

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 200 mg certolizumab pegol in one ml.

Certolizumab pegol is a recombinant, humanised antibody Fab' fragment against tumour necrosis factor alpha (TNF α) expressed in *Escherichia coli* and conjugated to polyethylene glycol (PEG).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe.

Clear to opalescent, colourless to yellow solution. The pH of the solution is approximately 4.7.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDs) including methotrexate, has been inadequate.

Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis. Patients should be given the special alert card.

Posology

The recommended starting dose of Cimzia for adult patients with rheumatoid arthritis is 400 mg (as 2 injections of 200 mg each on one day) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia where appropriate.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Missed dose

Patients who miss a dose should be advised to inject the next dose of Cimzia as soon as they remember and then continue injecting subsequent doses every 2 weeks as originally instructed.

Paediatric population (< 18 years old)

The safety and efficacy of Cimzia in children and adolescents below age 18 years have not yet been established. No data are available.

Elderly (≥65 years old)

No dose adjustment is required. Population pharmacokinetic analyses showed no effect of age (see section 5.2).

Renal and hepatic impairment

Cimzia has not been studied in these patient populations. No dose recommendations can be made (see section 5.2).

Method of administration

The total content (1 ml) of the pre-filled syringe should be administered as a subcutaneous injection only. Suitable sites for injection would include the thigh or abdomen.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Active tuberculosis or other severe infections such as sepsis or opportunistic infections (see section 4.4).

Moderate to severe heart failure (NHYA classes III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Infections

Patients must be monitored closely for signs and symptoms of infections including tuberculosis before, during and after treatment with Cimzia. Because the elimination of Cimzia may take up to 5 months, monitoring should be continued throughout this period (see section 4.3).

Treatment with Cimzia must not be initiated in patients with a clinically important active infection, including chronic or localised infections, until the infection is controlled (see section 4.3).

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 infection or with underlying conditions which may predispose patients to infections, including the use of concomitant immunosuppressive medications.

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

Serious infections, including sepsis and tuberculosis (including miliary, disseminated and extrapulmonary disease), and opportunistic infections (e.g. histoplasmosis, nocardia, candidiasis) have been reported in patients receiving Cimzia. Some of these events have been fatal.

Tuberculosis

Before initiation of therapy with Cimzia, all patients must be evaluated for both active or 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.

If active tuberculosis is diagnosed prior to or during treatment, Cimzia therapy must not be initiated and must be discontinued (see section 4.3).

If inactive ('latent') tuberculosis is suspected, a physician with expertise in the treatment of tuberculosis should be consulted. In all situations described below, the benefit/risk balance of Cimzia therapy should be very carefully considered.

If latent tuberculosis is diagnosed, appropriate anti-tuberculosis therapy must be started before initiating treatment with Cimzia and in accordance with local recommendations.

Use of anti-tuberculosis therapy should also be considered before the initiation of Cimzia in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and in patients who have significant risk factors for tuberculosis despite a negative test for latent tuberculosis. Biological tests for tuberculosis screening should be considered before starting Cimzia treatment if there is any potential latent tuberculosis infection, regardless of BCG vaccination.

Patients should be instructed to seek medical advice if signs/symptoms (e.g. persistent cough, wasting/weight loss, low grade fever, listlessness) suggestive of a tuberculosis infection occur during or after therapy with Cimzia.

Hepatitis B Virus (HBV) reactivation

Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist including Cimzia, who are chronic carriers of this virus (i.e., surface antigen positive). Some cases have had a fatal outcome.

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.

Carriers of HBV who require treatment with Cimzia should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF-antagonist therapy to prevent HBV reactivation are not available. In patients who develop HBV reactivation, Cimzia should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Malignancies and lymphoproliferative disorders

The potential role of TNF antagonist therapy in the development of malignancies is not known. Caution should be exercised when considering TNF antagonist therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

With the current knowledge, a possible risk for the development of lymphomas, leukaemia or other malignancies in patients treated with a TNF antagonist cannot be excluded.

In clinical trials with Cimzia and other TNF antagonists, more cases of lymphoma and other malignancies have been reported among patients receiving TNF antagonists than in control patients receiving placebo (see section 4.8). In the post marketing setting, cases of leukaemia have been reported in patients treated with a TNF antagonist. There is an increased background risk for lymphoma and leukaemia in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation.

No trials have been conducted that include patients with a history of malignancy, or that continue treatment in patients who develop malignancy, while receiving Cimzia.

Paediatric malignancy

Malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF antagonists (initiation of therapy \leq 18 years of age) in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with TNF antagonists cannot be excluded.

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.

Congestive heart failure

Cimzia is contraindicated in moderate or severe heart failure (see section 4.3). 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). Treatment with Cimzia must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Haematological reactions

Reports of pancytopenia, including aplastic anaemia, have been rare with TNF antagonists. Adverse reactions of the haematologic system, including medically significant cytopenia (e.g. leukopenia, pancytopenia, thrombocytopenia) have been reported with Cimzia (see section 4.8). 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 haematological abnormalities.

Neurological events

Use of TNF antagonists has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of TNF antagonist treatment should be carefully considered before initiation of Cimzia therapy. Rare cases of neurological disorders, including seizure disorder, neuritis and peripheral neuropathy, have been reported in patients treated with Cimzia.

Hypersensitivity

Severe hypersensitivity reactions have been reported rarely following Cimzia administration in trials. If severe reactions occur, administration of Cimzia should be discontinued immediately and appropriate therapy instituted.

There are limited data on the use of Cimzia in patients who have experienced a severe hypersensitivity reaction towards another TNF antagonist; in these patients caution is needed.

Immunosuppression

Since tumour necrosis factor (TNF) mediates inflammation and modulates cellular immune responses, the possibility exists for TNF antagonists, including Cimzia, to cause immunosuppression, affecting host defences against infections and malignancies.

Autoimmunity

Treatment with Cimzia may result in the formation of antinuclear antibodies (ANA) and, uncommonly, in the development of a lupus-like syndrome (see section 4.8). The impact of long-term treatment with Cimzia on the development of autoimmune diseases is unknown. If a patient develops

symptoms suggestive of a lupus-like syndrome following treatment with Cimzia, treatment must be discontinued. Cimzia has not been studied specifically in a lupus population (see section 4.8).

Vaccinations

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

Concomitant use with other biologics

Severe infections and neutropaenia were reported in clinical trials with concurrent use of anakinra (an interleukin-1 antagonist) or abatacept (a CD28 modulator) and another TNF antagonist, etanercept, 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 with either 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 is not recommended (see section 4.5).

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 and 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.

Elderly

In the clinical trials, there was an apparently higher incidence of infections among subjects ≥ 65 years of age, compared to younger subjects, although experience is limited. Caution should be exercised when treating the elderly, and particular attention paid with respect to occurrence of infections.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant treatment with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics showed no effect on the pharmacokinetics of certolizumab pegol based on a population pharmacokinetics analysis.

The combination of Cimzia and anakinra or abatacept is not recommended (see section 4.4).

Co-administration of Cimzia with methotrexate had no significant effect on the pharmacokinetics of methotrexate. In study-to-study comparison, the pharmacokinetics of certolizumab pegol appeared similar to those observed previously in healthy subjects.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

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

Animal studies using a rodent anti-rat TNF α did not reveal evidence of impaired fertility or harm to the foetus. However, these are insufficient with respect to human reproductive toxicity (see section 5.3). Due to its inhibition of TNF α , Cimzia administered during pregnancy could affect normal immune response in the newborn. Therefore, Cimzia should not be used in pregnancy.

Breast-feeding

There is insufficient information on the excretion of certolizumab pegol in human or animal breast milk. Since immunoglobulins are excreted into human breast milk, a risk to the breast-feeding 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.

Fertility

Effects on sperm motility measures and a trend of reduced sperm count in male rodents have been observed with no apparent effect on fertility (see section 5.3). The clinical relevance of this finding is unknown.

4.7 Effects on ability to drive and use machines

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 (see section 4.8).

4.8 Undesirable effects

Cimzia was studied in 2,367 patients with rheumatoid arthritis in controlled and open label trials for up to 57 months. The data in Table 1 are based primarily on the pivotal controlled Studies involving 1,774 patients receiving Cimzia and 647 patients receiving placebo during the controlled period.

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 whom were on placebo.

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.

The most common adverse reactions belonged to the system organ classes Infections and infestations, 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.

Adverse reactions reported in rheumatoid arthritis clinical trials and postmarketing at least possibly related to Cimzia are listed in Table 1 below, according to frequency and system organ class. Frequency categories are defined as follows: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1000$); Very rare ($< 1/10,000$), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table :1. Adverse drug reactions in clinical trials and postmarketing

System Organ Class	Frequency	Adverse Drug Reactions
Infections and infestations	Common	bacterial infections (including abscess), viral infections (including herpes, papillomavirus, influenza)

System Organ Class	Frequency	Adverse Drug Reactions
	Uncommon	sepsis (including multi-organ failure, septic shock), tuberculosis, 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
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
	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	vertigo
	Rare	tinnitus
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

System Organ Class	Frequency	Adverse Drug Reactions
Gastrointestinal disorders	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), asthenia, pruritis (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 ADRs have been observed uncommonly with Cimzia in other indications: gastrointestinal stenosis and obstructions, general physical health deterioration, abortion spontaneous and azoospermia.

Infections

The incidence of new cases of infections in placebo-controlled clinical trials 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 (see sections 4.3 and 4.4).

In the placebo-controlled clinical trials, there were more new cases of serious infection in the Cimzia treatment groups (0.06 per patient-year; all doses), compared with placebo (0.02 per patient-year). Serious infections included tuberculosis and invasive opportunistic infections (e.g. pneumocystosis,

fungal oesophagitis, nocardiosis and herpes zoster disseminated). There is no evidence of an increased risk of infections with continued exposure over time (see section 4.4).

Malignancies and lymphoproliferative disorders

Excluding non-melanoma of the skin, 30 malignancies including 3 cases of lymphoma were observed in the Cimzia RA clinical trials in which a total of 2,367 patients were treated, representing 4,136 patient-years. Cases of lymphoma occurred at an incidence rate of 0.07 per 100 patient-years and melanoma at an incidence rate of 0.02 per 100 patient-years with Cimzia in rheumatoid arthritis clinical trials (see section 4.4).

Autoimmunity

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. For subjects who were anti-dsDNA antibody negative at baseline, 2.2% of those treated with Cimzia developed positive anti-dsDNA antibody titers, compared with 1.0% of subjects in the placebo group. In both placebo-controlled and open-label follow-up clinical trials 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.

Injection site reactions

In the placebo-controlled rheumatoid arthritis clinical trials, 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. Injection site pain was observed in 1.5% of patients treated with Cimzia with no cases leading to withdrawal.

4.9 Overdose

No dose-limiting toxicity was observed during clinical trials. Multiple doses of up to 800 mg subcutaneously and 20 mg/kg intravenously have been administered. In cases of overdose, it is recommended that patients are monitored closely for any adverse reactions or effect, and appropriate symptomatic treatment initiated immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tumour necrosis factor alpha (TNF α) inhibitors, ATC code: L04AB05

Mechanism of action

Cimzia has a high affinity for human TNF α and binds with a dissociation constant (KD) of 90 pM. TNF α is a key pro-inflammatory cytokine with a central role in inflammatory processes. Cimzia selectively neutralises TNF α (IC₉₀ of 4 ng/ml for inhibition of human TNF α in the *in vitro* L929 murine fibrosarcoma cytotoxicity assay) but does not neutralise lymphotoxin α (TNF β).

Cimzia was shown to neutralise membrane associated and soluble human TNF α in a dose-dependant manner. Incubation of monocytes with Cimzia resulted in a dose-dependant inhibition of lipopolysaccharide (LPS)-induced TNF α and IL1 β production in human monocytes.

Cimzia does not contain a fragment crystallisable (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.

Clinical efficacy

The efficacy and safety of Cimzia have been assessed in 2 randomised, placebo-controlled, double-blind clinical trials in patients ≥ 18 years of age with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria, RA-I (RAPID 1) and RA-II (RAPID 2). Patients had ≥ 9 swollen and tender joints each and had active RA for at least 6 months prior to baseline. Cimzia was administered subcutaneously in combination with oral MTX for a minimum of 6 months with stable doses of at least 10 mg weekly for 2 months in both trials. There is no experience with Cimzia in combination with DMARDs other than MTX.

Table :2. Clinical trial description

Study number	Patient numbers	Dose regimen	Study objectives
RA-I (52 weeks)	982	400 mg (0,2,4 weeks) with MTX 200 mg or 400 mg every 2 weeks with MTX	Evaluation for treatment of signs and symptoms and inhibition of structural damage. Co-primary endpoints: ACR 20 at Week 24 and change from baseline in mTSS at Week 52
RA-II (24 weeks)	619	400 mg (0,2,4 weeks) with MTX 200 mg or 400 mg every 2 weeks with MTX	Evaluation for treatment of signs and symptoms and inhibition of structural damage. Primary endpoint: ACR 20 at Week 24.

mTSS: modified Total Sharp Score

ACR response

The results of clinical trials RA-I and RA-II are shown in Table 3. Statistically significantly greater ACR 20 and ACR 50 responses were achieved from Week 1 and Week 2, respectively, in both clinical trials compared to placebo. Responses were maintained through Weeks 52 (RA-I) and 24 (RA-II). Of the 783 patients initially randomised to active treatment in RA-I, 508 completed 52 weeks of placebo-controlled treatment and entered the open-label extension study. Of these, 427 completed 2 years of open-label follow-up and thus had a total exposure to Cimzia of 148 weeks overall. The observed ACR20 response rate at this timepoint was 91%. The reduction (RA-I) from Baseline in DAS28 (ESR) also was significantly greater ($p < 0.001$) at Week 52 (RA-I) and Week 24 (RA-II) compared to placebo and maintained through 2 years in the open-label extension trial to RA-I.

Table :3. ACR response in clinical trials RA-I and RA-II

Response	Study RA-I Methotrexate combination (24 and 52 weeks)		Study RA-II Methotrexate combination (24 weeks)	
	Placebo + MTX N=199	Cimzia 200 mg + MTX every 2 weeks N=393	Placebo + MTX N=127	Cimzia 200 mg + MTX every 2 weeks N=246
ACR 20				
Week 24	14%	59%**	9%	57%**
Week 52	13%	53%**	N/A	N/A
ACR 50				
Week 24	8%	37%**	3%	33%**
Week 52	8%	38%**	N/A	N/A
ACR 70				
Week 24	3%	21%**	1%	16%*
Week 52	4%	21%**	N/A	N/A
Major Clinical Response ^a	1%	13%**		

Cimzia vs. placebo: * $p \leq 0.01$, ** $p < 0.001$

^a. Major clinical response is defined as achieving ACR 70 response at every assessment over a continuous 6-month period

Wald p-values are quoted for the comparison of treatments using logistic regression with factors for treatment and region.

Percentage response based upon number of subjects contributing data (n) to that endpoint and time point which may differ from N

Radiographic response

In RA-I, structural joint damage was assessed radiographically and expressed as change in mTSS and its components, the erosion score and joint space narrowing (JSN) score, at Week 52, compared to baseline. Cimzia patients demonstrated significantly less radiographic progression than patients receiving placebo at Week 24 and Week 52 (see Table 4). In the placebo group, 52% of patients experienced no radiographic progression (mTSS \leq 0.0) at Week 52 compared to 69% in the Cimzia 200 mg treatment group.

Table :4. Changes over 12 months in RA-I

	Placebo + MTX N=199 Mean (SD)	Cimzia 200 mg + MTX N=393 Mean (SD)	Cimzia 200 mg + MTX – Placebo + MTX Mean Difference
mTSS			
Week 52	2.8 (7.8)	0.4 (5.7)	-2.4
Erosion Score			
Week 52	1.5 (4.3)	0.1 (2.5)	-1.4
JSN Score			
Week 52	1.4 (5.0)	0.4 (4.2)	-1.0

p-values were < 0.001 for both mTSS and erosion score and ≤ 0.01 for 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.

Of the 783 patients initially randomised 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.

Physical function response and health-related outcomes

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

Immunogenicity

The overall percentage of patients with antibodies to Cimzia detectable on at least 1 occasion was 7.7% in the Phase III RA placebo-controlled trials. Approximately one-third of antibody-positive patients (2.6% of the total population) 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. Antibody formation was associated with lowered drug plasma concentration and in some patients, reduced efficacy.

A pharmacodynamic model based on the Phase III trial data predicts that around 15% of the patients develop antibodies in 6 months at the recommended dose regimen (200 mg every 2 weeks following a loading dose) without MTX co-treatment. This number decreases with increasing doses of concomitant MTX treatment. These data are reasonably in agreement with observed data.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Cimzia in an ELISA, and are highly dependant on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medicinal products, and underlying disease. For these reasons, comparison of the incidence of antibodies to Cimzia with the incidence of antibodies to other TNF antagonists is not appropriate.

5.2 Pharmacokinetic properties

Certolizumab pegol plasma concentrations were broadly dose-proportional. Pharmacokinetics observed in patients with rheumatoid arthritis were consistent with those seen in healthy subjects.

Absorption

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

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, certolizumab pegol is an antibody Fab' fragment conjugated with PEG in order to extend the terminal plasma elimination half-life of the Fab' to a value comparable with a whole antibody product. The terminal elimination phase half-life ($t_{1/2}$) was approximately 14 days for all doses tested.

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 certolizumab pegol resulted in an approximately three-fold increase in clearance. Compared with a 70 kg person, clearance is 29% lower and 38% higher, respectively, in individual RA patients weighing 40 kg and 120 kg.

The Fab' fragment comprises protein compounds and is expected to be degraded to peptides and amino acids by proteolysis. The de-conjugated PEG component is rapidly eliminated from plasma and is to an unknown extent excreted renally.

Special populations

Renal impairment

Specific clinical trials have not been performed to assess the effect of renal impairment on the pharmacokinetics of certolizumab pegol 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 fraction of certolizumab pegol are expected to be dependent on renal function but have not been assessed in patients with renal impairment.

Hepatic impairment

Specific clinical trials have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of certolizumab pegol.

Elderly (≥ 65 years old)

Specific clinical trials 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.

Gender

There was no effect of gender on the pharmacokinetics of certolizumab pegol. As clearance decreases with decreasing body weight, females may generally obtain somewhat higher systemic exposure of certolizumab pegol.

Pharmacokinetic/pharmacodynamic relationship

On the basis of Phase II and Phase III clinical trial data, a population exposure-response relationship was established between average plasma concentration of certolizumab pegol during a dosing interval (C_{avg}) and efficacy (ACR 20 responder definition). The typical C_{avg} that produces half the maximum probability of ACR 20 response (EC50) was 17 $\mu\text{g/ml}$ (95% CI: 10-23 $\mu\text{g/ml}$).

5.3 Preclinical safety data

The pivotal non-clinical safety studies were conducted in the cynomolgus monkey. In rats and monkeys, at doses higher than those given to humans, histopathology revealed cellular vacuolation, present mainly in macrophages, in a number of organs (lymph nodes, injection sites, spleen, adrenal, uterine, cervix, choroid plexus of the brain, and in the epithelial cells of the choroid plexus). It is likely that this finding was caused by cellular uptake of the PEG moiety. *In vitro* functional studies of human vacuolated macrophages indicated all functions tested were retained. Studies in rats indicated that >90% of the administered PEG was eliminated in 3 months following a single dose, with the urine being the main route of excretion.

Certolizumab pegol does not cross-react with rodent TNF. Therefore, reproductive toxicology studies have been performed with a homologous reagent recognising rat TNF. The value of these data to the evaluation of human risk may be limited. No adverse effects were seen on maternal well-being or female fertility, embryo-foetal and peri- and post-natal reproductive indices in rats using a rodent anti-rat TNF α PEGylated Fab' (cTN3 PF) following sustained TNF α suppression. In male rats, reduced sperm motility and a trend of reduced sperm count were observed.

Distribution studies have demonstrated that placental and milk transfer of cTN3 PF to the foetal and neonatal circulation is negligible. It is presently unknown whether the same is true for Cimzia in humans.

No mutagenic or clastogenic effects were demonstrated in preclinical studies. Carcinogenicity studies have not been performed with Cimzia.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

6.5 Nature and contents of container

One ml pre-filled syringe (type I glass) with a plunger stopper (bromobutyl rubber), containing 200 mg of certolizumab pegol.

None of the components of the syringe contain latex.

Pack size of 2 syringes and 2 alcohol wipes, and multipack containing 6 (3 packs of 2) pre-filled syringes and 6 (3 packs of 2) alcohol wipes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

Comprehensive instructions for the preparation and administration of Cimzia in a pre-filled syringe are given in the package leaflet.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 October 2009

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURING AUTHORISATION
HOLDER RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Sandoz GmbH
Biochemiestraße 10
A-6250 Kundl
Austria

Name and address of the manufacturer responsible for batch release

UCB Pharma S.A.
Chemin du Foriest
B-1420 Braine l'Alleud
Belgium

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

• **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Cimzia are provided with a physician information pack containing the following:

- The Summary of Product Characteristics
- Physician information
- Patient Alert Card

The physician information should contain the following key messages:

- The risk of serious infections, including opportunistic bacterial, viral and fungal infections in patients treated with Cimzia,
- The need to evaluate patients for both active and inactive tuberculosis prior to starting the treatment, including use of appropriate screening tests,
- The contraindication of Cimzia in patients with history of moderate to severe heart failure (NYHA III/IV), and potential risk of congestive heart failure being worsened by Cimzia,
- The risk of acute injection-related reactions and delayed serious systemic hypersensitivity reactions, the need for instructing patients on techniques for administration, and guidance for Health Care Professionals on how to report administration errors,
- The role and use of patient alert card.

• **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as described in version 1.0 (28 February 2010) presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 3.0 (dated 15 May 2009) of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton (for packs of 2 pre-filled syringes and 2 alcohol wipes)

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 200 mg certolizumab pegol in one ml.

3. LIST OF EXCIPIENTS

Excipients: Sodium acetate, sodium chloride and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

- Solution for injection
- 2 single-use pre-filled syringes containing 1 ml solution for injection.
- 2 alcohol wipes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cimzia 200 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Multipack of 6 (3 packs of 2 pre-filled syringes and 2 alcohol wipes) – with blue box

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 200 mg certolizumab pegol in one ml.

3. LIST OF EXCIPIENTS

Excipients: Sodium acetate, sodium chloride and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

- Solution for injection
- Multipack: 6 (3 packs of 2) pre-filled syringes and 6 (3 packs of 2) alcohol wipes.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cimzia 200 mg

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

Intermediate carton within Multipack (for 2 pre-filled syringes and 2 alcohol wipes) – without blue box

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled syringe contains 200 mg certolizumab pegol in one ml.

3. LIST OF EXCIPIENTS

Excipients: Sodium acetate, sodium chloride and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

- Solution for injection
- 2 pre-filled syringes and 2 alcohol wipes. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

UCB Pharma SA
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cimzia 200 mg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SYRINGE LABEL**

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cimzia 200 mg solution for injection
certolizumab pegol
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cimzia 200 mg solution for injection certolizumab pegol

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Cimzia is and for what it is used
2. Before you use Cimzia
3. How to use Cimzia
4. Possible side effects
5. How to store Cimzia
6. Further information

Your physician will also give you a Patient Alert Card, which contains important safety information of which you need to be aware before you are given Cimzia and during treatment with Cimzia. Keep this Patient Alert Card with you.

1. WHAT CIMZIA IS AND WHAT IT IS USED FOR

Cimzia contains the active substance certolizumab pegol, a human antibody fragment. Antibodies are proteins that specifically recognise and bind to other proteins. Cimzia binds to a specific protein called tumour necrosis factor α (TNF α). Thereby this TNF α is blocked by Cimzia and this decreases inflammation in rheumatoid arthritis. Medicines that bind to TNF α are also called TNF blockers.

Cimzia is used for the treatment of moderate to severe rheumatoid arthritis in adult patients, when other medicines fail to control your symptoms. Cimzia is usually used together with another medicine called methotrexate. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

2. BEFORE YOU USE Cimzia

Do NOT use Cimzia

- If you are **ALLERGIC** (hypersensitive) to certolizumab pegol or any of the other ingredients of Cimzia
- If you have a severe infection, including active **TUBERCULOSIS (TB)**.
- If you have moderate to severe **HEART FAILURE**. Tell your doctor if you have had or have a serious heart condition.

Take special care with Cimzia

Tell your doctor before treatment with Cimzia if any of the following applies to you:

Allergic reactions

- If you experience **ALLERGIC REACTIONS** such as chest tightness, wheezing, dizziness, swelling or rash, stop using Cimzia and contact your doctor **IMMEDIATELY**.

Infections

- If you have had **RECURRENT INFECTIONS** or other conditions that increase the risk of infections (such as treatment with immunosuppressants, which are medicines that could reduce your ability to fight infections).
- If you have an infection or if you develop symptoms such as fever, wounds, tiredness or dental problems. You might get an infection more easily while you are being treated with Cimzia, including serious, or in rare cases, life-threatening infections.
- **TUBERCULOSIS (TB)** cases have been reported in patients treated with Cimzia, your doctor will check you for signs and symptoms of tuberculosis before starting Cimzia. This will include a thorough medical history, a chest X-ray and a tuberculin test. The conduct of these tests should be recorded on your Patient Alert Card. If latent (inactive) tuberculosis is diagnosed, you might be required to receive appropriate anti-tuberculosis medicines before starting Cimzia. It is very important that you tell your doctor if you have ever had tuberculosis, or if you have been in close contact with someone who has had tuberculosis. If symptoms of tuberculosis (persistent cough, weight loss, listlessness, mild fever), or any other infection appear during or after therapy with Cimzia tell your doctor immediately.
- If you are at risk of or are a carrier of or have active **HEPATITIS B VIRUS (HBV)** infection, Cimzia may increase the risk of reactivation in people who carry this virus. If this occurs, you should stop using Cimzia. Your doctor should test you for HBV before starting Cimzia.

Heart failure

- If you have mild **HEART FAILURE** and you are being treated with Cimzia, your heart failure status must be closely monitored by your doctor. It is important to tell your doctor if you have had or have a serious heart condition. If you develop new or worsening symptoms of heart failure (e.g. shortness of breath or swelling of your feet), you must contact your doctor immediately. Your doctor may decide to stop treatment with Cimzia.

Cancer

- It is uncommon, but cases of certain types of **CANCER** have been reported in patients treated with Cimzia or other TNF blockers. People with more severe rheumatoid arthritis that have had the disease for a long time may have a higher than average risk of getting a kind of cancer that affects the lymph system, called lymphoma. If you take Cimzia, your risk of getting lymphoma or other cancers may increase. In addition, uncommon cases of non-melanoma skin cancer have been observed in patients taking Cimzia. If new skin lesions appear during or after therapy with Cimzia or existing skin lesions change appearance, tell your doctor. Patients with chronic obstructive pulmonary disease (COPD), or who are heavy smokers, may be at increased risk for cancer with Cimzia treatment. If you have COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death (see further down “Children”).

Other disorders

- If you have a nervous system disorder, such as multiple sclerosis, your doctor will decide whether you should use Cimzia.
- In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor immediately. Your doctor may decide to stop treatment with Cimzia.
- It is uncommon, but symptoms of a disease called lupus (for example persistent rash, fever, joint pain and tiredness) may occur. If you experience these symptoms, contact your doctor. Your doctor may decide to stop treatment with Cimzia.

Vaccinations

- Talk to your doctor if you have had, or are due to have a vaccine. You should not receive certain (live) vaccines while using Cimzia.

Operations or dental procedures

- Talk to your doctor if you are going to have any operations or dental procedures. Tell your surgeon or dentist performing the procedure that you are having treatment with Cimzia by showing them your Patient Alert Card.

Children

Cimzia is not recommended for use in children and adolescents under the age of 18 years.

Taking other medicines

You should **NOT** take Cimzia if you are using the following medicines used to treat rheumatoid arthritis:

- anakinra
- abatacept

If you have questions, please ask your doctor.

Cimzia can be taken together with:

- methotrexate,
- corticosteroids, or
- pain medicines including nonsteroidal anti-inflammatory medicines (also called NSAIDs).

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

There is a lack of experience with Cimzia in pregnant women. Therefore, Cimzia should **NOT** be used in pregnant women. Women of childbearing potential must use adequate contraception while using Cimzia and for at least 5 months after the last Cimzia treatment.

It is not known whether Cimzia passes into breast milk. You should talk to your doctor before breast-feeding during Cimzia treatment.

Driving and using machines

Cimzia may have a minor influence on your ability to drive and use machines. Dizziness (including room spinning sensation, blurred vision and tiredness) may occur after you take Cimzia.

Important information about some of the ingredients of Cimzia

This medicinal product contains less than 1 mmol sodium (23 mg) per 400 mg, i.e. essentially 'sodium-free'.

3. HOW TO USE Cimzia

Always use Cimzia exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure of how to use Cimzia.

The **starting dose** for adults with rheumatoid arthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every other week **starting at week 6**. Methotrexate is continued while using Cimzia. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Cimzia will usually be given to you by a specialist doctor or healthcare professional. You will be given Cimzia as either one (200 mg dose) or two injections (400 mg dose) under the skin (subcutaneous use). It is usually injected into the thigh or tummy.

Instructions for preparing and giving an injection of Cimzia

After suitable training, your doctor may also allow you to inject Cimzia yourself. Please read the instructions at the end of this leaflet on how to inject Cimzia.

If your doctor has allowed you to self-inject, you should follow up with your doctor before the 7th dose to have the doctor determine if Cimzia is working for you or if another treatment needs to be considered.

If you use more Cimzia than you should

If your doctor has allowed you to self-inject and you accidentally inject Cimzia more frequently than prescribed, you should tell your doctor. Always take the Patient Alert Card and the outer carton from the Cimzia package with you, even if it is empty.

If you forget to use Cimzia

If your doctor has allowed you to self-inject and you forget to give yourself an injection, you should inject the next dose of Cimzia as soon as you remember. Then inject the following doses every 2 weeks as originally instructed.

If you stop using Cimzia

Do not stop using Cimzia without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cimzia can cause side effects, although not everybody gets them.

Tell your doctor **IMMEDIATELY** if you notice any of the following side effects:

- severe rash, hives or other signs of allergic reaction (urticaria)
- swollen face, hands, feet (angioedema)
- trouble breathing, swallowing (multiple causes for these symptoms)
- shortness of breath with exertion or upon lying down or swelling of the feet (heart failure)
- symptoms of blood disorders such as persistent fever, bruising, bleeding, paleness (pancytopenia, anaemia, low platelet count, low white blood cell count)

Tell your doctor **AS SOON AS POSSIBLE** if you notice any of the following side effects:

- signs of infection such as fever, malaise, wounds, dental problems, burning on urination feeling weak or tired
- coughing.
- tingling
- numbness
- double vision
- arm or leg weakness
- bump or open sore that doesn't heal

The symptoms described above can be due to some of the side effects listed below, which have been observed with Cimzia:

Side effects may occur with certain frequencies, which are defined as follows:

- Very common: affects at least 1 user in 10.
- Common: affects at least 1 user in 100 but less than 10 users in 100.
- Uncommon: affects at least 1 user in 1,000 but less than 10 users in 1,000.
- Rare: affects at least 1 user in 10,000 but less than 10 users in 10,000.
- Very rare: affects less than 1 user in 10,000.
- not known: frequency cannot be estimated from the available data.

Common side effects:

- bacterial infections in any site (a collection of pus)
- viral infections (including cold sores, shingles, and influenza)
- fever
- high blood pressure
- rash or itching
- headaches (including migraines)
- sensory abnormalities such as numbness, tingling, burning sensation
- feeling weak and generally unwell
- pain
- blood disorders
- liver problems
- injection site reactions

Uncommon side effects:

- allergic conditions including allergic rhinitis and allergic reactions to the drug (including anaphylactic shock)
- blood and lymphatic system cancers like lymphoma and leukaemia
- solid organ cancers
- skin cancers, pre-cancers
- benign (non-cancerous) tumours and cysts (including those of the skin)
- heart problems including weakened heart muscle, heart failure, heart attack, chest discomfort or chest pressure, abnormal heart rhythm including irregular heart beats
- oedema (swelling in the face or legs)
- lupus (immune/connective tissue disease) symptoms (joint pain, skin rashes, photosensitivity and fever)
- inflammation of the blood vessels
- sepsis (serious infection which can result in organ failure, shock or death)
- tuberculosis infection
- fungal infections (occur when the ability to fight off infection is lessened)
- respiratory disorders and inflammation (including asthma, shortness of breath, cough, blocked sinuses, pleurisy, or difficulty breathing)
- stomach problems including abdominal fluid collection, ulcers (including oral ulcers), perforation, distension, inflammation heartburn, upset, dry mouth
- bile problems
- muscle problems including increased muscle enzymes
- changes in blood levels of different salts
- changes in cholesterol and fat levels in the blood
- blood clots in the veins or lungs
- bleeding or bruising
- changed numbers of blood cells, including low red cell count (anaemia), low platelet counts, increased platelet counts
- swollen lymph nodes
- flu-like symptoms, chills, altered temperature perception, night sweats, flushing
- anxiety and mood disorders such as depression, appetite disorders, weight change
- vertigo (dizziness)
- feeling faint, including loss of consciousness
- nerve disorders in the extremities including symptoms of numbness, tingling, burning sensation, dizziness, tremor
- skin disorders such as new onset or worsening of psoriasis, sweat gland disorders, ulcers, photosensitivity, acne, hair loss, discoloration, nail separation, dry skin and injuries
- impaired healing
- kidney and urinary problems including impairment of kidney function, blood in the urine and urinary disturbances

- menstrual cycle (monthly period) disorders including lack of bleeding, or heavy or irregular bleeding
- breast disorders
- eye and eyelid inflammation, vision disturbances, problems with tears
- itching
- prolonged coagulation (clotting) test times

Rare side effects:

- gastrointestinal cancer, melanoma
- lung inflammation
- stroke, blockage in blood vessels, poor blood circulation which makes the toes and fingers numb and pale (Raynaud's phenomenon), mottled purplish skin discoloration, small veins near the surface of the skin may become visible
- enlarged spleen
- Formation of stones in the gall bladder
- immune disorders such as sarcoidosis (rash, joint pain, fever), serum sickness, inflammation of the fat tissue, angioneurotic oedema (swelling of the lips, face, throat)
- thyroid disorders (goitre, tiredness, weight loss)
- changes in blood levels of uric acid (increased)
- suicide attempt, mental impairment, delirium
- inflammation of the nerves for hearing, seeing, or of the face, impaired coordination or balance
- ringing in the ears
- increased gastrointestinal motility
- fistula (tract from one organ to another) (any site)
- oral disorders including pain on swallowing
- skin sloughing, blistering, hair texture disorder
- sexual dysfunction
- seizure

Other side effects

When Cimzia has been used to treat other diseases the following uncommon side effects have occurred:

- Gastrointestinal stenosis (narrowing of part of the digestive system).
- Gastrointestinal obstructions (blockages of the digestive system).
- General physical health deterioration.
- Spontaneous abortion.
- Azoospermia (lack of sperm production).

When other TNF blockers have been used to treat rheumatoid arthritis, multiple sclerosis or Guillain-Barré syndrome have occurred. The risk of multiple sclerosis or Guillain-Barré syndrome with Cimzia is not known.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE Cimzia

Keep out of the reach and sight of children.

Do not use Cimzia after the expiry date which is stated on the pack and syringe after EXP. The expiry date refers to the last day of the month.

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer need. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cimzia contains

- The active substance is certolizumab pegol. Each pre-filled syringe contains 200 mg of certolizumab pegol in one ml.
- The other ingredients are: sodium acetate, sodium chloride and water for injections.

What Cimzia looks like and contents of the pack

One Cimzia pack contains:

- two pre-filled syringes of solution, and
- two alcohol wipes (for cleansing the areas chosen for injection).

None of the components of the syringe contain latex.

Packs of 2 syringes and 2 alcohol wipes, and a multipack containing 6 (3 packs of 2) syringes and 6 (3 packs of 2) alcohol wipes are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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This leaflet was last approved in {MM/YYYY}

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

INSTRUCTIONS FOR PREPARING AND GIVING AN INJECTION OF CIMZIA

After proper training, the injection can be self-administered or given by another person, for example a family member or friend. The following instructions explain how to inject Cimzia. Please read the instructions carefully and follow them step by step. You will be instructed by your doctor or healthcare giver on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.

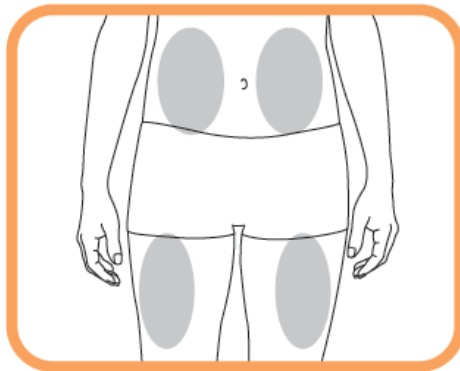
This injection should not be mixed in the same syringe with any other medicine.

1. Setting up

- Wash your hands thoroughly.
- Remove the following items from the Cimzia carton and set them up on a clean surface:
 - One pre-filled syringe
 - One alcohol wipe
- Look at the expiry date on the syringe and pack. Do not use Cimzia after the expiry date which is stated on the pack and syringe after EXP. The expiry date refers to the last day of the month shown.
- Allow the pre-filled syringe to reach room temperature. This will take up to 30 minutes. Do not try to warm up the syringe.

2. Choosing and preparing an injection site

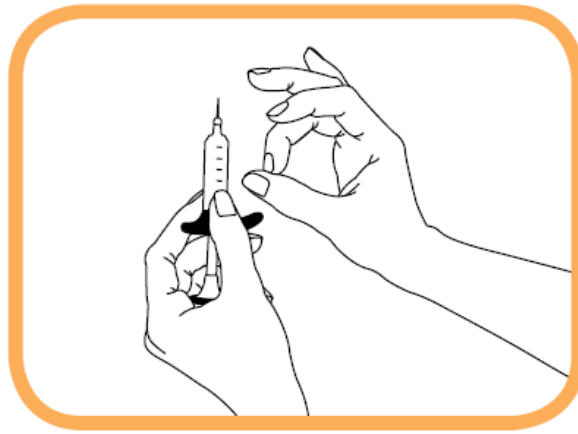
- Choose a site on your thigh or tummy.



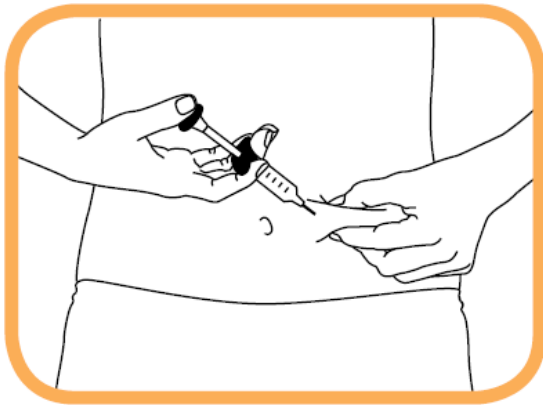
- Each new injection should be given on a separate site from the last injection site.
 - Do not inject in an area where the skin is reddened, bruised, or hard.
 - Wipe the injection site with the enclosed alcohol wipe, using a circular motion moving from the inside out.
 - Do not touch the area again before injecting.

3. Injection

- Do NOT shake the syringe.
- Remove the cap from the needle, being careful not to touch the needle or let the needle touch any surface.
- Hold the syringe with needle facing up.
- Tap the syringe to push any air bubbles to the top.



- Press the plunger slowly until you expel any air. Stop when a small drop appears at the tip of the needle.
- Gently grasp the cleaned area of skin with one hand and hold firmly.



- With the other hand, hold syringe at a 45-degree angle to skin.
- With one quick, short motion, push the needle all the way into the skin.
- Push plunger to inject solution. It can take up to 10 seconds to empty the syringe.
- When the syringe is empty, carefully remove the needle from the skin at the same angle at which it was inserted.
- Release the skin with the first hand.
- Use a piece of gauze, apply pressure over the injection site for a few seconds. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

4. Throwing away supplies

- You must NOT re-use the syringe or re-cap the needle.
- After injection, immediately throw away the used syringe in a special container as instructed by your doctor, nurse or pharmacist.
- Keep the container out of the reach and sight of children.