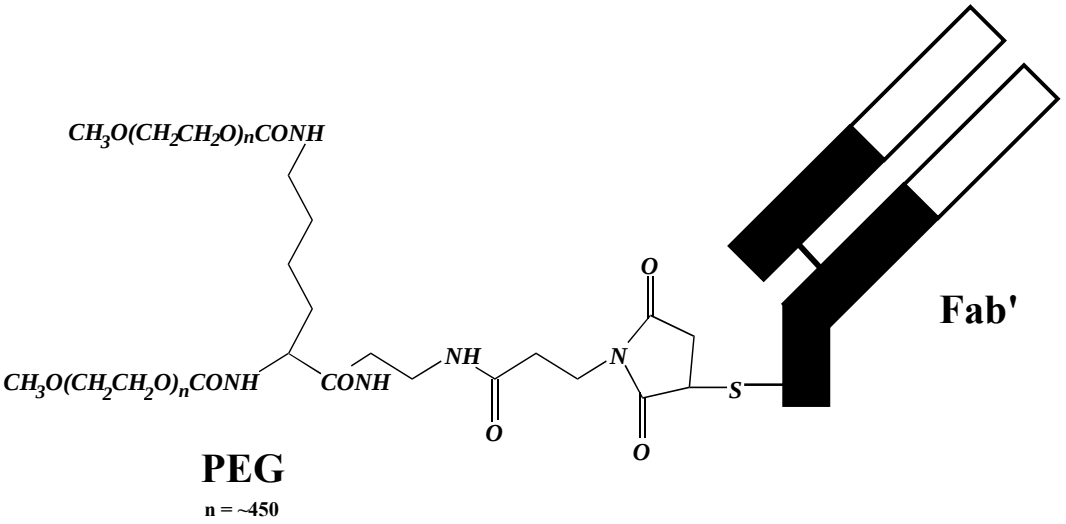
Attachment 1: Product information for AusPAR Cimzia Certolizumab pegol UCB Australia Pty Ltd PM-2015-01158-1-3 Final 21 June 2017. This Product Information was approved at the time this AusPAR was published.

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 sterile clear to opalescent solution that is colourless to yellow, essentially free of visible particles, 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 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 e*x 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

The pharmacokinetics of CIMZIA in rheumatoid arthritis psoriatic arthritis and ankylosing spondylitis patients are similar.

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.

Metabolism:

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 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 metabolism of certolizumab pegol has not been studied in human subjects.

Excretion:

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).

CLINICAL TRIALS

Rheumatoid arthritis

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. Over the time period of 6.5-years from first subject enrolled to final subject completed in the two pivotal extension studies to RA-I and RA-II, the overall withdrawal rate from the two open-label extension studies was approximately 40%. Approximately 16% of the total subjects from each study had subject decision as the reason for withdrawal and for approximately 17%, the reason was an adverse event. For both studies, less than 5% had reasons of lack of efficacy, protocol noncompliance, lost to follow-up or other.

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 enrolment. 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.

The efficacy and safety of CIMZIA was assessed in DMARD-naïve adult patients with active RA in a randomized, placebo-controlled, double-blind clinical trial (C-EARLY). In the C-EARLY trial patients were ≥ 18 years of age and must have been diagnosed with moderate to severe active and progressive RA within 1 year (as defined by the 2010

ACR/European League Against Rheumatism (EULAR) classification criteria). At baseline, 96.9% of subjects in the CIMZIA+MTX arm and 95.3% subjects in the PBO+MTX arm had severe RA defined as high disease activity > 5.1. Subjects that had active disease were defined by:

- ≥4 swollen and tender joints each (DAS28) at Screening and Baseline,
- DAS28 (ESR) >3.2 at Screening and Baseline,
- CRP ≥10mg/L at Screening and/or ESR ≥28mm/h at Screening and Baseline.

The progressive nature of disease in the study population is indicated by the high disease activity, high swollen joint count (SJC), elevated CRP and ESR, presence of ACPA and/or RA factor. At baseline 77.8% of subjects had erosion, indicating that many subjects already had radiographic progression. Patients had a mean time since diagnosis at baseline of 2.9 months and were DMARD naïve (including MTX). CIMZIA was administered subcutaneously in combination with orally administered MTX (no CIMZIA monotherapy arm). Patients were treated with a loading dose of 400 mg at Week 0, 2 and 4 or placebo followed by 200 mg of CIMZIA or placebo every 2 weeks during 52 weeks. For both the CIMZIA and placebo arms, MTX was initiated as of Week 0 (10 mg/week), titrated up to maximum tolerated dose by Week 8 (min 15 mg/week, max 25 mg/week allowed), and maintained throughout the study (average dose of MTX after Week 8 for placebo and CIMZIA was 22.3 mg/week and 21.1 mg/week respectively). Patients were evaluated for signs and symptoms using the proportion of subjects in sustained remission at Week 52. Sustained remission is defined as DAS28[ESR] <2.6 at both Week 40 and Week 52). Structural damage was also assessed. Subjects were withdrawn at Week 20 if no improvement in disease activity (change in DAS 28(ESR) ≤0) was observed. Subjects were withdrawn at Week 24 if insufficient improvement at Week 20 was confirmed at Week 24 (sufficient improvement in disease activity is defined as: Low Disease Activity (ie, DAS28 [ESR] ≤3.2) and/or, improvement in DAS 28(ESR) of ≥1.2 points since Baseline).

Clinical Response

The percentage 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 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)

	Study RA-I Methotrexate Combination (24 and 52 weeks)			Study RA-II Methotrexate Combination (24 weeks)		
Response	**Placebo +**	**CIMZIA[(a)]**	**CIMZIA[(a)]**	**Placebo +**	**CIMZIA[(a)]**	**CIMZIA[(a)]**

	MTX N=199	200 mg q2 weeks + MTX N=393	200 mg + MTX - Placebo + MTX (95% CI)[c]	MTX N=127	200 mg q2 weeks + MTX N=111	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

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

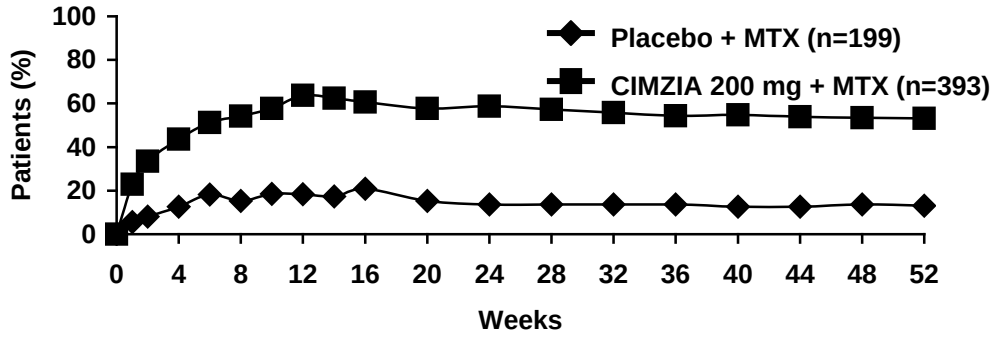
Parameter[†]	Study RA-I				Study RA-III			
	Placebo + MTX N=199		CIMZIA[(a)] 200 mg q2 weeks + MTX N=393		Placebo N=109		CIMZIA[(b)] 400 mg q4 weeks Monotherapy N=111	
	Baseline	**Week 24**	**Baseline**	**Week 24**	**Baseline**	**Week 24**	**Baseline**	**Week 24**
Number of tender joints (0-68)	28	27	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.

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).

The C-EARLY trial met its primary and key secondary endpoint. The key results from the study are presented in table 4.

Table 4: C-EARLY trial: percent of patients in sustained remission, sustained low disease activity and with ACR50 at Week 52

Response	**Placebo + MTX N=213**	**CIMZIA 200mg + MTX N = 655**
Sustained remission[(a)] (DAS28(ESR) <2.6 at both Week 40 and Week 52)	15.0%	28.9%[(b)]
Sustained low disease activity (DAS28(ESR) ≤3.2 at both Week 40 and Week 52)	28.6%	43.8%[(b)]
ACR 50	52.6%	61.8%[(c)]

[(a)] Primary endpoint of C-EARLY trial (to Week 52).
Full analysis set, non-responder imputation for missing values.
[(b)] p<0.001
[(c)] p<0.05
CIMZIA+MTX vs placebo+MTX: p value was estimated from a logistic regression model with factors for treatment, region, and time since rheumatoid arthritis diagnosis at Baseline (≤4 months vs >4 months)

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 5. 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.

Table 5: Radiographic Changes at 6 and 12 Months in Study RA-I and at 6 Months in Study RA-II

	Placebo + MTX Mean (SD)		**CIMZIA[(a)] 200 mg q2 weeks + MTX Mean (SD)**		**CIMZIA[(a)] 200 mg + MTX – Placebo + MTX Mean Difference**	
	RA-I N=199	**RA-II N=127**	**RA-I N=393**	**RA-II N= 246**	**RA-I**	**RA-II**
mTSS						
N	199	125	391	241	--	--
Baseline	39 (45)	47 (59)	38 (49)	40 (50)	--	--
N	180	112	353	214	--	--
Week 24	1.3 (3.8)	1.2 (4.1)	0.2 (3.2)	0.2 (2.7)	-1.1	-1.0
N	181	N/A	364	N/A		
Week 52	2.8 (7.8)	N/A	0.4 (5.7)	N/A	-2.4	N/A
Erosion Score[(b)]						
Baseline	14 (21)	23 (32)	15 (24)	19 (27)	--	--
Week 24	0.7 (2.1)	0.7 (2.6)	0.0 (1.5)	0.1 (2.0)	-0.7	-0.6
Week 52	1.5 (4.3)	N/A	0.1 (2.5)	N/A	-1.4	N/A
JSN Score[(b)]						
Baseline	25 (27)	23 (28)	24 (28)	21 (24)	--	--
Week 24	0.7 (2.4)	0.5 (2.3)	0.2 (2.5)	0.1 (1.4)	-0.5	-0.4
Week 52	1.4 (5.0)	N/A	0.4 (4.2)	N/A	-1.0	N/A

[(a)] CIMZIA administered every 2 weeks preceded by a loading dose of 400mg at Weeks 0, 2 and 4.
For RA-I, p-values were < 0.001 at Week 24 and 52 for both mTSS and erosion score and £ 0.01 at both time points for JSN. For RA-II, p-values were ≤0.01at Week 24 for mTSS, erosion score and JSN score.
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.
[(b)] n values for erosion score and JSN score are the same as for mTSS.

Of the 783 patients initially randomized to active treatment in RA-I, 508 completed 52 weeks of placebo-controlled treatment and entered the open-label extension study. Sustained inhibition of progression of structural damage was demonstrated in a subset of 449 of these patients who completed at least 2 years of treatment with CIMZIA (RA-I and open-label extension study) and had evaluable data at the 2-year timepoint. This was not a pre-planned analysis. Linear imputation was used for missing data. There were 177 patients in the control group, including 136 Withdrawers (subjects who received placebo + MTX for 12 weeks and failed to achieve an ACR20 response at Week 12, confirmed at

Week 14 who then participated in the open-label extension study from Week 16) and 41 Completers (subjects who received placebo + MTX for 52 weeks before participating in the open-label extension study). The efficacy of CIMZIA on radiographic endpoints has not been established in patients who are unable to tolerate MTX therapy.

In C-EARLY, at Week 52, the mean changes (SD) from Baseline in mTSS were:

- 0.2 (3.2) in the CIMZIA+MTX group and
- 1.8 (4.3) in the PBO+MTX group

The CIMZIA+MTX – PBO+MTX treatment difference was -0.978 (-1.005, -0.500) (Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) confidence interval). A p-value of <0.001 for the treatment difference was estimated from an ANCOVA model on the ranks with treatment, region, time since RA diagnosis at Baseline (≤4 months vs >4 months) as factors and Baseline rank as 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.

In C-EARLY, at Week 52, subjects in the CZP+MTX group had a statistically significant improvement in physical functioning over the PBO+MTX group (-1.0 vs -0.82 points; p<0.001), as assessed in the change from baseline in HAQ-DI.

Psoriatic arthritis

The efficacy and safety of CIMZIA were assessed in a multicenter, randomized, double-blind, placebo controlled clinical trial (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 received a loading dose of CIMZIA 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either CIMZIA 200 mg every 2 weeks or 400 mg every 4 weeks or placebo every 2 weeks. Patients receiving concomitant NSAIDs and conventional DMARDs were 72.6% and 70.2 % respectively. 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.

ACR response

The percentage of CIMZIA-treated patients achieving ACR20, 50 and 70 responses in the

PsA001 clinical trial are shown in Table 6. CIMZIA-treated patients had a statistically significant higher ACR20 response rate at Week 12 and Week 24 compared with placebo-treated patients (p<0.001). CIMZIA treated patients also had significant improvements in ACR50 and 70 response rates and for each ACR component at Week 12 and 24 compared to placebo (see Table 7). Responses were similar in patients receiving CIMZIA 200 mg every 2 weeks or CIMZIA 400 mg every 4 weeks.

Table 6: Key efficacy outcomes in PsA001 clinical trial (percent of patients)

Response	**Placebo N=136**	**CIMZIA[(a)]200 mg Q2W N=138**	**CIMZIA[(b)] 400 mg Q4W 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%**
Response	**Placebo N=86**	**CIMZIA[(a)]200 mg Q2W N=90**	**CIMZIA[(b)] 400 mg Q4W N=76**
PASI 75			
Week 12	14%	47%**	47%**
Week 24	15%	62%**	61%**
PASI 90			
Week 12	5%	22%**	20%*
Week 24	6%	47%**	36%**

N reflects number of randomised patients; number for PASI is based on the subset of patients with ≥ 3% body surface area (BSA) involvement at baseline.

[(a)] CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
[(b)] CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
**p<0.001, CIMZIA vs placebo
*p<0.01, 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. Non-responder Imputation (NRI) is used.

Table 7: Components of ACR response in PsA001 clinical trial

Parameter	**Placebo N=136**			**CIMZIA[(a)] 200 mg Q2W N=138**			**CIMZIA[(b)] 400 mg Q4W N=135**		
	Baseline	**Week**	**Week**	**Baseline**	**Week**	**Week**	**Baseline**	**Week**	**Week**

		12	**24**		**12**	**24**		**12**	**24**
Number of tender joints (0-68)[c]	19.9	16.5	17.0	21.5	11.2*	8.5*	19.6	11.2*	9.4*
Number of swollen joints (0-66)[c]	10.4	8.7	9.9	11.0	4.0*	3.1*	10.5	4.7*	3.0*
Physician Global assessment[c, d]	58.7	44.1	42.2	56.8	24.8*	19.6*	58.2	28.7*	21.1*
Patient global assessment[c, d]	57.0	50.2	49.0	60.2	32.6*	31.1*	60.2	39.6*	32.5*
Pain[c, e]	60.0	50.2	48.8	59.7	32.8*	31.1*	61.1	38.6*	32.7*
Disability index (HAQ)[c, f]	1.30	1.15	1.13	1.33	0.87*	0.81*	1.29	0.90*	0.86*
CRP (mg/L)	18.56	14.75	14.66	15.36	5.67*	4.58*	13.71	6.34*	7.37*

[a] CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
[b] CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
[c] Last Observation Carried Forward is used for missing data, early withdrawals or placebo escape.
[d] Patient and Physician Global Assessment of Disease Activity, VAS 0= best 100= worst
[e] The Patient Assessment of Arthritis Pain, VAS 0= no pain and 100= most severe pain
[f] The HAQ-DI, 4 point scale 0= without difficulty and 3= unable to do
All values presented represent the mean.
Results are from the randomized set (either with imputation or observed case). *p<0.001, CIMZIA vs placebo

The percentage of ACR20 responders was clinically relevant and significantly higher for the CIMZIA 200 mg every 2 weeks and CIMZIA 400 mg every 4 weeks treatment groups compared to placebo group at every visit after baseline through Week 24 ($p \leq 0.001$ at each visit).

Patients with enthesitis and dactylitis at baseline were evaluated for mean improvement in Leeds Enthesitis Index (LEI) and Leeds Dactylitis Index (LDI). CIMZIA-treated patients either 200 mg every 2 weeks or 400 mg every 4 weeks showed greater reduction in enthesitis (-1.8; -1.7) as compared with placebo-treated patients (-0.9) at week 12 ($p<0.001$ and $p<0.01$, respectively) and week 24 (200 mg every 2 weeks: -2.0; 400 mg every 4 weeks: 1.8; placebo: -1.1) ($p<0.001$; $p<0.01$, respectively). Also, the same dose regimens showed greater reduction in dactylitis (mean change from baseline -30.40; -45.46) as compared with placebo-treated patients (-16.79) at week 12 ($p<0.05$ and $p<0.001$, respectively) and week 24 (200 mg every 2 weeks: -40.69; 400 mg every 4 weeks: -53.47, placebo: -22.04) ($p<0.01$; $p<0.001$, respectively).

Radiographic response
In PsA001 clinical trial, 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 joints. Radiographic data for baseline or Week 24 were missing for 12% of randomized subjects; analysis was conducted using post-hoc imputation rules with a minimum of an 8-week time window between X-rays applied. CIMZIA treatment reduced the radiographic progression compared with placebo treatment at Week 24 as measured by change from baseline in total mTSS Score (LS mean [±SE] score was 0.28 [±0.07] in the placebo group compared with 0.06 [± 0.06] in the CIMZIA all doses group; p=0.007).

Physical function response and health-related outcomes

In PsA001 clinical trial, CIMZIA-treated patients reported significant improvements in physical function as assessed by the Health Assessment Questionnaire – Disability Index (HAQ-DI) and in pain as assessed by the Patient Assessment of Arthritis Pain (PAAP) from Week 1 through Week 24 as compared to placebo (see Table 7). CIMZIA-treated patients reported significant improvements in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) from Week 2 through Week 24 as compared to placebo. CIMZIA-treated patients reported significant improvements in health-related quality of life as measured by the psoriatic arthritis QoL (PsAQoL) and the SF-36 Physical and Mental Component Summaries in all domain scores from Week 4 through Week 24.

CIMZIA-treated patients reported improvements in psoriatic arthritis-related productivity at work and within household, as reported by the Work Productivity Survey from Week 4 through Week 24 compared to placebo.

Ankylosing Spondylitis

The efficacy and safety of CIMZIA were assessed in one multicenter, randomized, double-blind, placebo-controlled trial (AS001) in 325 patients ≥18 years of age with adult-onset active axial spondyloarthritis for at least 3 months as defined by the Assessment of Spondyloarthritis International Society (ASAS) Classification Criteria for axial spondyloarthritis. Axial spondyloarthritis refers to spondyloarthritis with predominantly axial involvement and includes the disease subgroup of patients with definitive signs of damage suggestive as consequence of sacroiliitis on x-ray (ankylosing spondylitis), as well as a disease subgroup with no definitive evidence of sacroiliitis on plain radiographs (non-radiographic axial spondyloarthritis). Patients had active disease as defined by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4, spinal pain ≥ 4 on a 0 to 10 Numerical Rating Scale (NRS) and increased CRP or current evidence of sacroiliitis on Magnetic Resonance Imaging (MRI). Patients must have been intolerant to or had an inadequate response to at least one NSAID.

Overall 20.2% of AS patients had prior TNF-antagonist exposure. Patients were treated with a loading dose of CIMZIA 400 mg at Weeks 0, 2 and 4 (for both treatment arms) or placebo followed by either 200 mg of CIMZIA every 2 weeks or 400 mg of CIMZIA every 4 weeks or placebo. 91% of AS patients received concomitant NSAIDs.The primary efficacy endpoint was the ASAS20 response rate at Week 12. One hundred and seventy eight patients (54.8%) patients in the study had active AS, and only these results are presented.

ASAS response

In AS001 clinical trial, at Week 12 ASAS20 responses were achieved by 57% of patients receiving CIMZIA 200 mg every 2 weeks and 64% of patients receiving CIMZIA 400 mg every 4 weeks as compared to 37% of patients receiving placebo ($p < 0.01$). At Weeks 12 and 24, the percentage of subjects with an ASAS40 response was greater in the CIMZIA-treated groups compared to placebo. Responses were similar in AS patients receiving CIMZIA 200 mg every 2 weeks or CIMZIA 400 mg every 4 weeks (see Table 8).

CIMZIA-treated patients also had significant improvement compared to placebo in multiple components of ankylosing spondylitis disease activity (see Table 9).

Table 8: Efficacy response in AS001 clinical trial: reduction of signs and symptoms in ankylosing spondylitis sub-populations (percent of patients)

Parameters	Ankylosing spondylitis			
	Placebo N=57	**CIMZIA 200 mg every 2 weeks N=65**	**CIMZIA 400 mg every 4 weeks N=56**	**CIMZIA all dosing regimens[a] N=121**
ASAS20[b,c]				
Week 12	37%	57%*	64%*	60%*
Week 24	33%	68%**	70%**	69%**
ASAS40[c,d]				
Week 12	19%	40%*	50%**	45%**
Week 24	16%	48%**	59%**	53%**
ASAS 5/6[c,d]				
Week 12	9%	48%**	36%**	42%**
Week 24	5%	34%**	46%**	40%**
Partial remission[c,d]				
Week 12	2%	20%**	20%*	20%**
Week 24	7%	31%**	25%*	28%**
BASDAI 50 [c,d]				
Week 12	11%	42%**	41%**	41%**
Week 24	16%	43%**	55%**	49%**

[a] CIMZIA all dosing regimen = data from CIMZIA 200 mg administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4 plus CIMZIA 400 mg administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
[b] Results are from the randomized set.
[c] 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.
[d] Full Analysis Set.
NA = not available
*$p \leq 0.05$, CIMZIA vs placebo
**$p<0.001$, CIMZIA vs placebo

Table 9: Components of the ASAS response criteria and other measures of disease activity in AS patients at baseline and Week 12 in study AS001

	Placebo N=57		**CIMZIA[a] 200mg Every 2 weeks N=65**		**CIMZIA[b] 400mg every 4 weeks N=56**	
ASAS response criteria	Baseline	Week12	Baseline	Week 12	Baseline	Week 12

-Patient Global Assessment (0-10)	6.9	5.6	7.3	4.2	6.8	3.8
-Total spinal pain (0-10)	7.3	5.8	7.0	4.3	6.9	4.0
-BASFI (0-10)[(c)]	6.0	5.2	5.6	3.8	5.7	3.8
-Inflammation (0-10)	6.7	5.5	6.7	3.8	6.4	3.4
BASDAI (0-10)[(d)]	6.4	5.4	6.5	3.9	6.2	3.7
BASMI [(e)]	4.7	4.4	4.2	3.6	4.3	3.9

(a)CIMZIA administered every 2 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
(b)CIMZIA administered every 4 weeks preceded by a loading dose of 400 mg at Weeks 0, 2 and 4.
(c)BASFI is Bath Ankylosing Spondylitis Functional Index
(d)BASDAI is Bath Ankylosing Spondylitis Disease Activity Index
(e)BASMI is Bath Ankylosing Spondylitis Metrology Index
All values presented represent the mean in the full analysis set.

In the AS subpopulation, the percentage of ASAS20 responders was clinically relevant and significantly higher for the CIMZIA 200 mg every 2 weeks and CIMZIA 400 mg every 4 weeks treatment groups compared to placebo group at every visit after baseline through Week 24 ($p<0.05$ at each visit).

Spinal Mobility
Spinal mobility was assessed by BASMI. The difference to placebo in mean change from baseline in BASMI linear at Week 24 was -0.32 points ($p<0.05$) in CIMZIA-treated patients.

Maastricht Ankylosis Spondylitis Enthesitis Score (MASES)
The assessment of enthesitis showed a clinically meaningful improvement ($p<0.001$) in CIMZIA-treated patients compared with placebo treated patients at Week 24.

Inhibition of inflammation in Magnetic Resonance imaging (MRI)
In an imaging sub-study signs of inflammation were assessed by MRI at week 12 and expressed as change from baseline in SPARCC (Spondyloarthritis Research Consortium of Canada) score for sacroiliac joints and ASspiMRI-a score in the Berlin modifications for the spine. Significant inhibition of inflammatory signs in both sacroiliac joints and the spine was observed in the CIMZIA-treated patient (all doses group), in the sub-population of ankylosing spondylitis patients, but not in placebo-treated patients.

Physical function response and health-related outcomes
In AS001 clinical trial, CIMZIA-treated AS patients reported significant improvements in physical function as assessed by the BASFI and in pain as assessed by the Nocturnal Back Pain NRS scales from Week 1 through Week 24 as compared to placebo. CIMZIA-treated AS patients reported significant improvements in tiredness (fatigue) as reported by the BASDAI-fatigue item from Week 1 through Week 24 as compared to placebo (see table 9). CIMZIA-treated patients reported significant improvements in health-related quality of life as measured by the ankylosing spondylitis QOL (ASQoL) at Week 24.

INDICATIONS

Rheumatoid arthritis

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).

CIMZIA has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.

CIMZIA in combination with MTX is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs.

Psoriatic arthritis
CIMZIA is indicated for the treatment of adult patients with active psoriatic arthritis where response to previous disease-modifying anti-rheumatic drug therapy (DMARDs) has been inadequate. CIMZIA has been shown to improve physical function.

Ankylosing Spondylitis
CIMZIA is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID).

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, psoriatic arthritis or ankylosing spondylitis 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. Because the elimination of certolizumab pegol may take up to 5 months, monitoring should be considered throughout this period. 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, opportunistic infection, chronic infections or with underlying conditions which may predispose patients to infections.

Serious infections due to bacterial, mycobacterial, invasive fungal, viral and / or parasitic pathogens, 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. Among opportunistic infections, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, nocardiosis, listeriosis, and pneumocystosis were the most frequently reported. 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.

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 and must be discontinued (see CONTRAINDICATIONS). 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). Despite previous or concomitant prophylactic treatment for tuberculosis, cases of active tuberculosis have occurred in patients treated with TNF-antagonists including CIMZIA.

Hepatitis B Virus (HBV) Reactivation:

Reactivation of hepatitis B occurred in patients receiving a TNF-antagonist including CIMZIA, who are chronic carriers of this virus (i.e. surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-antagonist 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-antagonist therapy, in conjunction with anti-viral therapy, to prevent HBV reactivation. Patients who are carriers of HBV and require treatment with TNF-antagonists 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-antagonist 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.

Malignancies and lymphoproliferative disorders:

In clinical studies with CIMZIA and other TNF-antagonist 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-antagonist 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-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-antagonist 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.

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-antagonists. The majority of the reported TNF-antagonist 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-antagonist prior to diagnosis.

In the CIMZIA RA clinical trials (placebo-controlled and open-label) a total of 5 cases of lymphoma were observed among 4,049 patients. 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-antagonists and may not predict the rates observed when CIMZIA is used in a broader patient population. The potential role of TNF-antagonist therapy in the development of malignancies in adults is not known.

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

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).

Skin cancers

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

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 active-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.

Congestive heart failure:

In a clinical trial with another TNF-antagonist, 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-antagonists. 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 on-going, 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-antagonists has been associated with rare cases of 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 nervous system demyelinating disorders. Rare cases of neurological disorders, including seizure disorder, cranial nerve neuritis, peripheral neuropathy and transverse myelitis, 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. Some of these reactions occurred after the first administration. 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-antagonist; 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 live vaccinations or the secondary transmission of infection by live vaccines in patients receiving CIMZIA. Live or live-attenuated vaccines should not be administered concurrently with CIMZIA. Patients treated with CIMZIA may receive inactivated vaccines on the basis of data from recently completed clinical trials.

In a placebo-controlled clinical trial of patients with rheumatoid arthritis (RA0017), no meaningful 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 (See Table 10).

Table 10: Satisfactory humoral response at week 6

	Cimzia % (n/N)	Placebo % (n/N)	Difference in proportion [95 % CI]
Pneumococcal vaccine	54.5% (48/88)	62.5% (55/88)	-0.080 [-0.225; 0.066]
Influenza vaccine	53.5% (46/86)	61.4% (51/83)	-0.080 [-0.229; 0.070]

(Note: A humoral responder is defined as a subject with:

- a ≥2-fold increase at Week 6 from vaccination at Week 2 in ≥3 of 6 pneumococcal antigens 6B, 9V, 14, 18C, 19F, and 23F;

- a ≥4-fold increase at Week 6 from vaccination at Week 2 in ≥2 of 3 influenza antigens H1N1 (nonpandemic), H3N2, and B).

However, patients receiving CIMZIA and concomitant methotrexate had a lower humoral response compared with patients receiving CIMZIA alone (See Table 11). The clinical significance of this is unknown.

Table 11: Satisfactory humoral response at week 6 per concomitant use of MTX

	Placebo % (n/N)	CIMZIA % (n/N)	Difference in proportion [95 % CI]	Placebo + MTX % (n/N)	CIMZIA + MTX % (n/N)	Difference in proportion [95 % CI]
Pneumococcal vaccine	89.3% (25/28)	80.0% (20/25)	-0.093 [-0.286; 0.100]	50.0% (30/60)	44.4% (28/63)	-0.056 [-0.232; 0.121]
Influenza vaccine	84.6% (22/26)	70.4% (19/27)	-0.142 [-0.368, 0.083]	50.9% (29/57)	45.8% (27/59)	-0.051 [-0.233; 0.131]

CIMZIA does not significantly suppress the protective humoral immune response to the pneumococcal polysaccharide vaccine or influenza vaccine.

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-antagonist agent, with no added benefit compared to TNF-antagonist therapy alone. Because of the nature of the adverse events seen with the combination of another TNF-antagonist agent with abatacept or anakinra therapy, similar toxicities may also result from the combination of anakinra or abatacept and other TNF-antagonists. 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.

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-antagonists, 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-antagonist. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-antagonist. 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 been observed with no apparent effect on fertility.

In a clinical trial to assess the effect of certolizumab pegol on semen quality parameters (primary variables: % total motility and % normal ovoid form morphology; secondary variables; semen volume, sperm count and concentration, % progressive motility, and % vitality), 20 healthy male subjects were randomized to receive a single subcutaneous dose of 400 mg of certolizumab pegol (n=15) or placebo (n=5). A linear repeated measures model with the interaction between treatment group (placebo or certolizumab pegol) and visit as fixed effect and subject as random effect was fitted to each variable. The 90% confidence intervals on the treatment effect were derived. During the 14 weeks follow-up certolizumab pegol 400mg treatment had no effect over that of placebo on semen quality variables (total motility point estimate -1.3, 90% CI -8.5 to 5.9; morphology point estimate -2.1, 90% CI -4.7 to 0.4).

Use in pregnancy (Category C)

Women of childbearing potential should use adequate contraception to prevent pregnancy and continue its use for at least 10 weeks after the last CIMZIA treatment. The elimination of certolizumab pegol may take up to 5 months.

There are no adequate and well-controlled studies of CIMZIA in pregnant women, CIMZIA should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

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.

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 foetus during gestation. However, there was little or no measurable transfer of cTN3 PF (surrogate Fab'fragment to certolizumab without an Fc) to the foetus when compared to maternal plasma concentrations, demonstrating the importance of the Fc for placental transfer.

Supporting data were also collected in a human closed-circuit placental transfer model in vitro where certolizumab pegol concentrations were found to be below or near the lowest level of quantification (LLOQ) level in foetal circuit.

In an independent clinical study in 10 patients with Crohn's disease treated with CIMZIA, certolizumab pegol concentrations were measured in maternal blood as well as in cord and infant blood (n=12) at the day of birth. Certolizumab pegol concentrations were very low in cord blood (<0.41 [Lower Level of Quantification] – 1.66 µg/mL) and infant blood (<0.41 – 1.58 µg/mL) compared to maternal blood levels (1.87 – 59.57 µg/mL). PEG concentrations were below Lower Level of Quantification, which ranged from 9 µg/mL (when sufficient sample was collected) up to 36 µg/mL (when sample needed to be diluted), in all cord and infant blood samples.

Pre-clinical and clinical data suggest a lack of active FcRn-dependent placental transfer of certolizumab pegol. Due to its inhibition of TNFα, CIMZIA administration during pregnancy could affect normal immune responses in the new-born. Although certolizumab pegol levels are low in the infant, the clinical significance of these low levels is unknown. The risk and benefits of administering live vaccines during the first 12 weeks should be discussed with a paediatrician (see Vaccinations). However, humoral response in adults in the presence of CIMZIA was similar to that of placebo with respect to inactivated vaccines.

Information from case reports of certolizumab pegol exposure during pregnancy

During clinical development and post-marketing surveillance, cases of pregnancy have been reported in patients treated with certolizumab pegol. Through March 2014, a total of 566 pregnancy reports had been received, 528 cases occurred in women treated with certolizumab pegol at any time during pregnancy, 38 were reported from men treated at time of conception.

Pregnancy outcomes were known for 304/528 cases of maternal exposure (197 prospective cases and 107 retrospective cases). Overall, 73% of the reported pregnancies resulted in live births, the remaining pregnancies resulted in miscarriage (15 %) or elective termination

(11%). In six infants (2%) born from treated mothers, 7 congenital malformations were reported (vesicoureteric reflux, talipes, polydactyly, bilateral hydronephrosis, Hirschsprung's disease, and club foot and right aortic arch with aberrant left subclavian), for which the causal role of certolizumab pegol is unknown.

Detailed information regarding period (trimester) or extent of exposure was not available. These data should be interpreted with caution due to limitations such as underreporting and incomplete information. They represent reporting rates and may not be representative of the general disease population experience.

Published data from the US population suggested that major birth defects occur in 2-4% of the general population and that miscarriage occurs in 15-20% of clinically recognized pregnancies.

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. There was an apparently higher incidence of infections among subjects ≥ 65 years of age.

Genotoxicity

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

Carcinogenicity

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

Effect on laboratory tests

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 effect 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.

Effect on ability to drive or operate machinery

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

INTERACTIONS WITH OTHER MEDICINES

Concomitant drug treatment with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs, analgesics, 5-amino salicylic 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 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.

ADVERSE EFFECTS

Rheumatoid arthritis

Cimzia was studied in 4049 patients with rheumatoid arthritis in controlled and open-label trials for up to 92 months. The data in Table 12 are based primarily on adverse reactions reported in placebo-controlled rheumatoid arthritis studies involving the 2965 patients receiving CIMZIA and 1137 patients receiving placebo during the controlled period. 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 34.0% of patients treated with CIMZIA and 24.9% 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 4.4% for patients treated with CIMZIA and 2.7% for patients treated with placebo.

In the placebo-controlled rheumatoid arthritis studies, the most common types of adverse reactions were infections reported in 14.4% of patients on CIMZIA and 8.0% of patients on placebo, general disorders and administration site conditions, reported in 8.8% of patients on CIMZIA and 7.4% of patients on placebo and skin and subcutaneous tissue disorders, reported in 7.0% of patients with CIMZIA and 2.4% of patients on placebo.

CIMZIA in combination with MTX was studied in 879 (3 subjects were randomised but did not receive the study medication) DMARD naïve patients with rheumatoid arthritis in a placebo + MTX controlled clinical trial (C-EARLY) for up to 52 weeks. The safety profile for the DMARD naïve patients with rheumatoid arthritis treated with CIMZIA is

summarised in Table 13 and Hepatic section.

Psoriatic arthritis

CIMZIA was studied in 409 patients with psoriatic arthritis in a placebo-controlled clinical trial (PsA001). The safety profile for psoriatic arthritis patients treated with CIMZIA was consistent with the safety profile in rheumatoid arthritis and previous experience with CIMZIA.

Ankylosing spondylitis

CIMZIA was studied in 325 patients with axial spondyloarthritis in a placebo-controlled clinical trial (AS001). The safety profile for axial spondyloarthritis patients treated with CIMZIA was consistent with the safety profile in rheumatoid arthritis and previous experience with CIMZIA.

Table 12: 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 RA clinical trials in patients with inadequate response to DMARDs.

System Organ Class	Adverse Event	PBO +/- MTX (n=1137) (%)	CZP +/- MTX (n=2965) (%)
Infections and infestations	Upper respiratory tract infection	4.3%	5.9%
	Nasopharyngitis	4.1%	5.3%
	Urinary tract infection	4.1%	4.5%
	Herpes simplex	0.7%	2.3%
	Sinusitis	1.6%	2.2%
	Pharyngitis	0.6%	1.7%
	Bronchitis acute	0.5%	1.6%
	Rhinitis	0.6%	1.6%
	Bacteriuria	0.6%	1.0%
Musculoskeletal and connective tissue disorders	Back pain	1.3%	3.3%
	Muscle spasms	0.9%	1.4%
Gastrointestinal disorders	Abdominal pain upper	0.9%	1.3%
	Abdominal pain	0.6%	1.3%
General disorders and administration site conditions	Injection site reactions	0.8%	1.4%
	Pyrexia	1.1%	2.2%
	Injection site erythema	0.7%	1.2%
Skin and subcutaneous tissue disorders	Pruritus	0.6%	1.6%
	Rash	1.1%	3.5%
Investigations	Aspartate aminotransferase increased	1.1%	1.2%
	Alanine aminotransferase increased	1.4%	1.8%
	Hepatic enzyme increased	0.8%	1.1%
Respiratory, thoracic and mediastinal disorders	Cough	2.6%	2.7%
Injury, poisoning and procedural complications	Contusion	0.5%	1.1%

Vascular disorders	Hypertension	1.4%	3.9%
Blood and Lymphatic system disorders	Eosinophilia	0.4%	1.0%
Renal and urinary disorders	Haematuria	0.6%	1.0%

Table 13: Summary of Adverse Events Regardless of Causality for event incidence ≥ 1% in the CZP group and exceeding that of the placebo group reported during C-EARLY clinical trial (DMARD naïve patients with rheumatoid arthritis in a placebo-controlled clinical trial).

System Organ Class	Adverse Event	PBO + MTX (n=217) (%)	CZP + MTX (n=659) (%)
Infections and infestations	Upper respiratory tract infection	5.1%	10.9%
	Nasopharyngitis	6.0%	7.0%
	Tooth abscess	0.5%	1.1%
	Conjunctivitis	0.0%	1.2%
	Oral herpes	0.9%	1.5%
	Herpes zoster	0.9%	1.1%
	Influenza	1.4%	2.1%
	Bronchitis	3.2%	4.4%
	Sinusitis	2.3%	3.6%
Ear and labyrinth Disorders	Vertigo	0.5%	1.1%
Musculoskeletal and connective tissue disorders	Back pain	2.8%	2.9%
	Myalgia	0.9%	1.1%
	Muscle spasms	0.9%	1.1%
	Arthralgia	1.8%	2.1%
	Pain in extremity	0.5%	1.7%
	Osteoarthritis	0.9%	1.5%
Gastrointestinal disorders	Abdominal pain upper	1.8%	2.1%
	Diarrhoea	1.8%	4.7%
	Gastritis	0.9%	2.1%
	Nausea	10.1%	12.6%
	Vomiting	1.4%	2.0%
	Mouth ulceration	1.4%	1.5%
	Stomatitis	0.0%	1.1%
	Abdominal pain	0.9%	2.3%
General disorders and administration site conditions	Injection site reaction	0.0%	1.1%
	Pyrexia	0.9%	1.5%
	Fatigue	0.0%	2.1%
	Malaise	0.5%	1.5%
	Injection site bruising	0.9%	1.2%
	Alopecia	3.2%	3.9%
	Dermatitis	0.9%	1.1%
Investigations	Aspartate aminotransferase increased	2.3%	3.0%
	Alanine aminotransferase increased	4.1%	6.4%
	Blood creatine phosphokinase increased	0.5%	2.0%

	Hypercholesterolaemia	2.3%	3.0%
	Hyperlipidaemia	0.9%	1.4%
Respiratory, thoracic and mediastinal disorders	Cough	3.2%	3.9%
	Epistaxis	0.0%	1.4%
Injury, poisoning and procedural complications	Contusion	0.5%	1.4%
	Fall	0.9%	1.1%
	Laceration	0.5%	1.5%
Nervous system disorders	Headache	3.7%	6.8%
	Paraesthesia	0.0%	1.1%
Vascular disorders	Hypertension	2.3%	2.4%
	Anaemia	1.4%	2.6%
Immune system disorders	Seasonal allergy	0.0%	1.7%
Renal and urinary disorders	Haematuria	0.0%	1.0%
Reproductive system and breast disorders	Menorrhagia	0.0%	1.1%
Psychiatric disorders	Anxiety	0.5%	1.2%

Within the organ system classes, adverse reactions by frequency are listed using the following categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), Uncommon (≥1/1000 to <1/100); Rare (≥1/10000 to <1/1000), not known (cannot be estimated from the available data) in Table 14 below.

Table 14: Adverse drug reactions in RA clinical trials and postmarketing

System Organ Class	Frequency	Adverse Drug Reactions
Infections and infestations	Common	bacterial infections (including abscess), viral infections (including herpes zoster and herpes simplex, papillomavirus, influenza)
	Uncommon	sepsis (including multi-organ failure, septic shock), tuberculosis (including miliary, disseminated and extrapulmonary disease), fungal infections (includes opportunistic)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Uncommon	blood and lymphatic system malignancies (including lymphoma and leukaemia), solid organ tumours, non-melanoma skin cancers, pre-cancerous lesions (including oral leukoplakia, melanocytic nevus), benign tumours and cysts (including skin papilloma)
	Rare	gastrointestinal tumours, melanoma
	Not Known	Merkel cell carcinoma*
Blood and the lymphatic system disorders	Common	eosinophilic disorders, leukopaenia (including neutropaenia, lymphopaenia)
	Uncommon	anaemia, lymphadenopathy, thrombocytopaenia, thrombocytosis
	Rare	pancytopaenia, splenomegaly, erythrocytosis, white blood cell morphology abnormal

Immune system disorders	Uncommon	vasculitides, lupus erythematosus, drug hypersensitivity (including anaphylactic shock), allergic disorders, autoantibody positive
	Rare	angioneurotic oedema, sarcoidosis, serum sickness, panniculitis (including erythema nodosum)
Endocrine disorders	Rare	thyroid disorders
Metabolism and nutrition disorders	Uncommon	electrolyte imbalance, dyslipidaemia, appetite disorders, weight change
	Rare	haemosiderosis
Psychiatric disorders	Uncommon	anxiety and mood disorders (including associated symptoms)
	Rare	suicide attempt, delirium, mental impairment
Nervous system disorders	Common	headaches (including migraine), sensory abnormalities
	Uncommon	peripheral neuropathies, dizziness, tremor
	Rare	seizure, cranial nerve inflammation, impaired coordination or balance, sleep disorder
	Not Known	multiple sclerosis*, Guillain-Barré syndrome*
Eye disorders	Uncommon	visual disorder (including decreased vision), eye and eyelid inflammation, lacrimation disorder
Ear and labyrinth Disorders	Uncommon	tinnitus, vertigo
Cardiac disorders	Uncommon	cardiomyopathies (including heart failure), ischaemic coronary artery disorders , arrhythmias (including atrial fibrillation), palpitations
	Rare	pericarditis, atrioventricular block
Vascular disorders	Common	hypertension
	Uncommon	haemorrhage or bleeding (any site), hypercoagulation (including thrombophlebitis, pulmonary embolism), syncope, oedema (including peripheral, facial), ecchymoses (including haematoma, petechiae)
	Rare	cerebrovascular accident, arteriosclerosis, Raynaud's phenomenon, livedo reticularis, telangiectasia
Respiratory, thoracic and mediastinal disorders	Uncommon	asthma and related symptoms, pleural effusion and symptoms, respiratory tract congestion and inflammation, cough
	Rare	interstitial lung disease, pneumonitis
Gastrointestinal disorders	Common	nausea
	Uncommon	ascites, gastrointestinal ulceration and perforation, gastrointestinal tract inflammation (any site), stomatitis, dyspepsia, abdominal distension, oropharyngeal dryness

	Rare	odynophagia, hypermotility
Hepatobiliary disorders	Common	hepatitis (including hepatic enzyme increased)
	Uncommon	hepatopathy (including cirrhosis), cholestasis, blood bilirubin increased
	Rare	cholelithiasis
Skin and subcutaneous tissue disorders	Common	rash
	Uncommon	alopecia, new onset or worsening of psoriasis (including 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
	Rare	skin exfoliation and desquamation, bullous conditions, hair texture disorder
Musculoskeletal, connective tissue and bone disorders	Uncommon	muscle disorders, blood creatine phosphokinase increased
Renal and urinary disorders	Uncommon	renal impairment, blood in urine, bladder and urethral symptoms
	Rare	nephropathy (including nephritis)
Reproductive system and breast disorders	Uncommon	menstrual cycle and uterine bleeding disorders (including amenorrhea), breast disorders
	Rare	sexual dysfunction
General disorders and administration site conditions	Common	pyrexia, pain (any site), asthaenia, pruritus (any site), injection site reactions
	Uncommon	chills, influenza-like illness, altered temperature perception, night sweats, flushing
	Rare	fistula (any site)
Investigations	Uncommon	blood alkaline phosphatase increased, coagulation time prolonged
	Rare	blood uric acid increased
Injury, poisoning and procedural complications	Uncommon	skin injuries, impaired healing

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

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, vaginal discharge and fistula (any site).

Infections

The incidence of new cases of infections in placebo-controlled clinical studies in rheumatoid arthritis was 1.03 per patient-year for all CIMZIA-treated patients and 0.92 per patient-year for placebo-treated patients. The infections consisted primarily of upper respiratory tract infections, urinary tract infections, lower respiratory tract infections and herpes viral 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 (0.07 per patient-year for all CIMZIA doses vs. 0.02 per patient-year for placebo). Rates of serious infections were 0.08 per patient-year in the 200 mg every 2 week dose group and 0.05 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). 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 50 cases of TB among 4049 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 increased occurred in 1.8% of CIMZIA-treated and 1.4% of placebo treated patients, and AST increased occurred in 1.2% of CIMZIA-treated and 1.1 % of placebo-treated patients. Hepatic adverse events occurred in 1.2% of CIMZIA-treated patients and 0.7% 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 1.88 per 100 patient-years, as compared to 2.88 per 100 patient-years during the placebo-controlled rheumatoid arthritis studies. In the C-EARLY study, the incidence of adverse events of ALT increased occurred in 6.4% and 4.1%, of AST increased in 3.0% and 2.3% and of hepatic enzyme increased in 2.4% and 2.8% in CIMZIA-treated and placebo-treated patients respectively, in DMARDs naïve subjects. Of note is that the MTX dose was higher in C-EARLY study compared to RA-I, RA-II and RA-IV.

Immunogenicity

Rheumatoid arthritis

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.

Psoriatic arthritis

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 number of patients with antibodies to CIMZIA in this trial was too small to make valid assessment of the impact of the antibody formation on efficacy.

Axial spondyloarthritis

The overall percentage of patients with antibodies to CIMZIA detectable on at least one occasion up to Week 24 was 4.4% in the phase III placebo controlled trial in patients with axial spondyloarthritis. Antibody formation was associated with lowered drug plasma concentration. The number of patients with antibodies to CIMZIA in these trials was too small to make valid assessment of the impact of the antibody formation on efficacy.

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 0.05 per 100 patient-years and melanoma at an incidence rate of 0.08 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).

Lymphoma

In rheumatoid arthritis placebo-controlled and open label studies combined, 5 cases of lymphoma were reported in patients treated with CIMZIA (1 case in the placebo-controlled studies and 4 in the open-label studies), corresponding to a rate of 0.05 /100 patient-years among 4049 patients. No lymphoma was reported among 1137 placebo-treated patients. One case of lymphoma was also observed in the phase III psoriatic arthritis clinical trial.

Non-Lymphoma Malignancies

In the rheumatoid arthritis placebo-controlled studies, 9 patients (0.3%) treated with CIMZIA and 4 patients (0.35%) in the placebo group experienced malignancies other than lymphomas and non-melanoma skin cancers.

In rheumatoid arthritis placebo-controlled and open-label studies combined, 68 malignancies other than lymphomas and non-melanoma skin cancers were observed at a rate of 0.7 /100 patient-years among 4049 CIMZIA-treated patients and 4 malignancies at a rate of 1.08 /100 patient-years among 1137 placebo-treated patients.

Non-Melanoma Skin Cancers

In the rheumatoid arthritis placebo-controlled studies, non-melanoma skin cancers occurred in 4 patients (0.1%) receiving CIMZIA and 1 patient in the placebo group. In the controlled and uncontrolled studies, there were a total of 28 (0.7%) subjects who experienced non-melanoma skin cancers.

Autoimmune disease

In the pivotal 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 PHARMACOLOGY).

Injection site reactions

In the placebo-controlled rheumatoid arthritis studies, 5.8% of patients treated with CIMZIA developed injection site reactions (erythema, itching, haematoma, pain, swelling or bruising), compared to 4.8% of patients receiving placebo. In particular, injection site pain was observed in 1.5% of patients treated with CIMZIA, in the placebo-controlled rheumatoid arthritis studies, with no cases leading to withdrawal.

DOSAGE AND ADMINISTRATION

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 via subcutaneous injection. Alternatively, CIMZIA 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).

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 can be considered.

Ankylosing spondylitis

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

For the above indications, available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continuation of therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

CIMZIA treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. 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 further information on the management of overdosage contact the Poisons Information Centre (telephone 13 11 26).

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^{o}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 first inclusion in the Australian Register of Therapeutic Goods: 20 January 2010
Date of most recent amendment: 07 November 2016