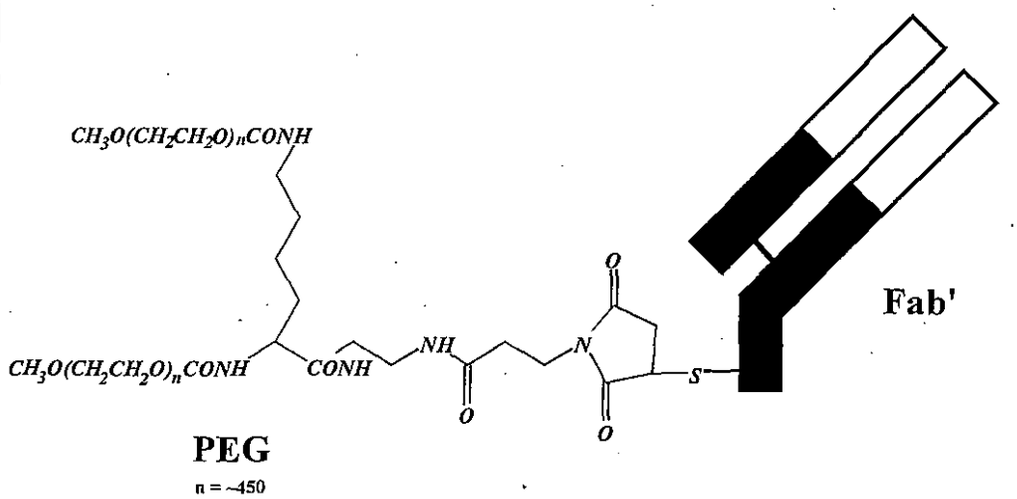
Attachment 1. Product Information

NAME OF THE MEDICINE

Cimzia® (certolizumab pegol)

CIMZIA 200 mg/mL Injection.

Chemical structure:



Chemical Name: gHTNF40 Fab'40 kDa PEG
MW: approximately 90,000 Da

CAS number: [428863-50-7]

DESCRIPTION

Certolizumab pegol is a recombinant, humanised antibody Fab' fragment that is expressed in an *Escherichia coli* bacterial expression system, subsequently purified and conjugated to polyethylene glycol (PEG).

200 mg/mL Injection in a single-use pre-filled syringe
Cimzia® injection is a clear, colourless, sterile solution containing 200 mg certolizumab pegol per mL. The inactive ingredients are sodium chloride, sodium acetate and water for injections. The pH of the solution is approximately 4.7.

PHARMACOLOGY

Mechanism of action

Certolizumab pegol has a high affinity for human TNFα and binds with a dissociation factor (K_D) of 90pM. TNFα is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralises 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 neutralise lymphotoxin α (TNFβ). Certolizumab pegol cross-reacts poorly with TNF from rodents and rabbits, therefore *in vivo* efficacy was evaluated using animal models in which human TNFα was the physiologically active

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molecule.

Certolizumab pegol was shown to neutralise 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 *in vitro*. It does not induce apoptosis *in vitro* in human peripheral blood-derived monocytes or lymphocytes or neutrophil degranulation.

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

Pharmacodynamic effects

Biological activities ascribed to TNFα include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNFα stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNFα have been implicated in the pathology of rheumatoid arthritis. Increased TNFα levels are found in the synovial fluid of rheumatoid arthritis patients and play an important role in the joint destruction that is a hallmark of this disease.

Pharmacokinetic properties

Absorption:

Following subcutaneous administration, peak plasma concentrations of CIMZIA were attained between 54 and 171 hours post-injection. CIMZIA has a bioavailability (F) of approximately 80% (range 76% to 88%) following subcutaneous administration compared to intravenous administration. Cimzia has predictable dose-related exposure with an approximately linear relationship between the dose administered and the maximum plasma concentration (C_{max}) or the area under the plasma concentration versus time curve (AUC). Pharmacokinetics observed in patients with rheumatoid arthritis were consistent with those seen in healthy subjects.

Distribution:

The apparent volume of distribution (V/F) was estimated at 8.01 L in a population pharmacokinetic analysis of patients with rheumatoid arthritis.

Biotransformation and elimination:

PEGylation, the covalent attachment of PEG polymers to peptides, delays the elimination of these entities from the circulation by a variety of mechanisms, including decreased renal clearance, decreased proteolysis, and decreased immunogenicity. Accordingly, CIMZIA is an antibody binding fragment (Fab') conjugated with PEG in order to extend the terminal plasma elimination half-life of the Fab' to a value comparable with a whole antibody product. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all

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doses tested. Clearance following subcutaneous dosing was estimated to be 21.0 mL/h in a rheumatoid arthritis population pharmacokinetic analysis, with an inter-subject variability of 30.8% (CV) and an inter-occasion variability of 22.0%. The presence of antibodies to CIMZIA results in approximately a three-fold increase in clearance. Compared with a 70 kg person, predicted clearance is 29% lower and 38% higher, respectively, for rheumatoid arthritis patients with extreme body weights of 40 kg and 120 kg, but pharmacodynamic exposure-response analysis showed that no additional therapeutic benefit would be expected from a weight-adjusted dose regimen.

The route of elimination of CIMZIA has not been studied in human subjects but studies in rats have shown that renal excretion is the major route of elimination of the de-conjugated PEG component of CIMZIA.

Renal impairment:

Specific clinical studies have not been performed to assess the effect of renal impairment on the pharmacokinetics of CIMZIA or its PEG fraction. However, population pharmacokinetic analysis based on subjects with mild renal impairment showed no effect of creatinine clearance. There are insufficient data to provide a dosing recommendation in moderate and severe renal impairment. The pharmacokinetics of the PEG (polyethylene glycol) fraction of CIMZIA are expected to be dependent on renal function but have not been assessed in renal impairment.

Hepatic impairment:

Specific clinical studies have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of CIMZIA.

Elderly:

Specific clinical studies have not been performed in elderly subjects. However, no effect of age was observed in a population pharmacokinetic analysis in patients with rheumatoid arthritis in which 78 subjects (13.2% of the population) were aged 65 or greater and the oldest subject was aged 83 years.

Paediatric:

CIMZIA has not been studied in children.

Gender:

There was no effect of gender on the pharmacokinetics of CIMZIA.

Pharmacokinetic/Pharmacodynamic relationship:

A population pharmacokinetic/pharmacodynamic analysis of Phase II and Phase III clinical study data showed an exposure-response relationship between plasma concentration of CIMZIA and efficacy using a maximum effect (E_{max}) model for ACR20 response. The typical average plasma concentration during the dose interval (C_{avg}) that produces half the maximum probability of ACR20 response (EC_{50}) was 17 µg/mL (95% CI: 10-23 µg/mL).

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CLINICAL TRIALS

The efficacy and safety of CIMZIA were assessed in four randomised, placebo-controlled, double-blind studies (RA-I, RA-II, RA-III, and RA-IV) in patients ≥ 18 years of age with moderately to severely active rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) criteria. Patients had ≥ 9 swollen and tender joints and had active disease for at least 6 months prior to baseline. Further inclusion criteria for these trials comprised women being postmenopausal, surgically incapable of child bearing or effectively practicing birth control. Exclusion criteria for these studies were based on medical assessment of conditions covered in the PRECAUTIONS and ADVERSE EFFECTS sections. CIMZIA was administered subcutaneously in combination with MTX at stable doses of at least 10 mg weekly in Studies RA-I and RA-II and stable doses of at least 15 mg weekly in study RA-IV. CIMZIA was administered as monotherapy in Study RA-III. There is no experience with Cimzia in combination with DMARDs other than MTX.

Study RA-I and Study RA-II, the pivotal efficacy and safety trials, evaluated patients who had received MTX for at least 6 months prior to study medication, but had an incomplete response to MTX alone. Patients were treated with a loading dose of 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg or 400 mg of CIMZIA or placebo every other week, in combination with MTX for 52 weeks in Study RA-I and for 24 weeks in Study RA-II. Patients were evaluated for signs and symptoms and structural damage using the ACR20 response at Week 24 (RA-I and RA-II) and modified Total Sharp Score (mTSS) at Week 52 (RA-I). The open-label extension follow-up studies to RA-I and RA-II enrolled 847 and 567 patients respectively, all of whom received 400 mg of CIMZIA+MTX every other week for at least 6 months and then 200 mg of CIMZIA+MTX every other week.

Study RA-III (monotherapy), a supportive efficacy and safety trial, evaluated 220 patients who had failed at least one DMARD prior to receiving CIMZIA. Patients were treated with CIMZIA 400 mg or placebo every 4 weeks for 24 weeks (the monotherapy maintenance dose of 200 mg every 2 weeks has not been formally evaluated in a clinical trial). Patients were evaluated for signs and symptoms using the ACR20 at Week 24.

Study RA-IV, another supportive efficacy and safety trial, evaluated 247 patients who had active disease despite receiving MTX for at least 6 months prior to study enrollment. Patients received 400 mg of CIMZIA every 4 weeks for 24 weeks without a prior loading dose, in combination with MTX. Patients were evaluated for signs and symptoms using the ACR20 at Week 24.

Clinical Response

The percent of CIMZIA-treated patients achieving ACR20, 50, and 70 responses in Studies RA-I, RA-II, RA-III and RA-IV are shown in Tables 1 and 2. In studies RA-I and II CIMZIA-treated patients had statistically significant higher ACR20, 50 and 70 response rates at 6 months compared to placebo-treated patients. There was no extra treatment benefit conferred by a dosage regimen of 400 mg every other week compared with 200 mg every other week. The results in study RA-II (619 patients) were similar to the results in RA-I at Week 24. The results in study RA-IV (247 patients) were similar to those seen in study RA-III..Over the one-year study RA-I, 13% of CIMZIA+MTX-treated patients achieved a major

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clinical response, defined as achieving an ACR70 response over a continuous 6-month period, compared to 1% of placebo+MTX-treated patients.

Table 1: ACR Responses in Studies RA-I and RA-II (Percent of Patients)

Response	Study RA-I Methotrexate Combination (24 and 52 weeks)			Study RA-II Methotrexate Combination (24 weeks)		
	Placebo + MTX N=199	CIMZIA[a] 200 mg q2 weeks + MTX N=393	CIMZIA[a] 200 mg + MTX - Placebo + MTX (95% CI)[c]	Placebo + MTX N=127	CIMZIA[a] 200 mg q2 weeks + MTX N=111	CIMZIA[a] 200 mg + MTX – Placebo + MTX (95% CI)[c]
ACR20						
Week 24	14%	59%*	45% (38%, 52%)	9%	57%*	49% (41%, 57%)
Week 52	13%	53%*	40% (33%, 47%)	NA	NA	NA
ACR50						
Week 24	8%	37%*	30% (24%, 36%)	3%	33%*	29% (23%, 36%)
Week 52	8%	38%*	30% (24%, 37%)	NA	NA	NA
ACR70						
Week 24	3%	21%*	18% (14%, 23%)	1%	16%**	15% (10%, 20%)
Week 52	4%	21%*	18% (13%, 22%)	NA	NA	NA
Major Clinical Response[b]	1%	13%*	12% (8%, 15%)			

[a] CIMZIA administered every 2 weeks preceded by a loading dose of 400mg at Weeks 0, 2 and 4.
[b] Major clinical response is defined as achieving ACR70 response over a continuous 6-month period.
[c] 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution. Wald p-values are quoted for the comparison of treatments using logistic regression with factors for treatment and region. CIMZIA vs. placebo: *p<0.001, **p≤0.01

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Table 2: ACR Responses in Studies RA-III and RA-IV

Response	Study RA-III Monotherapy (24 weeks)			Study RA-IV Methotrexate Combination (24 weeks)		
	Placebo N=109	CIMZIA[a] 400 mg q4 weeks N=111	CIMZIA[a] 400 mg - Placebo (95% CI)[b]	Placebo + MTX N=119	CIMZIA[a] 400mg q4 weeks + MTX N=119	CIMZIA[a] 400 mg + MTX – Placebo + MTX (95% CI)[b]
ACR20 Week 24	9%	46%*	36% (25%, 47%)	23%	46%*	23% (11%, 35%)
ACR50 Week 24	4%	23%*	19% (10%, 28%)	6%	18%**	12% (4%, 20%)
ACR70 Week 24	0%	6%***	6% (1%, 10%)	2%	0%	-2% (-4%, 1%)

[a] CIMZIA administered every 4 weeks not preceded by a loading dose regimen
[b] 95% Confidence Intervals constructed using the large sample approximation to the Normal Distribution. p-values are derived from the Cochran-Mantel-Haenszel test of treatment comparison stratified by country. CIMZIA vs. placebo: *p<0.001, **p≤0.01, ***p≤0.05

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Table 3: 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 q2 weeks + MTX N=393		Placebo N=109		CIMZIA[b] 400 mg q4 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 loading dose of 400mg at Weeks 0, 2 and 4

[b] CIMZIA administered every 4 weeks not preceded by a loading 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's 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. *p<0.001, CIMZIA vs. placebo, based on ANCOVA model with region or country and treatment as factors and baseline as covariate

†For Study RA-I, the median is presented. For Study RA-III, the mean (SD) is presented except for CRP which is presented as geometric mean.

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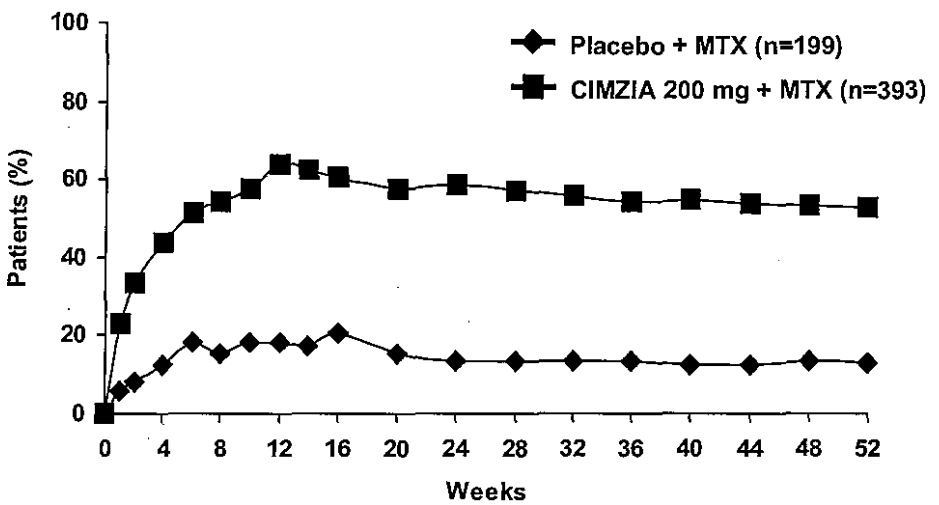
The percentage of patients achieving ACR20 response by visit for Study RA-I is shown in Figure 1. Among patients receiving CIMZIA 200 mg every 2 weeks + MTX, clinical responses were seen in some patients within one (22.9%) to two (33.5%) weeks after initiation of therapy.

Figure 1 Study RA-I ACR20 Response Over 52 Weeks



The safety and efficacy of 400 mg CIMZIA administered every 4 weeks in combination with MTX were evaluated Study RA-IV. The primary endpoint of this study was achieved; the proportion of subjects who achieved an ACR 20 response at Week 24 was significantly greater in the CIMZIA 400 mg + MTX group compared to the placebo + MTX group (45.9% compared to 22.9%, $p<0.001$).

Radiographic Response

In Study RA-I, inhibition of progression of structural damage was assessed radiographically and expressed as the change in modified total Sharp score (mTSS) and its components, the erosion score (ES) and joint space narrowing (JSN) score, at Week 52, compared to baseline. CIMZIA + MTX inhibited the progression of structural damage compared to placebo plus MTX after 12 months of treatment as shown in Table 4. In the CIMZIA 200 mg every other week + MTX treatment group, 69% of patients experienced no radiographic progression (mTSS ≤ 0.0), compared to 52% of patients in the placebo group. Study RA-II showed similar results to RA-I at Week 24.

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Table 4: Radiographic Changes at 6 and 12 Months in Study RA-I

	Placebo + MTX N=199 Mean (SD)	CIMZIA[(a)] 200 mg q2 weeks + MTX N=393 Mean (SD)	CIMZIA[(a)] 200 mg + MTX – Placebo + MTX Mean Difference
mTSS			
Baseline	40 (45)	38 (49)	--
Week 24	1.3 (3.8)	0.2 (3.2)	-1.1
Week 52	2.8 (7.8)	0.4 (5.7)	-2.4
Erosion Score			
Baseline	14 (21)	15 (24)	--
Week 24	0.7 (2.1)	0.0 (1.5)	-0.7
Week 52	1.5 (4.3)	0.1 (2.5)	-1.4
JSN Score			
Baseline	25 (27)	24 (28)	--
Week 24	0.7 (2.4)	0.2 (2.5)	-0.5
Week 52	1.4 (5.0)	0.4 (4.2)	-1.0

[(a)] CIMZIA administered every 2 weeks preceded by a loading dose of 400mg at Weeks 0, 2 and 4.
p-values were < 0.001 at Week 24 and 52 for both mTSS and erosion score and ≤ 0.01 at both timepoints for JSN.
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 Response and health-related outcomes

In studies RA-I, RA-II, RA-III and RA-IV, Cimzia-treated patients reported significant improvements in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) and in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) from Week 1 through to the end of the studies compared to placebo. In all clinical trials, Cimzia-treated patients reported significantly greater improvements in the SF-36 Physical and Mental Component Summaries and all domain scores. Improvements in physical function and HRQoL were maintained through 2 years in the open-label extension to RA-I. In studies RA-I and RA-II, Cimzia-treated patients reported statistically significant improvements in the Work Productivity Survey compared to placebo.

INDICATIONS

CIMZIA is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients.

- combined with MTX in case of either an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDs) or
- as monotherapy in case of a contraindication or intolerance to MTX (see DOSAGE AND ADMINISTRATION).

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CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (See PRECAUTIONS).

Active tuberculosis or other severe infections such as sepsis or opportunistic infections. (See PRECAUTIONS).

Concurrent administration of Cimzia and anakinra (an interleukin-1-receptor antagonist) is contraindicated.

Moderate to severe heart failure (NYHA classes III/IV) (See PRECAUTIONS).

PRECAUTIONS

Immunosuppression:

Since Tumour Necrosis Factor (TNF) mediates inflammation and modulates cellular immune responses, the possibility exists for TNF blocking agents, including CIMZIA, to affect host defences against infections and malignancies. Patients with rheumatoid arthritis may not manifest typical symptoms of infection, including fever, due to their disease and concomitant medications. Therefore, early detection of any infection is critical to minimise delays in diagnosis and initiation of treatment.

Infections:

Patients must be monitored closely for signs and symptoms of infections including tuberculosis before, during and after treatment with CIMZIA, taking into account the 14-day half-life of the product. Treatment with CIMZIA should not be initiated in patients with a clinically important active infection, including chronic or localised infections, until the infection is controlled (See CONTRAINDICATIONS)

Patients who develop a new infection while undergoing treatment with CIMZIA should be monitored closely. Administration of CIMZIA should be discontinued if a patient develops a new serious infection until the infection is controlled. Physicians should exercise caution when considering the use of CIMZIA in patients with a history of recurring or chronic infections or with underlying conditions which may predispose patients to infections.

Serious infections, sepsis, tuberculosis (including miliary, disseminated and extrapulmonary disease) and opportunistic infections have been reported in patients receiving TNF blocking agents including CIMZIA. Some of these events have been fatal. Many of the serious infections reported have occurred in patients on concomitant immunosuppressive therapy that, in addition to their rheumatoid arthritis, could predispose them to infections (See ADVERSE EFFECTS).

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.

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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. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating CIMZIA and periodically during therapy.

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 for patients with a personal history of tuberculosis, with possible previous exposure to others with active tuberculosis, and with previous and/or current use of immunosuppressive therapy. Appropriate screening tests, e.g. tuberculin skin test and chest X -ray, should be performed in all patients (local recommendations may apply). It is recommended that the conduct of these tests should be recorded in the patient's alert card. Prescribers are reminded of the risk of false negative tuberculin skin test results, especially in patients who are severely ill or immunocompromised. Biological tests for tuberculosis screening should be considered before starting CIMZIA treatment if there is any potential latent tuberculosis infection, regardless of BCG vaccination.

If active tuberculosis is diagnosed, CIMZIA therapy must not be initiated. If latent tuberculosis is diagnosed, appropriate anti-tuberculosis prophylaxis must be started before initiating treatment with CIMZIA and in accordance with local recommendations. 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 therapy with CIMZIA (See ADVERSE EFFECTS).

Hepatitis B Virus (HBV) Reactivation:

Use of TNF blockers, including CIMZIA, may increase the risk of reactivation of HBV in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with anti-TNF 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 at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating CIMZIA therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. 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 discontinued 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. Therefore, prescribers should exercise caution when considering resumption of CIMZIA therapy in this situation and monitor patients closely.

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Malignancies and lymphoproliferative disorders:
In clinical studies with CIMZIA and other TNF blocking agents, more cases of lymphoma and other malignancies have been observed among patients receiving TNF antagonists than in control patients receiving placebo. However, the occurrence was uncommon or rare, and the observation period for patients on placebo was shorter than for patients receiving TNF-blocker therapy. Furthermore, the background lymphoma risk in rheumatoid arthritis patients complicates the risk estimation. A possible risk for the development of lymphomas or other malignancies in patients treated with a TNF blocker cannot be excluded.

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 (See PAEDIATRIC USE). Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months of therapy (range 1 to 84 months). Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous post-marketing reports.

In the CIMZIA RA clinical trials (placebo-controlled and open-label) a total of 3 cases of lymphoma were observed among 2,367 patients. This is approximately 2-fold higher than expected in the general population. Patients with RA, particularly those with highly active disease, are at a higher risk for the development of lymphoma.

Rates in clinical studies for CIMZIA cannot be compared to the rates of clinical trials of other TNF blockers and may not predict the rates observed when CIMZIA is used in a broader patient population. The potential role of TNF blocker therapy in the development of malignancies in adults is not known.

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

No studies have been conducted that include patients with a history of malignancy, or that continue treatment in patients who develop malignancy, while receiving CIMZIA. Thus, particular caution should be exercised in considering CIMZIA treatment of these patients. Patients treated with Cimzia should be monitored for symptoms of malignancy and be instructed to inform their physician of any changes to their general health (See ADVERSE EFFECTS).

Chronic obstructive pulmonary disease (COPD):

In an exploratory clinical trial evaluating the use of another TNF antagonist, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

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Congestive heart failure:

In a clinical trial with another TNF blocker, worsening congestive heart failure and increased mortality due to congestive heart failure have been observed. Cases of congestive heart failure have also been reported in rheumatoid arthritis patients receiving CIMZIA. CIMZIA should be used with caution in patients with mild heart failure (NYHA class I/II). CIMZIA is contraindicated in moderate or severe heart failure. Treatment with CIMZIA must be discontinued in patients who develop new or worsening symptoms of congestive heart failure (See ADVERSE EFFECTS).

Haematologic events:

Reports of pancytopenia, including aplastic anaemia, have been rare with TNF blockers. Adverse events of the haematologic system, including medically significant cytopenia (e.g. leukopenia, pancytopenia, and thrombocytopenia) have been infrequently reported with CIMZIA. Although no high risk group has been identified, exercise caution in patients being treated with CIMZIA who have ongoing, or a history of, significant hematologic abnormalities. 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 haematologic abnormalities.

Neurological events:

Use of TNF blockers has been associated with rare cases of exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease. Prescribers should exercise caution in considering the use of CIMZIA in patients with pre-existing or recent-onset central nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, optic neuritis and peripheral neuropathy, have been reported in patients treated with CIMZIA.

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. If such reactions occur, discontinue further administration of CIMZIA and institute appropriate therapy. There are no data on the risks of using CIMZIA in patients who have experienced a severe hypersensitivity reaction towards another TNF blocker; in these patients caution is needed (See ADVERSE EFFECTS).

Autoimmune processes:

Treatment with CIMZIA may result in the formation of autoantibodies and, uncommonly, in the development of a lupus-like syndrome. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with CIMZIA, treatment should be discontinued. CIMZIA has not been studied specifically in a lupus population See ADVERSE EFFECTS).

Vaccinations:

No data are available on the response to vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA. Live vaccines or attenuated vaccines should not be administered concurrently with CIMZIA. No data are available

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concerning concomitant administration of CIMZIA and inactivated vaccines.

Concurrent administration of TNF-alpha inhibitor and other biologics:

Serious infections were seen in clinical studies with concurrent use of anakinra (an interleukin-1 antagonist) or abatacept and another TNF blocking agent, with no added benefit compared to TNF blocker therapy alone. Because of the nature of the adverse events seen with the combination of another TNF blocking agent with abatacept or anakinra therapy, similar toxicities may also result from the combination of anakinra or abatacept and other TNF-blockers. Therefore, the use of CIMZIA in combination with anakinra or abatacept, or any other biological response modifier, is not recommended.

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.

Activated partial thromboplastin time (aPTT) assay:

Interference with certain coagulation assays has been detected in patients treated with Cimzia. Cimzia may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-Lupus Anticoagulant (LA) test and Standard Target Activated Partial Thromboplastin time (STA-PTT) Automate tests from Diagnostica Stago, and the HemosIL APTT-SP liquid HemosIL lyophilised silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. There is no evidence that Cimzia therapy has an affect on coagulation in vivo. After patients receive Cimzia, careful attention should be given to interpretation of abnormal coagulation results. Interference with thrombin time (TT) and prothrombin time (PT) assays have not been observed.

Psoriasis - New-onset and Exacerbations:

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis and cases of exacerbation of pre-existing psoriasis have been reported with the use of TNF blockers, including Cimzia. Many of these patients were taking concomitant immunosuppressants (e.g. MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF blocker. Discontinuation of Cimzia should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Effects on fertility

Since CIMZIA does not cross-react with mouse or rat TNFα, reproductive studies have been performed in rats using a rodent anti-murine TNFα PEGylated Fab' fragment (cTN3 PF), similar to CIMZIA. cTN3 PF had no effects on the fertility and general reproductive performance of male and female rats at iv doses up to 100 mg/kg, administered twice weekly.

Effects on sperm motility measures and a trend of reduced sperm count in male rodents have

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been observed with no apparent effect on fertility. The clinical relevance of this finding is unknown.

Use in pregnancy (Category C)

There are no adequate data from the use of CIMZIA in pregnant women.

Animal studies using a rodent anti-rat TNFα reagent did not reveal evidence of impaired fertility or harm to the foetus. However, these are insufficient with respect to human reproductive toxicity.

CIMZIA should not be used in pregnancy.

Due to its inhibition of TNFα, CIMZIA administered during pregnancy could affect normal immune response in the newborn.

Women of childbearing potential are strongly recommended to use adequate contraception to prevent pregnancy and continue its use for at least 4 months after the last CIMZIA treatment.

Use in lactation

There is insufficient/limited information on the excretion of CIMZIA in human or animal breast milk. A risk to the nursing child cannot be excluded. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with CIMZIA should be made taking into account the benefit of breast-feeding to the child and the benefit of CIMZIA therapy to the woman.

Paediatric use

The safety and efficacy of CIMZIA in paediatric patients have not been established.

Use in the elderly

Specific clinical studies have not been performed in elderly subjects. However, no effect of age was observed in a population pharmacokinetic analysis in patients with rheumatoid arthritis in which 78 subjects (13.2% of the population) were aged 65 or greater and the oldest subject was aged 83 years. showed no effect of age. There was an apparently higher incidence of infections among subjects ≥65 years of age.

Carcinogenicity

Long-term animal studies of CIMZIA have not been conducted to assess its carcinogenic potential

Genotoxicity

CIMZIA was not genotoxic in the Ames test, the human peripheral blood lymphocytes chromosomal aberration assay, or the mouse bone marrow micronucleus assay.

Interactions with other medicines

Concomitant drug treatment with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics, 5-amino salicyclic acid analogs or anti-infectives had no effect on the pharmacokinetics of CIMZIA.

The pharmacokinetics of CIMZIA were evaluated in a pharmacokinetic interaction study in

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16 patients with rheumatoid arthritis receiving stable doses of methotrexate (ranging from 5 to 17.5 mg per week). Co-administration of CIMZIA with methotrexate had no significant effect on the pharmacokinetics of methotrexate while the pharmacokinetics of CIMZIA were similar to those observed previously in healthy subjects.

Hepatic or renal effects

No specific studies have been conducted to assess the effects of hepatic or renal impairment on the pharmacokinetics of CIMZIA or its PEG fraction.

Effect on ability to drive or operate machinery

No studies on the effects on the ability to drive use machines have been performed.

ADVERSE EFFECTS

A total of 2367 subjects with rheumatoid arthritis received CIMZIA and 647 received placebo in clinical trials. The data in Table 5 are based on adverse events reported in controlled and open-label rheumatoid arthritis studies involving the 2367 patients receiving CIMZIA. For placebo-controlled and open-label adverse drug reactions, all events recorded with causality at least "possibly" related to study medication were considered.

In the placebo-controlled studies, patients receiving CIMZIA had an approximately 4 times greater duration of exposure compared with the placebo group. This difference in exposure is primarily due to patients on placebo being more likely to withdraw early. In addition, Studies RA-I and RA-II had a mandatory withdrawal for non-responders at Week 16, the majority of who were on placebo. Adverse reactions were reported in 38.7% of patients treated with CIMZIA and 28.7% of patients treated with placebo in rheumatoid arthritis controlled clinical trials. The proportion of patients who discontinued treatment due to adverse events during the controlled trials was 5% for patients treated with CIMZIA and 2.5% for patients treated with placebo.

In the placebo-controlled rheumatoid arthritis studies, the most common types of adverse reactions were Infections reported in 15.5% of patients on CIMZIA and 7.6% of patients on placebo, and General disorders and administration site conditions, reported in 10.0% of patients on CIMZIA and 9.7% of patients on placebo.

Within the organ system classes, adverse events regardless of causality by frequency are listed using the following categories: very common $\geq$ 1/10 and common $\geq$ 1/100 to $<$ 1/10 in Table 5 below. An Adverse Event is defined as any reported event regardless of causality and an Adverse Reaction as at least having a possible causality to CIMZIA.

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Table 5 Summary of Adverse Events Regardless of Causality for event incidence ≥ 1% in the all CZP doses group and exceeding that of the placebo group reported during placebo-controlled clinical trials

Body system	Adverse Event	PBO +/- MTX (n=647) (%)	CZP +/- MTX (n=1774) (%)
Blood and lymphatic system	Activated partial thromboplastin time prolonged	0.3	1.4
	Anaemia	1.2	1.4
	Eosinophilia	0.5	1.7
Special senses	Vertigo	0.3	1.0
	Conjunctivitis	0.5	1.4
Digestive system	Abdominal pain	0.5	1.4
	Abdominal pain upper	1.2	1.4
	Dyspepsia	2.2	2.3
	Gastritis	0.2	1.2
	Toothache	0.5	1.2
Body as a whole	Asthenia	0.8	1.0
	Bacterial infections not elsewhere classified	1.7	3.3
	Influenza	1.4	1.8
	Pyrexia	1.7	2.8
	Viral infections not elsewhere classified	1.2	2.6
Injection site reactions	Injection site erythema	1.1	1.2
	Injection site reaction	1.1	1.5
Hepatobiliary system	Liver function analyses abnormal	4.8	6.7
Musculoskeletal system	Back pain	1.1	3.7
	Muscle spasms	0.5	1.3
	Pain in extremity	1.2	1.4
Nervous system	Headache	6.0	6.8
Urogenital system	Haematuria	1.1	1.4
	Urinary tract infections	4.5	5.8
Respiratory system	Lower respiratory tract and lung infections	3.4	5.6
	Pharyngolaryngeal pain	0.8	1.7
	Upper respiratory tract infections	9.4	19.8
Skin and appendages	Herpes viral infections	1.2	3.6
	Pruritis	0.5	1.5
	Rash	1.5	3.4
Vascular disorders	Hypertension	1.2	5.0

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

Other infrequent serious adverse drug reactions occurring at an incidence of less than 1% in rheumatoid arthritis patients treated with CIMZIA in clinical trials were:

Neoplasia: solid organ tumours, lymphoma, leukaemia, gastrointestinal tumours, melanoma, non-melanoma skin cancers, pre-cancerous lesions, benign tumours and cysts

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Blood and lymphatic system: leukocytosis, leukopaenia, pancytopaenia, splenomegaly, lympadenopathy, haemosiderosis, thrombocytopaenia, thrombocytosis, erythrocytosis, white blood cell morphology abnormal

Metabolic and nutritional system: thyroid disorders, electrolyte imbalance, dyslipidaemia, appetite disorders, weight change, blood uric acid increased, blood alkaline phosphatase increased

Special senses: ear infections, visual disorder, eye and eyelid inflammation, tinnitus, lacrimation disorder

Cardiac system: cardiomyopathies, congestive heart failure, ischaemic coronary artery disorders, myocarditis, arteriosclerosis, arrhythmias including atrial fibrillation, syncope, pericarditis and pericardial effusion, atrioventricular block, palpitations

Digestive system: ascites, gastrointestinal ulceration and perforation, gastrointestinal fistula, gastrointestinal infections, gastrointestinal tract inflammation, dental infections, stomatitis, odynophagia, abdominal distension, hypermotility, oropharyngeal dryness

Body as a whole: sepsis, tuberculosis, fungal infections, haemorrhage or bleeding at any site, pancreatitis, facial oedema, pain, oedema peripheral, chills, influenza-like illness, altered temperature perception, night sweats, flushing

Hepatobiliary system: hepatitis, hepatopathy (including cirrhosis), cholestasis, cholelithiasis, blood bilirubin increased

Immune system: angioneurotic oedema, vasculitides, lupus erythematosus, sarcoidosis, serum sickness, drug hypersensitivity, panniculitis, allergic disorders, autoantibody positive

Injury: skin injuries, impaired healing

Musculoskeletal system: muscle disorders, blood creatine phosphokinase increased

Nervous system: cranial nerve inflammation and impairment, seizure, impaired coordination or balance, dysaesthesia, peripheral neuropathies, dizziness, tremor, paraesthesia

Psychiatric system: anxiety, mood disorders, somnolence, suicide attempt, delirium, mental impairment

Respiratory system: interstitial lung disease, pneumonitis, asthma, pleuritis and pleural effusion, respiratory tract congestion and inflammation, cough

Skin and appendages: skin exfoliation and desquamation, bullous conditions, alopecia, psoriasis, dermatitis and eczema, ecchymoses, sweat gland disorder, skin ulcer, photosensitivity, acne, skin discolouration, dry skin, nail and nail bed disorders, hair texture disorder

Vascular disorders: cerebrovascular accident (includes transient ischaemic attack), hypercoagulation (includes pulmonary embolism, thrombophlebitis), Raynaud's phenomenon, livedo reticularis, telangiectasia

Urogenital system: renal impairment, nephropathy, nephritis, nephrolithiasis, menstrual cycle and uterine bleeding disorders, reproductive tract infections, bladder and urethral

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symptoms, breast disorders, sexual dysfunction

Additional postmarketing events: demyelination, anaphylactic shock

The additional following Adverse Drug Reactions (ADRs) have been observed uncommonly with CIMZIA in other indications: gastrointestinal stenosis and obstructions, general physical health deterioration, grand mal convulsion, optic neuritis, abortion spontaneous and azoospermia.

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 with the placebo groups (0.06 per patient-year for all CIMZIA doses vs. 0.02 per patient-year for placebo). Rates of serious infections were 0.07 per patient-year in the 200 mg every 2 week dose group and 0.04 in the 400 mg every 4 weeks dose group. Serious infections included tuberculosis and invasive opportunistic infections (e.g., *Pneumocystis*, fungal oesophagitis, *Nocardia* and herpes zoster disseminated). 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 PRECAUTIONS).

Tuberculosis and Opportunistic Infections

In completed and ongoing global clinical studies in all indications 5,118 CIMZIA treated patients, the overall rate of tuberculosis is approximately 0.61 per 100 patient-years across all indications.

The majority of cases occurred in countries with high endemic rates of TB. Across all indications, no cases of TB have been reported in Australia (0/140) and 1 case (1/53) in New Zealand. In total across the region and all indications, this represents 1 case among 193 patients. Reports include cases of miliary, lymphatic, peritoneal, as well as pulmonary TB. The median time to onset of TB for all patients exposed to CIMZIA across all indications was 345 days. In the studies with CIMZIA in RA, there were 36 cases of TB among 2,367 exposed patients, including some fatal cases (see PRECAUTIONS).

Congestive heart failure

In placebo controlled and open-label rheumatoid arthritis clinical trials, cases of new or worsening heart failure have been reported for CIMZIA-treated patients. The majority of these cases were mild to moderate and occurred during the first year of exposure (see PRECAUTIONS).

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

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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.

Immunogenicity

The overall percentage of patients with antibodies to CIMZIA detectable on at least one occasion was 8% (105 of 1,509) in the phase III RA placebo-controlled trials. The percentage of patients with antibodies to CIMZIA at 6 months, for each of the approved dosing regimens, was 5.1% and 8.5% for the 200 mg every 2 weeks + MTX regimen (studies RA-I and RA-II respectively), 4% for the 400 mg every 4 weeks + MTX regimen (study RA-IV), and 22.5% for the 400 mg every 4 weeks monotherapy regimen (study RA-III).

Approximately one-third of antibody-positive patients (3%, 39 of 1,509) had antibodies with neutralising activity *in vitro*. Patients treated with concomitant immunosuppressants (MTX) had a lower rate of antibody development than patients not taking immunosuppressants at baseline (2% vs 8%).

Antibody formation was associated with lowered drug plasma concentration and in some patients, 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, and are highly dependent on the sensitivity and specificity of the assay. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to certolizumab pegol with the incidence of antibodies to other products may be misleading.

Hypersensitivity reactions

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

Malignancies and lymphoproliferative disorders

In placebo-controlled and open-label rheumatoid arthritis studies combined, observed malignancies included breast and ovarian cancers, basal cell carcinoma, and lymphoma. Cases of lymphoma occurred at an incidence rate of 0.06 per 100 patient-years and melanoma at an incidence rate of 0.02 per 100 patient-years with CIMZIA in rheumatoid arthritis clinical trials. The number of cases reported is insufficient to identify a treatment effect (see PRECAUTIONS).

<u>Lymphoma</u>

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

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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.

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 pf 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.

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) subjects who experienced non-melanoma skin cancers.

Autoimmune disease

In placebo-controlled rheumatoid arthritis studies, there was no clinically meaningful increase in ANA or anti-double-stranded DNA antibody 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 open-label follow-up studies for rheumatoid arthritis, cases of lupus-like syndrome were reported uncommonly. 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 (See PRECAUTIONS).

Laboratory abnormalities

Liver enzyme elevations

In controlled rheumatoid arthritis trials (studies RA-I to RA-IV), when corrected for exposure, the incidence of hepatic enzyme elevations was similar in the subjects receiving placebo as compared to CIMZIA (see PRECAUTIONS).

Injection site reactions

In the placebo-controlled rheumatoid arthritis studies, 6.4% of patients treated with CIMZIA developed injection site reactions (erythema, itching, haematoma, pain, swelling or bruising), compared to 6.5% of patients receiving placebo. In particular, injection site pain was observed in 1.5% of patients treated with CIMZIA, in the placebo-controlled

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rheumatoid arthritis studies, with no cases leading to withdrawal.

DOSAGE AND ADMINISTRATION

The recommended dose of CIMZIA for adult patients with rheumatoid arthritis is 400 mg (2 x 200 mg subcutaneous injections) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks via subcutaneous injection.

Alternatively, when a maintenance dose of 200 mg every 2 weeks is not practical, a maintenance dose of 400 mg every 4 weeks has been shown to be safe and effective.

No additional benefit has been observed with doses above a total dose of 400mg/monthly (see CLINICAL TRIALS Section)

CIMZIA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

After proper training in injection technique, patients may self-inject with CIMZIA if their physician determines that it is appropriate and with medical follow-up as necessary.

Children and adolescents:

There is no experience in children or adolescents below 18 years of age.

Elderly:

No dose adjustment is required. Population pharmacokinetic analyses showed no effect of age.

Renal impairment:

There are insufficient data to provide dosing recommendations in moderate and severe renal impairment (see **Pharmacokinetic properties**).

Hepatic impairment:

Specific clinical studies have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of CIMZIA.

OVERDOSAGE

No case of CIMZIA overdose has been reported.

The maximum tolerated dose of CIMZIA has not been established. No dose-limiting toxicity was observed during clinical trials. Multiple doses of up to 800mg subcutaneously and 20mg/kg intravenously have been administered and well tolerated.

In cases of overdosage, it is recommended that patients are monitored closely for any adverse reactions or effect, and appropriate symptomatic treatment initiated immediately. For advice on the management of overdose please contact the Poisons Information centre.

For further information on the management of overdosage contact the Poisons Information Centre (telephone 13 11 26).

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PRESENTATION AND STORAGE CONDITIONS

Cimzia® Injection is supplied in a carton containing two single use prefilled glass syringes of 200 mg (1mL) CIMZIA and two alcohol pads.

Storage at 2 to 8°C (Refrigerate. Do not freeze.)

Product is for single use in one patient only. Discard any residue.

Protect from light.

NAME AND ADDRESS OF THE SPONSOR

UCB Pharma
A division of UCB Australia Pty Ltd
Level 1, 1155 Malvern Road
Malvern VIC 3144, Australia

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF APPROVAL

Date of TGA approval:

22/12/2009