and at a frequency higher than placebo in the phase III AS-1 placebo-controlled study.

Table 1: Adverse Reactions Reported by ≥1% of Patients Treated with CIMZIA 200 mg Dosed Every Other Week during Phase III Rheumatoid Arthritis Placebo-Controlled Studies, with Concomitant Methotrexate

Primary System Organ Class **Adverse Event (Preferred Term)**	**Placebo + MTX (N=324) n (%)**	**CIMZIA 200 mg EOW + MTX (N=640) n (%)**
Blood and lymphatic system disorders		
Eosinophilia	3 (0.9)	17 (2.7)
Leukopenia	4 (1.2)	8 (1.3)
Eye disorders		
Conjunctivitis	1 (0.3)	8(1.3)
Gastrointestinal disorders		
Abdominal pain	1 (0.3)	8 (1.3)
Abdominal pain upper	1 (0.3)	11 (1.7)
Diarrhoea	5 (1.5)	10 (1.6)
Dyspepsia	7 (2.2)	15 (2.3)
Gastritis	0 (0.0)	9 (1.4)
Toothache	3 (0.9)	10 (1.6)
Vomiting	3 (0.9)	11 (1.7)

Primary System Organ Class **Adverse Event (Preferred Term)**	**Placebo + MTX (N=324) n (%)**	**CIMZIA 200 mg EOW + MTX (N=640) n (%)**
General disorders and administration site conditions		
Fatigue	7 (2.2)	19 (3.0)
Injection site discolouration	0 (0.0)	7 (1.1)
Injection site erythema	0 (0.0)	7 (1.1)
Injection site haematoma	0 (0.0)	8 (1.3)
Injection site pain	0 (0.0)	8 (1.3)
Injection site reaction	0 (0.0)	9 (1.4)
Pyrexia	6 (1.9)	21 (3.3)
Infections and infestations		
Bronchitis	4 (1.2)	9 (1.4)
Bronchitis acute	4 (1.2)	19 (3.0)
Herpes simplex	1 (0.3)	16 (2.5)
Influenza	7 (2.2)	18 (2.8)
Nasopharyngitis	4 (1.2)	29 (4.5)
Pharyngitis	3 (0.9)	20 (3.1)
Respiratory tract infection	0 (0.0)	15 (2.3)
Respiratory tract infection viral	2 (0.6)	10 (1.6)
Rhinitis	2 (0.6)	13 (2.0)
Sinusitis	3 (0.9)	14 (2.2)
Tonsillitis	1 (0.3)	7 (1.1)
Upper respiratory tract infection	7 (2.2)	35 (5.5)
Viral infection	0 (0.0)	9 (1.4)
Investigations		
Activated partial thromboplastin time prolonged	2 (0.6)	12 (1.9)
Blood alkaline phosphatase increased	0 (0.0)	7 (1.1)
Gamma-glutamyltransferase increased	3 (0.9)	10 (1.6)
Hepatic enzyme increased	6 (1.9)	14 (2.2)
Musculoskeletal and connective tissue disorders		
Arthralgia	6 (1.9)	16 (2.5)
Back pain	3 (0.9)	23 (3.6)
Pain in extremity	2 (0.6)	8 (1.3)
Nervous system disorders		
Headache	12 (3.7)	31 (4.8)
Psychiatric disorders		
Anxiety	2 (0.6)	10 (1.6)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (0.6)	12 (1.9)
Pharyngolaryngeal pain	0 (0.0)	9 (1.4)
Skin and subcutaneous tissue disorders		
Rash	2 (0.6)	20 (3.1)
Vascular disorders		
Hypertension	4 (1.2)	31 (4.8)

EOW = Every Other Week, MTX = Methotrexate

Table 2: Adverse Reactions Reported by ≥1% of Patients Treated with CIMZIA 400 mg Dosed Every 4 Weeks during the Phase III Rheumatoid Arthritis Placebo-Controlled Study, without Concomitant Methotrexate

Primary System Organ Class Adverse Event (Preferred Term)	Placebo (N=109) n (%)	CIMZIA 400 mg E4W (N=111) n (%)
Gastrointestinal disorders		
Diarrhoea	3 (2.8)	8 (7.2)
Dry mouth	0 (0.0)	2 (1.8)
Gastritis	0 (0.0)	2 (1.8)
General disorders and administration site conditions		
Chest pain	1 (0.9)	3 (2.7)
Injection site rash	0 (0.0)	2 (1.8)
Injection site reaction	2 (1.8)	3 (2.7)
Infections and infestations		
Influenza	0 (0.0)	5 (4.5)
Sinusitis	4 (3.7)	6 (5.4)
Upper respiratory tract infection	6 (5.5)	10 (9.0)
Injury, poisoning and procedural complications		
Arthropod bite	0 (0.0)	2 (1.8)
Investigations		
Blood creatine phosphokinase increased	0 (0.0)	4 (3.6)
Gamma-glutamyltransferase increased	2 (1.8)	3 (2.7)
Haemoglobin decreased	1 (0.9)	2 (1.8)
Musculoskeletal and connective tissue disorders		
Muscle cramp	0 (0.0)	3 (2.7)
Myalgia	0 (0.0)	2 (1.8)
Osteoporosis	0 (0.0)	2 (1.8)
Rheumatoid arthritis aggravated	0 (0.0)	2 (1.8)
Nervous System Disorders		
Dizziness	1 (0.9)	2 (1.8)
Headache	9 (8.3)	13 (11.7)
Psychiatric disorders		
Depression	0 (0.0)	3 (2.7)
Reproductive system and breast disorders		
Menometrorrhagia	0 (0.0)	2 (1.8)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	1 (0.9)	2 (1.8)
Nasopharyngitis	4 (3.7)	6 (5.4)
Pharyngitis	1 (0.9)	3 (2.7)
Respiratory tract congestion	0 (0.0)	2 (1.8)
Sinus congestion	1 (0.9)	4 (3.6)
Skin and subcutaneous tissue disorders		
Hypotrichosis	0 (0.0)	2 (1.8)
Pruritus	0 (0.0)	3 (2.7)

E4W = Every 4 Weeks

Table 3: Adverse Reactions Reported by ≥1% of Patients Treated with CIMZIA 200 mg Dosed Every Other Week or 400 mg Dosed Every 4 Weeks and at a Frequency Higher than Placebo in the Phase III PsA Placebo-Controlled Study

Primary System Organ Class **Adverse Event (Preferred Term)**	**Placebo** **(N=136)** **n (%)**	**CIMZIA 200 mg EOW** **(N=138)** **n (%)**	**CIMZIA 400 mg E4W** **(N=135)** **n (%)**
Blood and lymphatic system disorders			
Neutropenia	0 (0.0)	0 (0.0)	4 (3.0)
Gastrointestinal disorders			
Diarrhoea	0 (0.0)	0 (0.0)	2 (1.5)
General disorders and administration site conditions			
Fatigue	1 (0.7)	2 (1.4)	2 (1.5)
Injection site erythema	0 (0.0)	0 (0.0)	2 (1.5)
Injection site haematoma	0 (0.0)	0 (0.0)	3 (2.2)
Injection site pain	2 (1.5)	3 (2.2)	1 (0.7)
Injection site reaction	1 (0.7)	2 (1.4)	4 (3.0)
Infections and infestations			
Cellulitis	0 (0.0)	1 (0.7)	2 (1.5)
Influenza	1 (0.7)	2 (1.4)	2 (1.5)
Nasopharyngitis	3 (2.2)	4 (2.9)	2 (1.5)
Pharyngitis	0 (0.0)	3 (2.2)	2 (1.5)
Pneumonia	0 (0.0)	1 (0.7)	2 (1.5)
Upper respiratory tract infection	3 (2.2)	3 (2.2)	4 (3.0)
Vaginal infection	0 (0.0)	2 (1.4)	0 (0.0)
Investigations			
Alanine aminotransferase increased	2 (1.5)	4 (2.9)	3 (2.2)
Aspartate aminotransferase increased	1 (0.7)	3 (2.2)	1 (0.7)
Blood creatine phosphokinase increased	1 (0.7)	2 (1.4)	1 (0.7)
Gamma-glutamyltransferase increased	1 (0.7)	2 (1.4)	1 (0.7)
Hepatic enzyme increased	1 (0.7)	5 (3.6)	1 (0.7)
Nervous system disorders			
Headache	0 (0.0)	3 (2.2)	1 (0.7)

EOW= Every Other Week, E4W= Every 4 Weeks

Table 4: Adverse Reactions Reported by ≥1% of Patients Treated with CIMZIA 200 mg Dosed Every Other Week or 400 mg Dosed Every 4 Weeks and at a Frequency Higher than Placebo in the Phase III AS-1 Placebo-Controlled Study

Primary System Organ Class **Adverse Event (Preferred Term)**	**Placebo (N=107) n (%)**	**CIMZIA 200 mg EOW (N=111) n (%)**	**CIMZIA 400 mg E4W (N=107) n (%)**
Blood and lymphatic system disorders			
Neutropenia	0 (0.0)	2 (1.8)	1 (0.9)
General disorders and administration site conditions			
Fatigue	0 (0.0)	3 (2.7)	1 (0.9)
Injection site erythema	0 (0.0)	3 (2.7)	3 (2.8)
Injection site haematoma	0 (0.0)	3 (2.7)	0 (0.0)
Immune system disorders			
Hypersensitivity	0 (0.0)	0 (0.0)	2 (1.9)
Infections and infestations			
Bronchitis	0 (0.0)	2 (1.8)	0 (0.0)
Oral herpes	0 (0.0)	2 (1.8)	1 (0.9)
Pharyngitis	0 (0.0)	3 (2.7)	1 (0.9)
Nasopharyngitis	0 (0.0)	3 (2.7)	4 (3.7)
Tonsillitis	0 (0.0)	2 (1.8)	0 (0.0)
Upper respiratory tract infections	1 (0.9)	3 (2.7)	3 (2.8)
Investigations			
Alanine aminotransferase increased	0 (0.0)	2 (1.8)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	2 (1.8)	0 (0.0)
Blood creatine phosphokinase increased	0 (0.0)	3 (2.7)	2 (1.9)
Metabolism and nutrition disorders			
Decreased appetite	0 (0.0)	2 (1.8)	0 (0.0)
Nervous system disorders			
Headache	2 (1.9)	3 (2.7)	0 (0.0)
Psychiatric disorders			
Sleep disorder	0 (0.0)	0 (0.0)	2 (1.9)
Respiratory, thoracic and mediastinal disorders			
Cough	0 (0.0)	2 (1.8)	0 (0.0)
Skin and subcutaneous tissue disorders			
Dermatitis allergic	0 (0.0)	0 (0.0)	2 (1.9)
Pruritus generalised	1 (0.9)	2 (1.8)	0 (0.0)

EOW= Every Other Week, E4W= Every 4 Weeks

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Other infrequent adverse drug reactions occurring at an incidence of less than 1% in patients treated with CIMZIA in placebo-controlled and open label trials were:

Blood and lymphatic system disorders: anaemia, thrombocytopenia, neutropenia, lymphopenia, lymphadenopathy, thrombocytosis, pancytopenia, splenomegaly, erythrocytosis, white blood cell morphology abnormal

Cardiac disorders: cardiomyopathies (includes heart failure), ischemic coronary artery disorders (includes myocardial infarction, angina pectoris), arrhythmias (includes atrial fibrillation), palpitations, pericarditis, atrioventricular block, tachycardia

Ear and labyrinth disorders: vertigo, hearing loss, tinnitus

Endocrine disorders: thyroid disorders

Eye disorders: eye and eyelid inflammation, visual disorder (includes decreased vision), lacrimation disorder, corneal erosion

Gastrointestinal disorders: nausea, ascites, gastrointestinal ulceration and perforation, gastrointestinal tract inflammation (any site), stomatitis, abdominal distension, oropharyngeal dryness, odynophagia, hypermotility, palatitis

General disorders and administration site conditions: chills, altered temperature perception, night sweats, flushing, face edema

Hepatobiliary disorders: hepatitis (includes hepatic enzyme increased), hepatopathy (includes cirrhosis), cholestasis, blood bilirubin increased, cholelithiasis

Immune system disorders: vasculitides, lupus erythematosus, drug hypersensitivity (including anaphylactic shock), autoantibody positive, allergic disorders, sarcoidosis, serum sickness, angioneurotic edema, panniculitis (includes erythema nodosum)

Infections and infestations: fungal infections (includes opportunistic), bacterial infections (including abscess and legionella), sepsis (includes multi-organ failure, septic shock)

Injury, poisoning and procedural complications: skin injuries, impaired healing

Investigations: blood uric acid increased

Metabolism and nutrition disorders: weight change, blood glucose changes, electrolyte imbalance, dyslipidemia, appetite disorders, hemosiderosis

Musculoskeletal, connective tissue and bone disorders: muscle disorders, neck pain

Neoplasms benign, malignant and unspecified (including cysts and polyps): solid organ tumor, benign tumor and cysts (includes skin papilloma), non-melanoma skin cancers, blood and lymphatic system malignancies (includes lymphoma and leukemia), gastrointestinal tumor, melanoma, precancerous lesions (includes oral leukoplakia, melanocytic nevus), merkel cell carcinoma*

Nervous system disorders: peripheral neuropathies, tremor, seizure, cranial nerve inflammation, impaired coordination or balance, multiple sclerosis*, Guillain-Barré syndrome*

Psychiatric disorders: suicide attempt, anxiety and mood disorders (includes associated symptoms), delirium, mental impairment

Renal and urinary disorders: renal impairment, blood in urine, bladder and urethral symptoms nephropathy (including nephritis)

Reproductive system and breast disorders: menstrual cycle and uterine bleeding disorders (includes amenorrhea), breast disorders, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: pleural effusion (and related symptoms), asthma and related symptoms, interstitial lung disease, pneumonitis

Skin and subcutaneous tissue disorders: alopecia, new onset or worsening of psoriasis (includes palmoplantar pustular psoriasis) and related conditions, dermatitis and eczema, sweat gland disorder, skin ulcer, photosensitivity, acne, skin discolouration, dry skin, nail and nail bed disorders, skin exfoliation and desquamation, bullous conditions, hair texture disorder

Vascular disorders: hemorrhage or bleeding (any site), hypercoagulation (includes pulmonary embolism, thrombophlebitis), syncope, edema (includes peripheral, facial), ecchymoses (includes hematoma, petechiae) cerebrovascular accident, arteriosclerosis, Raynaud's phenomenon, livedo reticularis, telangiectasia

*These events have been related to the class of TNF-blockers, but incidence with CIMZIA is not known.

Post-Market Adverse Drug Reactions

Additional adverse events have been identified during post-marketing use of CIMZIA. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to CIMZIA exposure. These adverse events include, but are not limited to, the following (listed by system organ class):

Gastrointestinal disorders: intestinal obstruction

General disorders and administration site conditions: asthenia, fistula (any site)

Infections and Infestations: herpes viral infections (includes herpes zoster)

Nervous system disorders: sensory abnormalities

Pregnancy, puerperium and perinatal conditions: spontaneous miscarriage

Vascular disorders: hypotension

DRUG INTERACTIONS

Overview
CIMZIA (certolizumab pegol) may be used alone or in combination with methotrexate (MTX). Co-administration of certolizumab pegol with methotrexate had no significant effect on the pharmacokinetics of methotrexate.

Drug-Drug Interactions
Use with Other Biologic Medicines: 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. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of CIMZIA and other biologic DMARDs. Therefore, the use of CIMZIA in combination with other biologic DMARDs is not recommended (see WARNINGS AND PRECAUTIONS, Use with Other Biologic Medicines).

Live Vaccines: Live vaccines should not be given concurrently with CIMZIA (see WARNINGS AND PRECAUTIONS, Immunizations).

Drug-Food Interactions
CIMZIA is administered as a subcutaneous injection. Interactions with food are therefore not applicable.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interference with certain coagulation assays has been detected in patients treated with CIMZIA. Certolizumab pegol may cause erroneously elevated activated partial thromboplastin time (aPTT) assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-Lupus Anticoagulant (LA) and Standard Target Activated Partial

Thromboplastin time (STA-PTT) tests manufactured by Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilized silica tests manufactured by Instrumentation Laboratory. Other aPTT assays may be affected as well. Interference with thrombin time (TT) and prothrombin time (PT) assays has not been observed. There is no evidence that CIMZIA therapy has an effect on *in vivo* coagulation (see WARNINGS AND PRECAUTIONS, Laboratory Tests).

Drug-Lifestyle Interactions

CIMZIA may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of CIMZIA.

DOSAGE AND ADMINISTRATION

Dosing Considerations

CIMZIA (certolizumab pegol) is intended for use under the guidance and supervision of a healthcare professional. A patient may self-inject CIMZIA if a physician determines that it is appropriate, and with medical follow-up, as necessary, after proper training in subcutaneous injection technique.

CIMZIA may be used alone or in combination with methotrexate (MTX). In the psoriatic arthritis and ankylosing spondylitis clinical study, oral corticosteroids, DMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) and non-steroidal anti-inflammatory drugs (NSAIDs) were permitted as concomitant therapy (see CLINICAL TRIALS, Psoriatic Arthritis, Study Demographics and Trial Design and CLINICAL TRIALS, Ankylosing Spondylitis, Study Demographics and Trial Design).

CIMZIA should not be used in combination with other biologic disease modifying anti-rheumatic drugs (DMARDs) or other TNF blocking agents.

Recommended Dose and Dosage Adjustment

Loading Dose

The recommended loading dose of CIMZIA for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially (Week 0) and at Weeks 2 and 4.

Maintenance Dose

Rheumatoid Arthritis

After the loading dose, the recommended maintenance dose of CIMZIA for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. Alternatively, CIMZIA 400 mg every 4 weeks may be considered.

Psoriatic Arthritis
After the loading dose, the recommended maintenance dose of CIMZIA for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Alternatively, CIMZIA 400 mg every 4 weeks may be considered (see CLINICAL TRIALS, Psoriatic Arthritis, Study Results).

Ankylosing Spondylitis
After the loading dose, the recommended maintenance dose of CIMZIA for adult patients with ankylosing spondylitis is 200 mg every 2 weeks or 400 mg every 4 weeks.

Missed Dose
Patients who miss a dose of CIMZIA should be advised as follows: if the next scheduled dose is within 1 week, patients should wait until the next scheduled dose. If the next scheduled dose is 1 week or longer away, patients should inject the missed dose as soon as they become aware of it, then follow with their next scheduled dose.

Administration
CIMZIA is administered by subcutaneous injection.

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

Patients using CIMZIA should be instructed to inject the full amount in the syringe (1.0 mL), which provides 200 mg of CIMZIA, according to the directions provided in the Consumer Information Leaflet.

Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard. When a 400 mg dose is needed, each 200 mg injection should occur at separate sites in the thigh or abdomen.

OVERDOSAGE
Doses of up to 800 mg SC and 20 mg/kg intravenous (IV) have been administered to patients in clinical studies without evidence of dose-limiting toxicities. In cases of overdosage, it is recommended that patients are monitored closely for any signs and symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Certolizumab pegol has a high affinity for human TNFα and binds with a K_D of 90pM. TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNFα (90% inhibitory concentration [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 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 lipopolysaccharide-induced TNFα and interleukin-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. It does not induce apoptosis *in vitro* in human peripheral blood-derived monocytes or lymphocytes, or neutrophil degranulation.

Pharmacodynamics

Biological activities ascribed to TNFα include the up regulation 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 rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. CIMZIA (certolizumab pegol) binds to TNFα, inhibiting its role as a key mediator of the inflammation, disease progression, and joint destruction associated with these diseases.

Pharmacokinetics

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 IV and SC doses of certolizumab pegol have predictable dose-related plasma concentrations with a linear relationship between the dose administered and the maximum plasma concentration (C_{max}), and the Area Under the certolizumab pegol plasma concentration versus time Curve (AUC). A mean C_{max} of approximately 43 to 49 μg/mL occurred at Week 5 during the initial starting dose period using 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 pharmacokinetics observed in patients with rheumatoid arthritis were consistent with those seen in healthy subjects.

Absorption: Following subcutaneous administration, peak plasma concentrations of

certolizumab pegol were attained between 54 and 171 hours post-injection. Certolizumab pegol has a bioavailability (F) of approximately 80% (ranging from 76% to 88%) following SC administration compared to IV administration.

Distribution: The apparent volume of distribution (V/F) was estimated at 8.01 L in the RA population pharmacokinetic analysis.

Metabolism: 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 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 ($t_{1/2}$) of the Fab'. 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: The terminal elimination phase half-life ($t_{1/2}$) 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 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 PEG component is via urinary excretion.

Special Populations and Conditions

Pediatrics (< 18 years of age): Certolizumab pegol has not been studied in pediatric patients.

Geriatrics (≥ 65 years of age): Specific clinical studies have not been performed in elderly subjects.

Gender: Specific clinical studies have not been performed to assess the effect of gender on the pharmacokinetics of certolizumab pegol.

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

Hepatic Impairment: Specific clinical studies have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of certolizumab pegol.

Renal Impairment: Specific clinical studies have not been performed to assess the effect of renal impairment on the pharmacokinetics of certolizumab pegol. There are insufficient data to provide a dosing recommendation in moderate and severe renal impairment. 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.

STORAGE AND STABILITY

Store CIMZIA (certolizumab pegol) at 2°C – 8°C (36°F – 46°F). Do not freeze. Protect from light. Do not use beyond the expiration date. Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

See Consumer Information Leaflet.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CIMZIA (certolizumab pegol) is a sterile, preservative-free solution of certolizumab pegol for subcutaneous administration supplied as a single-use pre-filled 1 mL glass syringe with a fixed 25 gauge ½ inch needle, providing 200 mg (1.0 mL) of CIMZIA. The solution of CIMZIA is clear and colourless to pale yellow and essentially free from particulates, with a pH of approximately 4.7. Each 1.0 mL of CIMZIA contains 200 mg of certolizumab pegol, 1.36 mg of sodium acetate, 7.31 mg sodium chloride, and Water for Injection, USP.

CIMZIA is dispensed in a carton containing two alcohol swabs and two single use pre-filled glass syringes, each providing 200 mg (1.0 mL) of CIMZIA.

The syringe components do not contain any latex or dry natural rubber.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

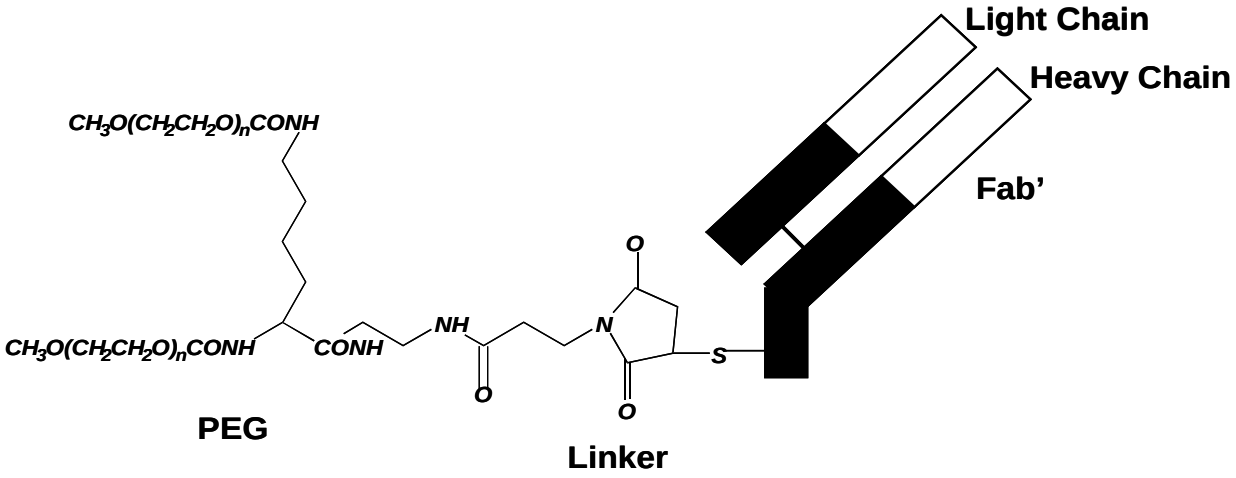
Drug Substance

Proper name: certolizumab pegol

Chemical name: gHTNF40 Fab'-40K PEG

Molecular formula and molecular mass: $C_{2115}H_{3252}N_{556}O_{673}S_{16,}$ 90.8 kDa

Structural formula:



Physicochemical properties: Certolizumab pegol is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα). The Fab' fragment is manufactured in *Escherichia coli* and is subsequently purified and conjugated to polyethylene glycol (PEG) via a maleimide linker. The light chain is composed of 214 amino acid residues and the heavy chain is composed of 229 amino acid residues.

Product Characteristics

CIMZIA (certolizumab pegol) is a recombinant, humanized antibody Fab' fragment, with specificity for human tumor necrosis factor alpha (TNFα). The Fab' fragment is manufactured in *Escherichia coli* and is subsequently purified and conjugated to polyethylene glycol (PEG).

CLINICAL TRIALS

Rheumatoid Arthritis

Study Demographics and Trial Design

The efficacy and safety of CIMZIA (certolizumab pegol) were assessed in three randomized, placebo-controlled, double-blind studies (RA-I, RA-II, and RA-III) in patients ≥ 18 years of age with moderately to severely active rheumatoid arthritis (RA) diagnosed according to 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 methotrexate (MTX) at stable doses of at least 10 mg weekly in Studies RA-I and RA-II. CIMZIA was administered as monotherapy in Study RA-III.

Table 5: Summary of Patient Demographics for Clinical Trials in Patients with Rheumatoid Arthritis

Study #	Trial Design and Duration	Dosage and Route of Administration	Study Subjects (N)	Mean Age (Range)	Gender (% Female)
Study RA-I (RAPID 1)	52-week, multicentre, double-blind, multiple dose, parallel group, placebo-controlled study	CIMZIA 400 mg SC EOW + MTX	390	52.4 (21-83)	83.6
		CIMZIA 200 mg SC EOW[(a)] + MTX	393	51.4 (19-81)	82.4
		Placebo EOW + MTX	199	52.2 (18-78)	83.9
Study RA-II (RAPID 2)	24-week, multicentre, double-blind, multiple dose, parallel group, placebo-controlled study	CIMZIA 400 mg SC EOW + MTX	246	51.9 (19-77)	78.0
		CIMZIA 200 mg SC EOW[(a)] + MTX	246	52.2 (22-81)	83.7
		Placebo EOW + MTX	127	51.5 (22-78)	84.3
Study RA-III (FAST4WARD)	24-week, multicentre, double-blind, multiple dose, parallel group, placebo-controlled study	CIMZIA 400 mg SC E4W	111	52.7 (21-80)	78.4
		Placebo E4W	109	54.9 (28-79)	89.0

[a] Patients assigned to CIMZIA 200 mg SC EOW received starting doses of CIMZIA 400 mg SC at Weeks 0, 2, and 4, followed by CIMZIA 200 mg SC EOW for the remainder of the study.
Abbreviations: SC, subcutaneous; EOW, every other week; MTX, methotrexate; E4W, every 4 weeks.

Study RA-I and RA-II evaluated patients who had received MTX for at least 6 months prior to study medication, but still had an incomplete response to MTX alone. Patients received starting doses 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 treatment of signs and symptoms of RA (measured by ACR 20 response) at Week 24 for both studies (RA-I and RA-II) and for inhibition of progression of structural damage (modified Total Sharp Score [mTSS]) at Week 52 (RA-I only). The open-label extension follow-up studies enrolled 846 patients from Study RA-I and 567 patients from Study RA-II, who received 400 mg of CIMZIA every other week.

Patients who had prior experience with anti-TNF therapies other than CIMZIA were not prohibited from participating in Study RA-I and RA-II.

Study RA-III (monotherapy) evaluated 220 patients receiving CIMZIA 400 mg or placebo every 4 weeks for 24 weeks, and who had discontinued all disease modifying anti-rheumatic drug (DMARD) use prior to receiving CIMZIA. Patients were evaluated for treatment of signs and symptoms of active RA with a primary endpoint of ACR 20 at Week 24. The open-label extension enrolled 186 patients from this study who received 400 mg of CIMZIA every 4 weeks.

Study Results

Clinical Response

The results of Study RA-I and RA-II were similar at Week 24. The percentage of patients treated every other week with CIMZIA 200 mg who achieved an ACR 20 response was statistically significantly greater than in the placebo group ($p< 0.001$) and in both studies, CIMZIA-treated patients achieved ACR 20, 50, and 70 responses faster and more often than placebo patients. Responses were seen irrespective of baseline MTX dose. Major clinical response (defined as achieving an ACR 70 response over a continuous 6 month period) in Study RA-I was greater in CIMZIA-treated patients than placebo patients. ACR response rates for the CIMZIA 200 mg every other week treatment groups were rapid and comparable in both studies RA-I and RA-II through Week 24.

In Study RA-III, patients receiving CIMZIA 400 mg every 4 weeks achieved significant ACR 20 responses. Rapid onset of clinical action was evident after the first injection with 37% of patients achieving an ACR 20 response by Week 1. ACR 50 responses were seen as early as Week 1 for CIMZIA-treated patients and maintained at all other time points through Week 24.

The results of Studies RA-I and RA-III are shown in Table 6.

Table 6: ACR Responses in Studies RA-I and RA-III (Percent of Patients)

Response	Study RA-I Methotrexate (MTX) combination (24 and 52 weeks)			Study RA-III Monotherapy (24 weeks)		
	Placebo + MTX N=199	**CIMZIA [(a)] 200 mg every 2 weeks + MTX N=393**	**CIMZIA [(a)] 200 mg + MTX – Placebo + MTX (95% CI) [(d)]**	**Placebo N=109**	**CIMZIA [(b)] 400 mg every 4 weeks N=111**	**CIMZIA [(b)] 400 mg – Placebo (95% CI) [(d)]**
ACR 20						
Week 24	14%	59%	45% (38%, 52%)	9%	46%	36% (25%, 47%)
Week 52	13%	53%	40% (33%, 47%)	N/A	N/A	
ACR 50						
Week 24	8%	37%	30% (24%, 36%)	4%	23%	19% (10%, 28%)
Week 52	8%	38%	30% (24%, 37%)	N/A	N/A	
ACR 70						
Week 24	3%	21%	18% (14%, 23%)	0%	6%	6% (1%, 10%)
Week 52	4%	21%	18% (13%, 22%)	N/A	N/A	
Major Clinical Response[(c)]	1%	13%	12% (8%, 15%)			

[(a)] CIMZIA administered every 2 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2, and 4
[(b)] CIMZIA administered every 4 weeks not preceded by a starting dose regimen
[(c)] Major clinical response is defined as achieving ACR 70 response over a continuous 6 month period
[(d)] 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution

The results of the components of ACR response criteria are shown in Table 7 for Studies RA-I and RA-III. ACR response rates and improvement in all components of ACR response were seen as early as Week 1 and maintained through to the end of each study. In studies RA-I, RA-II and RA-III, CIMZIA-treated patients reported pain relief, as assessed by the Patient Assessment of Arthritis Pain, as early as the first assessment at Week 1 (RA-I, RA-II and RA-III) through to the end of all three studies, demonstrating durability of the results.

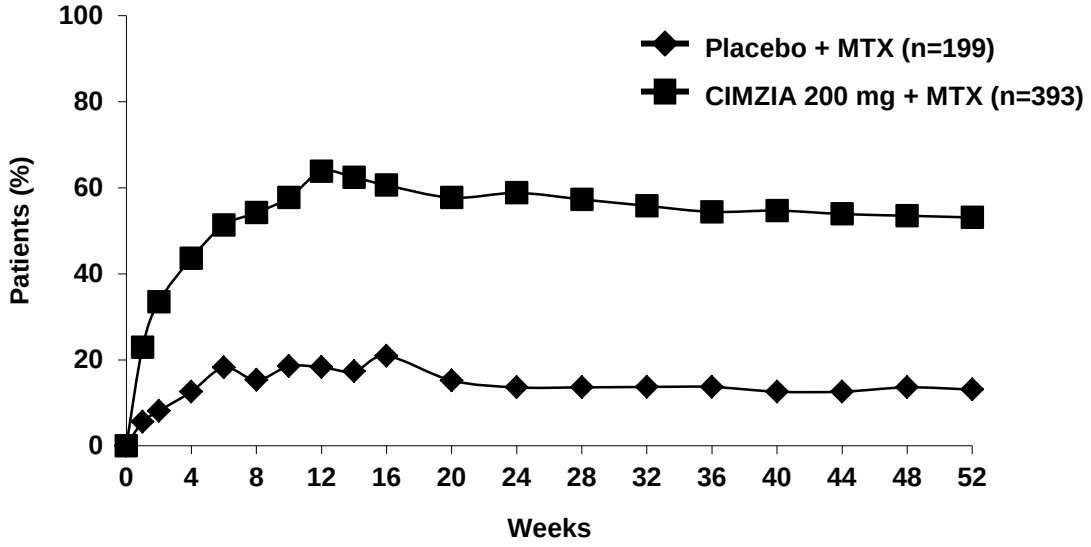
Table 7: Components of ACR Response in Studies RA-I and RA-III

Parameter[+]	Study RA-I				Study RA-III			
	Placebo + MTX N=199		CIMZIA[(a)] 200 mg + MTX every 2 weeks N=393		Placebo N=109		CIMZIA[(b)] 400 mg every 4 weeks Monotherapy N=111	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
Number of tender joints (0-68)	28	27	29	9	28 (12.5)	24 (15.4)	30 (13.7)	16 (15.8)
Number of swollen joints (0-66)	20	19	20	4	20 (9.3)	16 (12.5)	21 (10.1)	12 (11.2)
Physician global assessment[(c)]	66	56	65	25	4 (0.6)	3 (1.0)	4 (0.7)	3 (1.1)
Patient global assessment[(c)]	67	60	64	32	3 (0.8)	3 (1.0)	3 (0.8)	3 (1.0)
Pain[(c)(d)]	65	60	65	32	55 (20.8)	60 (26.7)	58 (21.9)	39 (29.6)
Disability index (HAQ)[(e)]	1.75	1.63	1.75	1.00	1.55 (0.65)	1.62 (0.68)	1.43 (0.63)	1.04 (0.74)
CRP (mg/L)	16.0	14.0	16.0	4.0	11.3	13.5	11.6	6.4

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

Figure 1 shows ACR 20 response over 52 weeks in Study RA-I. Response rates for ACR 20 were seen as early as Week 1 for patients receiving CIMZIA. ACR 50 responses for patients receiving CIMZIA were achieved by Week 2. ACR 20 and 50 responses nearly always occurred within 12 weeks and were maintained through Week 52.

Figure 1: Study RA-I ACR 20 Response Over 52 Weeks*



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

The proportion of patients who achieved DAS28 (ESR) remission (DAS28<2.6) in Study RA-I was greater in the CIMZIA 200 mg treatment group compared with placebo at Week 24 and at Week 52, demonstrating that a greater percentage of patients receiving CIMZIA were able to achieve remission.

Radiographic Response

In Study RA-I, inhibition of progression of structural joint damage was assessed radiographically and expressed as 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. The results are shown in Table 8. Significantly less radiographic progression (mTSS) and joint damage was observed with CIMZIA compared with placebo at Week 52. 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 treatment group.

Table 8: Radiographic Changes Over 12 months in Study RA-I

	Placebo + MTX N=199 Mean (SD)	CIMZIA 200 mg + MTX N=393 Mean (SD)	CIMZIA 200 mg + MTX – Placebo + MTX Mean Difference
Linear Extrapolation			
mTSS Week 52	2.8 (7.8)	0.4 (5.7)	-2.4
Erosion Score Week 52	1.5 (4.3)	0.1 (2.5)	-1.4
JSN Score Week 52	1.4 (5.0)	0.4 (4.2)	-1.0
Last Observation Carried Forward			
mTSS Week 52	1.1 (3.0)	0.1 (3.2)	-1.0
Erosion Score Week 52	0.6 (1.8)	0.0 (1.7)	-0.6
JSN Score Week 52	0.5 (1.8)	0.2 (2.2)	-0.3

Missing data imputed using both linear extrapolation and Last Observation Carried Forward (LOCF) methodologies.
p-values were < 0.001 at Week 52 for both mTSS and erosion score and ≤0.01 for JSN (both methodologies).
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.

Physical Function and Health Related Quality of Life

In studies RA-I, RA-II, and RA-III, CIMZIA-treated patients reported significant improvements in the Health Assessment Questionnaire – Disability Index (HAQ-DI) and Fatigue Assessment Scale (FAS) compared to placebo. In all three studies, CIMZIA-treated patients reported significantly greater improvements in the SF-36 Physical and Mental Component Summaries (PCS and MCS) and all eight domains compared to placebo.

In studies RA-I and RA-II, CIMZIA-treated patients reported significant improvements in the Work Productivity Survey compared to placebo.

Psoriatic Arthritis

Study Demographics and Trial Design

The efficacy and safety of CIMZIA were assessed in a multicentre, randomized, double-blind, placebo controlled study (PsA001) in 409 patients ≥18 years of age with adult-onset active psoriatic arthritis for at least 6 months as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria. Patients had ≥ 3 swollen and tender joints and increased acute phase reactants. Patients also had active psoriatic skin lesions or a documented history of psoriasis and had failed 1 or more DMARDs. Previous treatment with one TNF-antagonist was allowed and 20% of patients had prior TNF-antagonist exposure. Patients receiving concomitant

NSAIDs and conventional DMARDs were 72.6% and 70.2% respectively, including 63.6% receiving concomitant methotrexate (MTX).

Table 9: Summary of Patient Demographics for Clinical Trial in Patients with Psoriatic Arthritis

Study #	Trial Design and Duration	Dosage and Route of Administration	Study Subjects (N)	Mean Age (Range)	Gender (% Female)
Study PsA001 (RAPID-PsA)	24-week, multicentre, randomized, double-blind, parallel-group, placebo-controlled study	CIMZIA[(a)] 200 mg SC EOW	138	48.2 (19-73)	53.6
		CIMZIA[(b)] 400 mg SC E4W	135	47.1 (22-70)	54.1
		Placebo EOW	136	47.3 (22-75)	58.1

[(a)] CIMZIA administered every 2 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
[(b)] CIMZIA administered every 4 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
Abbreviations: SC, subcutaneous; EOW, every other week; E4W, every 4 weeks.

Patients received a starting dose regimen 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. The two primary endpoints were the percentage of patients achieving ACR20 response at Week 12 and change from baseline in modified Total Sharp Score (mTSS) at Week 24.

Study Results

Clinical Response

The percentage of CIMZIA-treated patients achieving ACR20, 50 and 70 responses in study PsA001 are shown in Table 10. CIMZIA-treated patients had a statistically significant higher ACR 20 response rate at Week 12 compared with placebo-treated patients ($p<0.001$). ACR20 responses observed in the CIMZIA-treated patients were similar in the patients receiving and not receiving concomitant DMARDs.

Table 10: ACR Responders in Study PsA001 (Percent of Patients)

Response	Placebo N=136	CIMZIA[(a)] 200 mg every 2 weeks N=138	CIMZIA[(b)] 400 mg every 4 weeks N=135
ACR20			
Week 12	24%	58%*	52%*
Week 24	24%	64%	56%
ACR50			
Week 12	11%	36%	33%
Week 24	13%	44%	40%
ACR70			
Week 12	3%	25%	13%
Week 24	4%	28%	24%

[(a)] CIMZIA administered every 2 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
[(b)] CIMZIA administered every 4 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
*p<0.001, CIMZIA vs placebo
Results are from the randomized set. Treatment Difference: CIMZIA 200 mg-placebo, CIMZIA 400 mg-placebo (and corresponding 95% CI and p-value) are estimated using a standard two-sided Wald asymptotic standard errors.
Note: Non-responder Imputation (NRI) is used.

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 inhibition of radiographic progression compared with placebo-treated patients at Week 24 as measured by change from baseline in total modified mTSS Score (LS mean [±SE] score was 0.28 [±0.07] in the placebo group compared with 0.01 [±0.07] in the CIMZIA 200 mg every other week group. No statistically significant change was seen in patients treated with CIMZIA 400 mg every four weeks.

Physical Function and Health Related Quality of Life

In Study PsA001, CIMZIA-treated patients reported improvements in physical function as assessed by the Health Assessment Questionnaire –Disability Index (HAQ-DI), in pain as assessed by the Patient Assessment of Arthritis Pain (PAAP), and in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) at Week 24 as compared to placebo. CIMZIA-

treated patients reported improvements in health-related quality of life as measured by the psoriatic arthritis QoL (PsAQoL), and in the SF-36 Physical and Mental Component Summaries at Week 24 as compared to placebo.

Ankylosing Spondylitis

Study Demographics and Trial Design

The efficacy and safety of CIMZIA were assessed in a multicentre, 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 ankylosing spondylitis (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. Overall 20% of patients had prior exposure to TNF-blockers.

Table 11: Summary of Ankylosing Spondylitis Patient Demographics for Clinical Trial AS-1

Study #	Trial Design and Duration	Dosage and Route of Administration	Study Subjects (N)	Mean Age (Range)	Gender (% Female)
Study AS-1	24-week, multicentre, randomized, double-blind, parallel-group, placebo-controlled study	CIMZIA[(a)] 200 mg SC EOW	65	41.0 (24-64)	27.7
		CIMZIA[(b)] 400 mg SC E4W	56	41.9 (19-66)	26.8
		Placebo EOW	57	41.6 (21-68)	28.1

[(a)] CIMZIA administered every 2 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
[(b)] CIMZIA administered every 4 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
Abbreviations: SC, subcutaneous; EOW, every other week; E4W, every 4 weeks.

Patients were treated with a starting dose regimen of CIMZIA 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg of CIMZIA every other week or 400 mg of CIMZIA every 4 weeks or placebo. 91% of patients received concomitant NSAIDs, 17.5% received concomitant methotrexate (MTX), and 17.4% received concomitant corticosteroids. The primary efficacy variable was the ASAS20 response at Week 12.

Study Results

Clinical Response

In study AS-1, at Week 12, ASAS20 responses were achieved by 57% of AS patients receiving CIMZIA 200 mg every other week and 64% of AS patients receiving CIMZIA 400 mg every 4 weeks as compared to 37% of patients receiving placebo (p=0.026 and p=0.003, respectively). At Weeks 12 and 24, the percentage of AS subjects with an ASAS40 response was greater in the CIMZIA-treated groups compared to placebo. Responses were similar in patients receiving CIMZIA 200 mg every other week or CIMZIA 400 mg every 4 weeks (Table 12).

Table 12: ASAS Responses in AS Patients at Week 12 and Week 24 in Study AS-1 (Proportion of Patients)

Parameters	**Placebo** **N=57**	**CIMZIA[(a)] 200 mg every 2 weeks** **N=65**	**CIMZIA[(b)] 400 mg every 4 weeks** **N=56**
ASAS 20[(d,e)]			
Week 12	37%	57%*	64%**
Week 24	33%	68%	70%
ASAS 40 [(d, f)]			
Week 12	19%	40%	50%
Week 24	16%	47%	59%

[(a)] CIMZIA administered every 2 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
[(b)] CIMZIA administered every 4 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
[(d)] Treatment difference: CIMZIA 200-placebo, CIMZIA 400-placebo (and corresponding 95% CI and p-value) are estimated using a standard two-sided Wald asymptotic test. Non-responder imputation (NRI) is used.
[(e)] Results are from the randomized set
[(f)] Results are from the full analysis set
*p=0.026, CIMZIA vs placebo
**p=0.003, CIMZIA vs placebo

The results of the components of the ASAS response criteria are shown in Table 13.

Table 13: Components of the ASAS Response Criteria in AS Patients in study AS-1

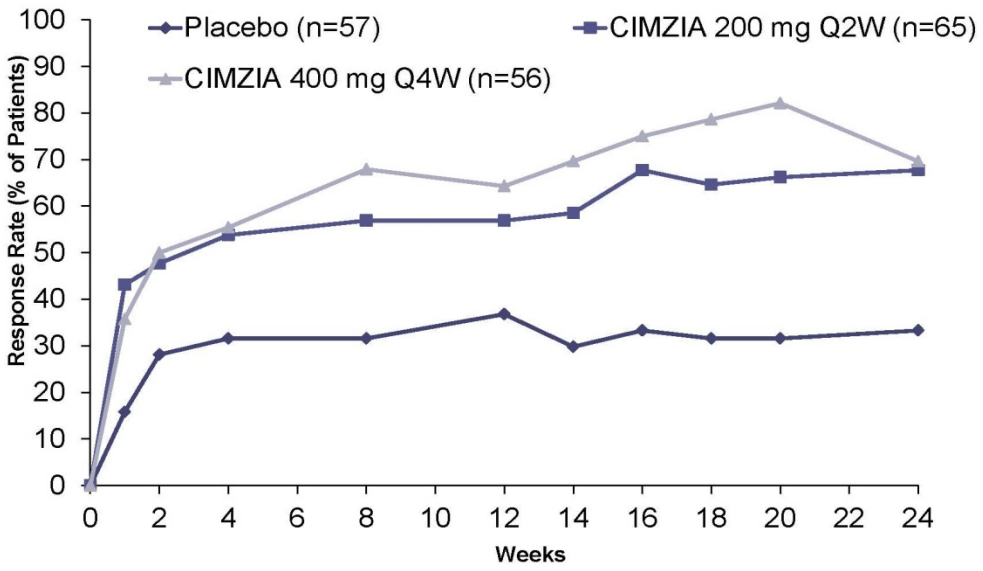
Parameters	**Placebo N=57**			**CIMZIA[(a)] 200 mg every 2 weeks N=65**			**CIMZIA[(b)] 400 mg every 4 weeks N=56**		
	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24
ASAS20 response criteria									
-Global Assessment [PtGADA][(c, d)]	6.89	5.63	5.98	7.31	4.22	3.85	6.77	3.79	3.55
-Pain [Total spinal pain][(c, e)]	7.30	5.79	5.91	7.00	4.31	4.06	6.91	4.00	3.41
-Function [BASFI][(c, f)]	5.98	5.23	5.12	5.61	3.80	3.27	5.65	3.75	3.31
-Inflammation [BASDAI mean of Q5/6][(c, g)]	6.71	5.54	5.36	6.70	3.78	3.91	6.38	3.38	2.92

[(a)] CIMZIA administered every 2 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
[(b)] CIMZIA administered every 4 weeks preceded by a starting dose regimen of 400 mg at Weeks 0, 2 and 4
[(c)] ANCOVA model with treatment, region, modified NY criteria (Y/N) and prior TNF-blocker exposure (Y/N) as factors and Baseline score as covariate. Note: Last observation carried forward (LOCF) is used.
[(d)] PtGADA, NRS where 0 = not active and 10 = very active
[(e)] Total spinal pain NRS where 0=no pain and 10=most severe pain
[(f)] BASFI NRS where 0= easy and 10= impossible
[(g)] BASDAI Q5 is an NRS where 0= none and 10 is very severe; BASDAI Q 6 is an NRS where 0=0hrs and 10= 2 or more hrs
All values presented represent the mean in the full analysis set

CIMIZA-treated patients showed improvement compared with placebo-treated patients in additional key secondary measures of efficacy including change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Weeks 12 and 24, change from baseline in BASDAI at Weeks 12 and 24, and change in Bath Ankylosing Spondylitis Metrology Index (BASMI) at Weeks 12 and 24.

The percentage of AS patients achieving ASAS20 responses by visit for study AS-1 is shown in Figure 2. Among patients receiving CIMZIA, ASAS20 responses were seen within one to two weeks after initiation of therapy.

Figure 2: Study AS-1: ASAS20 Response Over 24 weeks in AS patients*



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

Physical Function and Health Related Quality of Life

In Study AS-1, CIMZIA-treated AS patients reported improvements in physical function as assessed by the BASFI and in pain as assessed by the Total and Nocturnal Back Pain NRS scales as compared to placebo. CIMZIA-treated AS patients reported improvements in tiredness (fatigue) as reported by the BASDAI-fatigue item and in health-related quality of life as measured by the ankylosing spondylitis QOL (ASQoL) and the SF-36 Physical Component Summaries as compared to placebo.

DETAILED PHARMACOLOGY

Pharmacodynamics

Certolizumab pegol shows a high affinity to human TNFα and *in vitro* potency for soluble and membrane TNFα. Owing to the species specificity of certolizumab pegol (primates being the only responsive species), *in vivo* pharmacodynamic activity was demonstrated by showing inhibition of responses elicited by human TNFα. Mechanistically oriented studies suggested that the key factor contributing towards the mode of action of certolizumab pegol in RA is likely to be neutralization of soluble and membrane TNF-mediated effects, without any associated killing of TNF expressing cells. In addition, certolizumab pegol has the potential to block cytokine production from cells. In contrast to other anti-TNF agents, certolizumab pegol did not increase the proportion of apoptotic T lymphocytes or monocytes, cause neutrophil degranulation or cell death and did not activate antibody-dependent cell cytotoxicity and complement-mediated cytotoxicity.

Pharmacokinetics

PEGylation of the Fab' fragment (to produce certolizumab pegol) resulted in an extended absorption phase from the subcutaneous space and a slow elimination from the circulation, compared to the non-PEGylated Fab'. These disposition characteristics allowed for once a week dosing in repeat-dose studies in the cynomolgus monkey. Such studies showed certolizumab pegol to be well tolerated with no findings of toxicological significance. Observations of dose-related macrophage vacuolation in some tissues and a slow clearance of the vacuoles, was a consistent finding without any deleterious effects, which supports the contention that such findings are unlikely to be of toxicological significance. The histiocytic vacuolation is consistent with published findings following administration of PEGylated drugs and is considered to reflect phagocytic uptake by cells as part of the physiological processing of high molecular weight polyethylene glycols.

TOXICOLOGY

Acute Toxicity

A single-dose toxicity study was conducted in cynomolgus monkeys at dose levels of 50, 100 or 400 mg/kg administered by intravenous infusion (with a 28-day observation period). Dose levels up to 400 mg/kg were well tolerated and without overt toxicity. The no observed adverse effect level (NOAEL) was 400 mg/kg.

Repeat Dose Toxicity

Repeat-dose toxicity studies were conducted in cynomolgus monkeys.

In a 28 day study, four weekly intravenous infusions of 0, 50, 100 or 400 mg/kg (with a 28-day treatment-free period) were administered. Certolizumab pegol was well tolerated at all dose levels, with no treatment-related signs of overt toxicity. There was a dose-related increase in

activated partial thromboplastin time (aPTT) in all treated groups but this was not associated with any abnormal bleeding events in the animals. The main systemic finding in 100 mg/kg and 400 mg/kg animals of both sexes was histiocyte (macrophage) vacuolation. After the 28-day treatment-free period, histiocyte vacuolation was still evident, but to a lesser extent, suggesting a partial recovery. These findings were not accompanied by any adverse morphological changes and do not appear to have had any adverse effects on the general health and well-being of the animals. The NOAEL was considered to be 400 mg/kg. This represented 280-fold the monthly dose in man at the maximum recommended human dose (and 200-fold the exposure based on AUC).

In a combined 13/26-week study, weekly subcutaneous injections of 10 or 100 mg/kg for either 13 or 26 weeks (each dosing period followed by 13 week treatment-free period) were administered. There were no treatment-related macroscopic changes at necropsy. Microscopically, foamy macrophages were reported in animals treated at 100 mg/kg for either 13 or 26 weeks in various organs. These changes were not completely resolved following 13 weeks treatment-free. No vacuolation was seen at 10 mg/kg. No additional morphological changes were associated with the vacuolation in any tissues. Certolizumab pegol was well tolerated at both dose levels and not associated with any changes considered to be of toxicological significance.

In a 52-week study, weekly subcutaneous injections of 50 or 100 mg/kg for 52 weeks were administered (followed by a 26 week treatment-free period). Certolizumab pegol was well tolerated throughout the study and during the treatment-free period, with no signs of local or systemic toxicity and with no adverse effects of treatment on bodyweights, ocular structures, clinical chemistry or hematology, including lymphocyte counts and subset numbers. There was no evidence of any proliferative, inflammatory or degenerative changes. Treatment with certolizumab pegol at 50 or 100 mg/kg resulted in up to 30% increases in aPTT during the treatment period however prothrombin times were unaffected, indicating the finding is of unlikely toxicological significance, particularly in the absence of adverse bleeding events. Whilst the mechanism underlying this increase is not fully understood, it has been shown that the *ex vivo* addition of certolizumab pegol to monkey plasma resulted in increased aPTT times, suggesting such findings may be partly due to assay interference by certolizumab pegol. Histological findings were restricted to histiocytic/macrophage vacuolation, principally of the hemolymphoreticular system. Vacuolation was present in several organs of animals receiving 100 mg/kg. In animals receiving certolizumab pegol at 50 mg/kg/week, vacuolation was present at a reduced incidence and in a limited number of organs when compared to the high dose level. Following a 26 week treatment-free period, vacuolation was still present, although there were reductions in the incidence or severity of the vacuolation compared to that observed at the end of 52 weeks of treatment. The 100 mg/kg/week dose used in the long term safety studies represents approximately 90-fold the exposure based on $AUC_{0\text{-}t}$ estimates for a 70 kg rheumatoid arthritis patient at the recommended human dose (200 mg every 2 weeks).

Carcinogenicity
No conventional carcinogenicity testing was performed with certolizumab pegol.

Mutagenicity
Certolizumab pegol demonstrated no evidence of mutagenicity, clastogenicity or aneugenicity, using a standard battery of *in vitro* and *in vivo* genotoxicity tests.

Reproductive and Developmental Toxicity
Fertility, embryo-fetal and peri-postnatal toxicity studies were conducted in the Sprague-Dawley rat with cTN3 PF (a homologous PEGylated Fab' of an antibody raised to murine TNFα). No adverse effects on reproductive functions were noted in any of the studies at dose levels up to 100 mg/kg twice weekly, the highest dose tested. The reproductive safety studies conducted in rats using cTN3 PF revealed there was limited trans-placental transfer (as it does not have a Fc region) and there were no findings of concern. Fetal plasma samples showed limited concentrations (< 0.3% of maternal values) and the transfer into milk also was restricted; no more than 10% of maternal plasma concentrations. In addition there were no detectable plasma concentrations of cTN3 PF in nursing pups during lactation.

REFERENCES

1. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum1988; 31:315-324.

2. Canadian Tuberculosis Standards. 6th Edition. 2007. Joint project of Tuberculosis Prevention and Control, Public Health Agency of Canada, and the Canadian Lung Association/Canadian Thoracic Society.

3. Keystone E, van der Heijde D, Mason D Jr, et al. Certolizumab Pegol Plus Methotrexate Is Significantly More Effective Than Placebo Plus Methotrexate in Active Rheumatoid Arthritis Findings of a Fifty-Two–Week, Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study. Arthritis Rheum 2008; 58:3319-3329.

4. Smolen J, Landewe R, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009; 68(6):797-804.

5. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009; 68:805–811.

6. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24 week results of a phase 3 double blind randomized placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2013; 0:1-8.

7. Landewe R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2013; 0:1-9.

PART III: CONSUMER INFORMATION

CIMZIA®
certolizumab pegol

This leaflet is part III of a three-part "Product Monograph" published when CIMZIA (SIM-zee-uh) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CIMZIA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

CIMZIA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis (RA) and/or psoriatic arthritis (PsA) and/or ankylosing spondylitis (AS) and familiar with the CIMZIA efficacy and safety profile.

What the medication is used for:
CIMZIA is a medicine that is used to treat adults with:

- moderate to severe rheumatoid arthritis (RA)
- psoriatic arthritis (PsA)
- ankylosing spondylitis (AS)

Rheumatoid arthritis is an inflammatory disease of the joints. Psoriatic arthritis is an inflammatory disease of the joints and skin. Ankylosing spondylitis is an inflammatory disease of the spine. People with RA, PsA or AS may be given other medicines for their disease before they are given CIMZIA. If you do not respond well enough to these medicines, you will be given CIMZIA to reduce the signs and symptoms of your disease.

What it does:
Because it blocks the action of a substance in your body called tumor necrosis factor (TNF) alpha (TNFα), you may hear CIMZIA referred to as a "TNF blocker". People with rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis usually have too much TNFα in their bodies, which can lead to painful and swollen joints. CIMZIA can help reduce the amount of TNFα in the body to normal levels helping to treat joint damage. CIMZIA helps to reduce the signs and symptoms of rheumatoid arthritis (such as pain, swollen joints, and fatigue), may help improve your ability to perform daily activities (such as dressing, walking and climbing stairs), and may help prevent further damage to your bones and joints. In addition, CIMZIA helps reduce the signs and symptoms of ankylosing spondylitis (back pain and morning stiffness).

When it should not be used:
You should not take CIMZIA if you have had an allergic reaction to CIMZIA or any of its ingredients. See the "medicinal ingredient" and "nonmedicinal ingredients" sections below for a list of all ingredients in CIMZIA. If you have a severe infection, such as sepsis (an infection in the bloodstream), abscess, tuberculosis, or other serious infection, you must not take CIMZIA. If you have heart failure that is moderate or severe, you must not take CIMZIA.

What the medicinal ingredient is:
certolizumab pegol

What the important nonmedicinal ingredients are:
Sodium acetate, sodium chloride (salt) and water (water for injection). No preservatives are present. The pre-filled syringe parts do not contain any latex or dry natural rubber.

What dosage forms it comes in:
CIMZIA is supplied as a solution for injection in a single-use pre-filled glass syringe (200 mg/mL).

WARNINGS AND PRECAUTIONS

Before initiation, during and after treatment with CIMZIA, you should be evaluated for active or latent tuberculosis infection with, for example, a tuberculin skin test.

Any medicine can have side effects. Like all medicines that affect your immune system, CIMZIA can cause serious side effects. The possible serious side effects include:

Serious Warnings and Precautions

- Serious infections: Serious infections have been reported in patients receiving CIMZIA and other TNF blockers. Some of these cases have been life-threatening. Such infections include tuberculosis (TB), infections caused by bacteria or fungi, bacterial infections that have spread throughout the body (sepsis), and very rare cases of hepatitis B infection relapse.
- Cardiovascular system diseases: There have been rare cases of disorders called (congestive) heart failure that affect the people taking CIMZIA or other TNF blockers. Signs that you could be experiencing a problem affecting your cardiovascular system include: shortness of breath and swelling of the ankles or feet.
- Nervous system diseases: Rare cases of disorders that affect the nervous system have been reported in patients receiving CIMZIA and other TNF blockers. Signs that you could be experiencing a problem affecting your nervous system include: numbness or tingling, problems with your vision, weakness in your legs, and dizziness.
- Malignancies: Very rare cases of certain kinds of cancer have been reported in patients receiving CIMZIA and other TNF blockers. Some patients receiving CIMZIA have developed types of cancer called non-melanoma skin cancer. Tell your doctor if new skin lesions appear during or after therapy with CIMZIA or existing skin lesions change appearance or you have a bump or open sore that does not heal. People with more serious RA that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. There have been cases of unusual cancers in children and teenage patients using TNF-blocking agents. If you take CIMZIA or other TNF blockers, your risk of getting lymphoma or other cancers may increase.
- Lupus-like symptoms: Some patients have developed lupus-like symptoms that got better after their treatment was stopped. If you have chest pains that do not go away, shortness of breath, joint pain, or a rash on your cheeks or arms that is sensitive to the sun, call your doctor right away.
- Allergic reactions: If you develop a severe rash, swollen face or difficulty breathing while taking CIMZIA, call your doctor right away.

Serious infections

CIMZIA is a medicine that affects your immune system. Because CIMZIA, like other anti-TNF therapies, may lower your immune function as a part of treating your condition you may be more likely to get a serious infection. These serious infections include tuberculosis (TB), legionellosis (a serious bacterial pneumonia), listeriosis (an infection that usually develops after eating food contaminated by bacteria called listeria) and other and infections caused by viruses, fungi or bacteria that have spread throughout the body. Some of these infections may be fatal.

It is very important to tell your doctor immediately if you:

- have any symptoms of an infection including fever, cough, or any flu-like symptoms
- are currently being treated for an infection
- have any open cuts or sores on your body
- have a history of getting frequent infections
- have or have had a Hepatitis B infection
- are or have been infected with TB, or have been in close contact with someone who has TB. You can be infected with TB and have no symptoms whatsoever, so it's important that your doctor give you a test for TB before you start CIMZIA therapy. If your doctor prescribes any medicine for the treatment of TB, you should start taking it before starting CIMZIA and take the full course of TB medicine prescribed.
- were born in, lived in, or traveled to countries where there is more risk for getting TB. Ask your doctor if you are not sure.
- have lived in or traveled to an area 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 doctor.
- develop signs and symptoms of lupus (persistent rash, fever, joint pain, and tiredness)
- are also being treated with other biologic medicines or have had a recent vaccination

If, at any time, while you are receiving treatment with CIMZIA, you have any signs or symptoms of an infection such as fever, cough, or flu-like symptoms, or develop any open cuts or sores on your body, call your doctor right away.

Some types of cancer

While rare, there have been reported cases of a cancer called lymphoma in patients on CIMZIA or other TNF blockers. People who have been treated with a TNF blocker like CIMZIA for a long period of time may have a higher risk of developing lymphoma. Cancers other than lymphoma have also been reported in patients treated with CIMZIA. It is not known whether there is an increased risk of cancer associated with CIMZIA treatment.

Heart failure

If you have been told that you have a heart problem called (congestive) heart failure and you are currently being treated with CIMZIA, you will need to be closely monitored by your doctor. Important symptoms to watch for include shortness of breath and swelling of the ankles or feet.

Hepatitis B virus reactivation

Your doctor should test you to see if you carry the Hepatitis B virus in your blood before starting treatment with CIMZIA. If you have had Hepatitis B, or know that you carry the virus, your doctor will need to monitor you during treatment to be sure the virus has not become active again.

Blood problems

In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. Important symptoms to watch for include persistent fever, unusual bruising or bleeding and extremely pale skin.

Nervous system disorders
There have been rare cases of disorders that affect the nervous system of people taking CIMZIA or other TNF blockers. Signs that you could be experiencing a problem affecting your nervous system include: dizziness, numbness or tingling, problems with your vision, and weakness in your legs.

Allergic reactions
In rare cases, patients taking CIMZIA have had difficulty breathing, low blood pressure, and/or loss of consciousness, which may represent an allergic reaction. Allergic reactions can happen after your first dose or may not happen until after you have taken CIMZIA many times. Symptoms to watch for include skin rash, swollen face, or difficulty breathing. **If you develop these symptoms, call your doctor and seek emergency care immediately**.

Immune reactions
Some patients on CIMZIA develop lupus-like symptoms including shortness of breath, joint pain, or a rash on the cheeks or arms that worsens with sun exposure.

If you develop any of the above serious side effects while on CIMZIA, or any other unusual symptom, call your doctor right away. Your doctor may decide that your treatment with CIMZIA should be stopped.

Before taking CIMZIA and to help your doctor decide whether or not CIMZIA is right for you, you need to **tell your doctor** if you have or have had any of the following:
- an infection of any kind
- new or worsening symptoms of heart failure (e.g. shortness of breath, or swelling of your feet)
- cancer (such as lymphoma)
- a blood disorder, or symptoms of a blood disorder such as persistent bruising, bleeding, or fever
- any numbness or tingling or a disease that affects your nervous system such as multiple sclerosis, Guillain-Barré syndrome or seizures

Tell your doctor if you have had or are scheduled to have:
- major surgery
- any vaccination(s). You should not receive certain (live vaccines) while using CIMZIA

Tell your doctor if you are pregnant or breastfeeding; or if you and your partner are planning to conceive a child. The effects of CIMZIA on pregnant women have not been studied and are unknown. If you are pregnant, breastfeeding, or planning to conceive a child, your doctor will help you decide whether or not to use CIMZIA.

Certain vaccinations may cause infections. If you have received CIMZIA while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately five months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your CIMZIA use so they can decide when your baby should receive any vaccine.

If you are not sure or have any questions about any of this information, ask your doctor.

INTERACTIONS WITH THIS MEDICATION

Be sure to also tell your doctor about all the medicines you take (both prescription and nonprescription), as well as about any vitamin or herbal supplements. Your doctor will tell you if you may take other medications or supplements while you are on CIMZIA therapy. It's especially important to tell your doctor if you take other biologic medicines such as Kineret (anakinra) or Orencia (abatacept). Studies with another TNF blocker have shown that taking other biologic medicines while on TNF blocker therapy may increase your chances for developing serious infections or a low white blood cell count, with no additional health benefit.

Only you know all the medicines you are taking. Keep a list to show your doctor and your pharmacist each and every time you are prescribed a new medicine.

PROPER USE OF THIS MEDICATION

CIMZIA is given by an injection under the skin. **Please use CIMZIA exactly as prescribed by your doctor, and use it only as often as prescribed.** Ask your healthcare professional to show you how to inject CIMZIA before trying to do it yourself. When you are taking CIMZIA at home, you may want to have someone you know help you with your injection. You can call your doctor if you have any questions about giving yourself an injection.

Usual dose:

Rheumatoid Arthritis
The **starting dose** for adults with rheumatoid arthritis is 400 mg of CIMZIA given at **weeks 0, 2, and 4**. This is followed by a **maintenance dose** of 200 mg of CIMZIA given every other week. For some patients, a **maintenance dose** of 400 mg of CIMZIA given every 4 weeks may be prescribed by your doctor.

Psoriatic Arthritis
The **starting dose** for adults with psoriatic arthritis is 400 mg of CIMZIA given at **weeks 0, 2 and 4.** This is followed by a **maintenance dose** of 200 mg of CIMZIA given every other week. For some patients, a **maintenance dose** of 400 mg of CIMZIA given every 4 weeks may be prescribed by your doctor.

Ankylosing Spondylitis
The **starting dose** for adults with ankylosing spondylitis is 400 mg of CIMZIA given at **weeks 0, 2 and 4.** This is followed by a **maintenance dose** of 200 mg of CIMZIA given every other week **or** 400 mg of CIMZIA given every 4 weeks.

Overdose:
If you take more CIMZIA than you were told to take, call your doctor.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Be sure to take your medicine exactly as prescribed and do not miss any doses of CIMZIA. If you forget to take your dose of CIMZIA at your regularly scheduled time, do as follows: if your next scheduled dose is within 1 week, wait until your next scheduled dose. If your next scheduled dose is 1 week or longer away, inject the missed dose as soon as you become aware of it, then follow with your next scheduled dose.

Patient Instructions for Proper Use

What do I need to do to prepare and give an injection of CIMZIA?
Do not use the CIMZIA pre-filled syringe if:

- any name other than "CIMZIA" is on the package and pre-filled syringe label
- the expiration date on the container has passed
- the packaging is torn or if the tamper evident seals are missing or broken on the top and bottom of carton when you receive it. If this is the case, contact your pharmacist.
- the pre-filled syringe is frozen or has been left in direct sunlight
- the medicine in the pre-filled syringe is not clear to pale yellow, or has large, colored particles in it

Preparing to use the CIMZIA pre-filled syringe

Each CIMZIA pre-filled syringe package comes with these items in a tray:

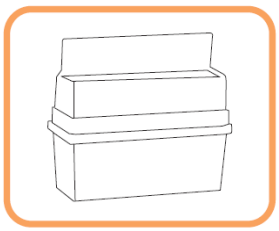
- 2 glass pre-filled syringes of CIMZIA. Each has a fixed needle.
- 2 alcohol swabs

For each injection you will use:

- 1 pre-filled syringe of CIMZIA with needle
- 1 alcohol swab

For each injection you will also need:

- 1 clean cotton ball or gauze pads. These are not included in the CIMZIA pre-filled syringe package.
- a puncture-proof container for disposing of used needles and syringes. (See the section entitled "How should I dispose of needles and syringes?")



If you do not have all the supplies you need, talk to your pharmacist.

- Each pre-filled syringe contains the right dose of medicine for one injection (200 mg).
- Depending on the amount of CIMZIA prescribed by your doctor, you may need to take more than one injection.
- If you are prescribed to take 400 mg of CIMZIA, you will need to take two injections. You will need to use two CIMZIA pre-filled syringes.
- CIMZIA may be injected into your abdomen or thigh area. If you are prescribed to take more than one injection, each injection should be given at a different injection site, in your abdomen and thigh.

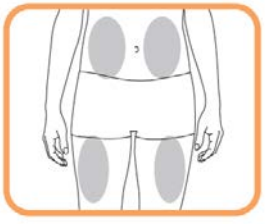
1. Take either one or two CIMZIA pre-filled syringes and alcohol swabs out of the refrigerator for injection, depending on your prescribed dose. If there is still a pre-filled syringe in the carton, put it back in the refrigerator right away. If both pre-filled syringes are used, throw away the empty carton after you finish your injection.

2. Let the medicine in the syringe come to room temperature before injection. This will take about 30 minutes.

For your protection, it's important that you carefully follow these instructions:
Choosing and preparing an injection site

3. Wash your hands thoroughly.

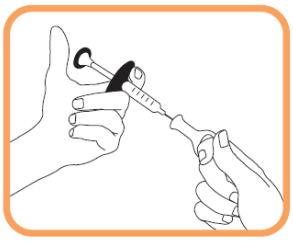
4. Choose a different site on your abdomen or thigh for each injection. Each new injection should be given at least one inch from a site you used before. If you choose the abdomen, avoid the 2 inches around your navel. Do not inject into areas where the skin is tender, bruised, red or hard or where you have scars or stretch marks. Change injection sites between your abdomen and thighs to reduce the risk of reaction. You may find it helpful to keep notes on the locations of injection sites you use.



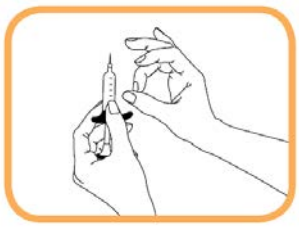
5. Use an alcohol swab to wipe over the site where you will inject CIMZIA. Do not touch the clean area again until you are ready for the injection.

Using the CIMZIA pre-filled syringe

6. Remove the needle cover by pulling straight up on the plastic ring. Take care not to touch the needle and do not allow the needle to touch any surface. Place the needle cover to the side.

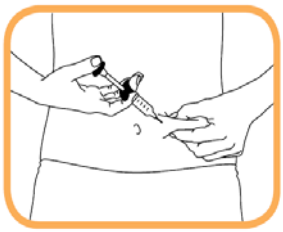


7. Hold the syringe so the needle is pointing up. Lightly tap the syringe to push any air bubbles to the top. Push the plunger slowly to remove any bubbles. Stop pushing the plunger once all of the air bubbles are gone. If a small drop of liquid comes out of the needle that is okay.

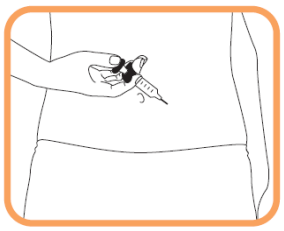


8. Hold the syringe with the needle facing down. Do not touch the needle with your fingers or let it touch any surface.

9. Hold the syringe in one hand. Use the other hand to gently pinch a fold of cleaned area of skin. Insert the needle at about a 45 degree angle with a quick, short, "dart-like" motion.



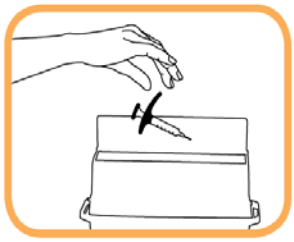
10. Release the skin pinch, keeping the syringe in position. If blood enters the syringe, this means you have entered a blood vessel. Do not inject CIMZIA. Pull the needle out and throw away the pre-filled syringe and needle in a puncture-proof container. Repeat the steps to prepare for an injection using a new pre-filled syringe. **Do not use the same pre-filled syringe.**



11. If no blood appears, inject all of the medicine in the pre-filled syringe under the skin.

12. When the syringe is empty, remove the needle from the skin and press the clean cotton ball or gauze pad over the injection site for ten seconds. Do not rub the injection site. You may have a slight amount of bleeding. This is normal.

13. To avoid needle-stick injury, do not try to recap the needle. Throw away the used pre-filled syringe and needle in a special puncture-proof container. (**See the section entitled "How should I dispose of needles and syringes?"**)



14. Repeat steps 5-13 above if you are prescribed to take a second injection of CIMZIA (total 400 mg dose).

How should I dispose of needles and syringes?

To avoid needle-stick injury, do not try to recap the needle. Before you start injecting CIMZIA at home, check with your doctor for instructions on the right way to throw away your used needles and used pre-filled syringes.

Ask your doctor or pharmacist about how to get a puncture-proof container ("sharps" container) that will meet local requirements.

When the container is about two-thirds full, tape the lid closed. Dispose of the container as instructed by your doctor, nurse or pharmacist. Do not throw away the container in the trash or recycle.

Alcohol swabs may be placed in the trash, unless you are instructed otherwise.

Always keep CIMZIA, injection supplies, puncture-proof container, and all other medicines out of the reach of children.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects reported by patients treated with CIMZIA were upper respiratory tract infections (such as flu, cold), fatigue, skin infections, and liver function elevations (from blood tests). Some patients may experience a reaction at the site

where the injection was given. These reactions are usually mild and may include pain, redness, rash, swelling, itching, or bruising.

These are not all of the side effects that may be experienced with CIMZIA. Ask your doctor or pharmacist for more information and be sure to tell your doctor if you experience any side effects, including ones that are not listed in this leaflet.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common [in less than 10% of patients (less than one in 10)]	Upper respiratory tract infections (such as flu, cold), other serious infections including pneumonia, bronchopneumonia, bronchitis, and herpes zoster (shingles)		√	
Uncommon [in less than 1% of patients (less than one in 100)]	Tuberculosis Other serious infections, liver function elevations (from blood tests), localized form of lupus affecting the skin, infection affecting the lung lining (pleurisy), fungal infection of esophagus (esophageal candidiasis), appendicitis, hypersensitivity		√	√

This is not a complete list of side effects. For any unexpected effects while taking CIMZIA, contact your doctor or pharmacist.

HOW TO STORE IT

- Keep CIMZIA in the refrigerator at 2ºC – 8ºC (36ºF – 46ºF).
- Let CIMZIA come to room temperature before injecting it.
- **Do not freeze** CIMZIA.
- **Protect** CIMZIA **from light.** Store CIMZIA in the carton.
- Do not use CIMZIA if the medication is expired (today's date is past the date printed on the pre-filled syringe or carton), or if the liquid looks cloudy or discoloured.

The pre-filled syringes are glass. Do not drop or crush them.

Always keep CIMZIA, injection supplies, puncture-proof container, and all other medicines out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

Online: www.healthcanada.gc.ca/medeffect
Toll-free telephone: 1-866-234-2345
Toll-free fax: 1-866-678-6789
Postage Paid Mail: Canada Vigilance Program
Health Canada
AL 0701C
Ottawa, ON, K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the CIMZIA customer service support line toll free at: 1-800-908-5555.

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