

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled syringe

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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

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 MTX, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate
- the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs.

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 MTX.

Axial spondyloarthritis

Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and /or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs.

Psoriatic arthritis

Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate.

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

For details on therapeutic effects, see section 5.1.

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Cimzia is indicated. Patients should be given the special alert card.

Posology

Loading dose

The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. For rheumatoid arthritis and psoriatic arthritis, MTX should be continued during treatment with Cimzia where appropriate.

Maintenance dose

Rheumatoid arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate.

Axial spondyloarthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.

Psoriatic arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate.

For the above indications, 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 as instructed.

Special populations

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 patients (≥ 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 using the pre-filled syringe if their physician determines that it is appropriate and with medical follow-up as necessary. The pre-filled syringe with needle guard should only be used by healthcare professionals. The physician should discuss with the patient which injection presentation option is the most appropriate.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Moderate to severe heart failure (NYHA 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 certolizumab pegol 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 or opportunistic 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.

Despite previous or concomitant prophylactic treatment for tuberculosis, cases of active tuberculosis have occurred in patients treated with TNF-antagonists including Cimzia. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Cimzia.

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 certolizumab pegol, 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.

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-antagonists including certolizumab pegol (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

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.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), have been reported in patients treated with TNF-antagonists. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of 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 at or prior to diagnosis. A risk for development of hepatosplenic T-cell lymphoma in patients treated with Cimzia 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 cytopaenia (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. Some of these reactions occurred after the first administration of Cimzia. 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

Patients treated with Cimzia may receive vaccinations, except for live vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving Cimzia. Live vaccines should not be administered concurrently with Cimzia.

In a placebo-controlled clinical trial in patients with rheumatoid arthritis, similar antibody response between Cimzia and placebo treatment were observed when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with Cimzia. Patients receiving Cimzia and concomitant methotrexate had a lower humoral response compared with patients receiving Cimzia alone. The clinical significance of this is unknown.

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 certolizumab pegol 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 patients

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 patients, 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 certolizumab pegol 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

The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Cimzia dose due to its elimination rate (see section 5.2), but the need for treatment of the woman should also be taken into account (see below).

Pregnancy

Data from more than 500 prospectively collected pregnancies exposed to Cimzia with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of Cimzia. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with Cimzia administration during pregnancy.

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.

Cimzia should only be used during pregnancy if clinically needed.

Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol (no Fc region) (see section 5.3).

In a clinical study 16 women were treated with certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) during pregnancy. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 $\mu\text{g/ml}$ with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant concentrations were BLQ. The clinical significance of low levels certolizumab pegol for infants is unknown. It is recommended to wait a minimum of 5 months following the mother's last Cimzia administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants.

Breastfeeding

In a clinical study in 17 lactating women treated with Cimzia, minimal transfer of certolizumab pegol from plasma to breast milk was observed. The percentage of the maternal certolizumab pegol dose reaching an infant during a 24 hour period was estimated to 0.04% to 0.30 %. In addition, since certolizumab pegol is a protein that is degraded in the gastrointestinal tract after oral administration, the absolute bioavailability is expected to be very low in a breastfed infant.

Consequently, Cimzia can be used during breastfeeding.

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).

In a clinical trial to assess the effect of certolizumab pegol on semen quality parameters, 20 healthy male subjects were randomized to receive a single subcutaneous dose of 400 mg of certolizumab pegol or placebo. During the 14-week follow-up, no treatment effects of certolizumab pegol were seen on semen quality parameters compared to placebo.

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

Summary of the safety profile

Rheumatoid arthritis

Cimzia was studied in 4,049 patients with rheumatoid arthritis in controlled and open label trials for up to 92 months. The data in Table 1 are based primarily on the placebo controlled Studies involving 2,965 patients receiving Cimzia and 1,137 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 4.4% for patients treated with Cimzia and 2.7% for patients treated with placebo.

The most common adverse reactions belonged to the system organ classes Infections and infestations, 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 on Cimzia and 2.4% of patients on placebo.

Axial spondyloarthritis

Cimzia was studied in 325 patients with active axial spondyloarthritis in the AS001 clinical study for up to 4 years, which includes a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 156-week open-label treatment period. The safety profile for axial spondyloarthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

Psoriatic arthritis

Cimzia was studied in 409 patients with psoriatic arthritis in the PsA001 clinical study for up to 4 years which includes a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 168-week open-label treatment period. The safety profile for psoriatic arthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

Tabulated list of adverse reactions

Adverse reactions reported in rheumatoid arthritis clinical trials and postmarketing cases 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 reactions in clinical trials and postmarketing

| System Organ Class | Frequency | Adverse reactions |
|--|------------------|--|
| Infections and infestations | Common | bacterial infections (including abscess), viral infections (including herpes zoster, 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, auto-antibody positive |
| | Rare | angioneurotic oedema, sarcoidosis, serum sickness, panniculitis (including erythema nodosum), worsening of symptoms of dermatomyositis** |
| 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 | tinnitus, vertigo |
| Cardiac disorders | Uncommon | cardiomyopathies (including heart failure), ischaemic coronary artery disorders, arrhythmias (including atrial fibrillation), palpitations |
| | Rare | pericarditis, atrioventricular block |

| System Organ Class | Frequency | Adverse reactions |
|---|------------------|---|
| 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, Stevens-Johnson syndrome**, erythema multiforme** |
| 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, 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 certolizumab pegol is not known.

**These events have been related to the class of TNF-antagonists.

The additional following adverse reactions have been observed uncommonly with Cimzia in other indications: gastrointestinal stenosis and obstructions, general physical health deterioration, abortion spontaneous and azoospermia.

Description of selected adverse reactions

Infections

The incidence rate of new cases of infections in placebo-controlled clinical trials 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, and lower respiratory tract infections and herpes viral 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 (0.07 per patient-year; all doses), compared with placebo (0.02 per patient-year). The most frequent serious infections included pneumonia, tuberculosis infections. Serious infections also included 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, 121 malignancies including 5 cases of lymphoma were observed in the Cimzia RA clinical trials in which a total of 4,049 patients were treated, representing 9,277 patient-years. 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 (see section 4.4). One case of lymphoma was also observed in the Phase III psoriatic arthritis clinical trial.

Autoimmunity

In the pivotal studies, 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, 5.8% of patients treated with Cimzia developed injection site reactions such as erythema, itching, haematoma, pain, swelling or bruising, compared to 4.8% of patients receiving placebo. Injection site pain was observed in 1.5% of patients treated with Cimzia with no cases leading to withdrawal.

Creatine phosphokinase elevations

The frequency of creatine phosphokinase (CPK) elevations was generally higher in patients with axSpA as compared to the RA population. The frequency was increased both in patients treated with placebo (2.8% vs 0.4% in axSpA and RA populations, respectively) as well as in patients treated with Cimzia (4.7% vs 0.8% in axSpA and RA populations, respectively). The CPK elevations in the axSpA study were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

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: immunosuppressants, 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-dependent manner. Incubation of monocytes with Cimzia resulted in a dose-dependent 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

Rheumatoid arthritis

The efficacy and safety of Cimzia have been assessed in 2 randomised, placebo-controlled, double-blind clinical trials in patients \geq 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 \geq 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.

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 \geq 18 years of age and had \geq 4 swollen and tender joints each 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). Patients had a mean time since diagnosis at baseline of 2.9 months and were DMARD naïve (including MTX). 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).

Table 2 Clinical trial description

| Study number | Patient numbers | Active 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. |
| C-EARLY (to 52 weeks) | 879 | 400 mg (0,2,4 weeks) with MTX 200 mg every 2 weeks with MTX | Evaluation for treatment of signs and symptoms and inhibition of structural damage in DMARD naïve patients. Primary endpoint: proportion of subjects in sustained remission* at Week 52 |

mTSS: modified Total Sharp Score

*Sustained remission at Week 52 is defined as DAS28[ESR] <2.6 at both Week 40 and Week 52.

Signs and symptoms

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 ACR 20 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

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

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

| Response | Placebo+MTX N= 213 | Cimzia 200 mg + MTX N= 655 |
|--|-----------------------|-------------------------------|
| Sustained remission* (DAS28(ESR) <2.6 at both Week 40 and Week 52) | 15.0 % | 28.9%** |
| Sustained low disease activity (DAS28(ESR) ≤3.2 at both Week 40 and Week 52) | 28.6 % | 43.8%** |

*Primary endpoint of C-EARLY trial (to Week 52)

Full analysis set, non-responder imputation for missing values.

**Cimzia+MTX vs placebo+MTX: p<0.001

p value was estimated from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months)

Patients in the Cimzia+MTX group had a greater reduction from baseline in DAS 28 (ESR) compared with the placebo+MTX group observed as early as Week 2 and continued through Week 52 (p<0.001 at each visit). Assessments on remission (DAS28(ESR) <2.6), Low Disease Activity (DAS28(ESR) ≤3.2) status, ACR50 and ACR 70 by visit demonstrated that Cimzia+MTX treatment led to faster and greater responses than PBO+MTX treatment. These results were maintained over 52 weeks of treatment in DMARD-naïve subjects.

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 5). In the placebo group, 52% of patients experienced no radiographic progression (mTSS ≤ 0.0) at Week 52 compared to 69% in the Cimzia 200 mg treatment group.

Table 5 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.

In C-EARLY, Cimzia+ MTX inhibited the radiographic progression compared to placebo+MTX at Week 52 (see Table 6). In the placebo+MTX group, 49.7% of patients experienced no radiographic progression (change in mTSS ≤ 0.5) at Week 52 compared to 70.3% in the Cimzia+MTX group ($p < 0.001$).

Table 6 Radiographic change at Week 52 in trial C-EARLY

| | Placebo +MTX N= 163 Mean (SD) | Cimzia 200 mg + MTX N = 528 Mean (SD) | Cimzia 200 mg + MTX – Placebo +MTX Difference* |
|---------------------------------|--|--|--|
| mTSS Week 52 | 1.8 (4.3) | 0.2 (3.2)** | -0.978 (-1.005, -0.500) |
| Erosion score Week 52 | 1.1 (3.0) | 0.1 (2.1)** | -0.500 (-0.508, -0.366) |
| JSN score Week 52 | 0.7 (2.3) | 0.1 (1.7)** | 0.000 (0.000, 0.000) |

Radiographic set with linear extrapolation.

* Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) confidence interval.

**Cimzia+MTX vs placebo+MTX $p < 0.001$. p value 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 a covariate.

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.

In C-EARLY, Cimzia+MTX-treated patients reported significant improvements at Week 52 compared to placebo+MTX in pain as assessed by the Patient Assessment of Arthritis Pain (PAAP) – 48,5 vs - 44,0 (least square mean) ($p < 0.05$).

DoseFlex clinical trial

The efficacy and safety of 2 dose regimens (200 mg every 2 weeks and 400 mg every 4 weeks) of Cimzia versus placebo were assessed in an 18-week, open-label, run-in, and 16-week randomised, double-blind, placebo-controlled clinical trial in adult patients with active rheumatoid arthritis diagnosed according to the ACR criteria who had inadequate response to MTX.

Patients received loading doses of Cimzia 400 mg at weeks 0, 2, and 4 followed by Cimzia 200 mg every 2 weeks during the initial open label period. Responders (achieved ACR 20) at week 16 were randomised at week 18 to Cimzia 200 mg every 2 weeks, Cimzia 400 mg every 4 weeks, or placebo in combination with MTX for an additional 16 weeks (total trial length: 34 weeks). These 3 groups were well balanced with regards to clinical response following the active run-in period (ACR 20: 83-84% at week 18).

The primary endpoint of the study was the ACR 20 responder rate at week 34. The results at week 34 are shown in Table 7. Both Cimzia regimens showed sustained clinical response and were statistically significant compared to placebo at week 34. The ACR 20 endpoint was achieved for both Cimzia 200 mg every 2 weeks and 400 mg every 4 weeks.

Table 7 ACR response in DoseFlex clinical trial at week 34

| Treatment regimen week 0 to 16 | Cimzia 400 mg + MTX at week 0, 2 and 4, followed by Cimzia 200 mg + MTX every 2 weeks | | |
|--|---|-----------------------------------|-----------------------------------|
| Randomised, double-blind treatment regimen week 18 to 34 | Placebo + MTX | Cimzia 200 mg + MTX every 2 weeks | Cimzia 400 mg + MTX every 4 weeks |
| | N=69 | N=70 | N=69 |
| ACR 20 p-value* | 45% N/A | 67% 0.009 | 65% 0.017 |
| ACR 50 p-value* | 30% N/A | 50% 0.020 | 52% 0.010 |
| ACR 70 p-value* | 16% N/A | 30% 0.052 | 38% 0.005 |

N/A: Not Applicable

*Wald p-values for Cimzia 200 mg vs. placebo and Cimzia 400 mg vs. placebo comparisons are estimated from a logistic regression model with factors for treatment

Axial spondyloarthritis

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. The axial spondyloarthritis overall population included subpopulations with and without (non-radiographic axial spondyloarthritis [nr-axSpA]) radiographic evidence for ankylosing spondylitis (AS). 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, 16% of 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. 87.7% of patients received concomitant NSAIDs. The primary efficacy endpoint was the ASAS20 response rate at Week 12. The 24-week double-blind, placebo-controlled treatment period of the study was followed by a 24-week dose-blind treatment period, and a 156-week open-label treatment period. The maximum duration of the study was 204 weeks. All patients received Cimzia in both the dose-blind and open-label follow-up periods. A total of 199 subjects (61.2% of randomized subjects) completed the study through Week 204.

Key efficacy outcomes

In AS001 clinical trial, at Week 12 ASAS20 responses were achieved by 58% of patients receiving Cimzia 200 mg every 2 weeks and 64% of patients receiving Cimzia 400 mg every 4 weeks as compared to 38% of patients receiving placebo ($p < 0.01$). In the overall population, 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 from Week 1 through Week 24 ($p \leq 0.001$ at each visit). At Weeks 12 and 24, the percentage of subjects with an ASAS40 response was greater in the Cimzia-treated groups compared to placebo.

Similar results were achieved in both the ankylosing spondylitis and non-radiographic axial spondyloarthritis subpopulations. In women, ASAS20 responses were not statistically significantly different from placebo until after the Week 12 time point.

Improvements in ASAS5/6, Partial Remission and BASDAI-50 were statistically significant at Week 12 and Week 24 and were sustained up to Week 48 in the overall population as well as in the subpopulations. Key efficacy outcomes from the AS001 clinical trial are shown in Table -8. Among patients remaining in the study, improvements in all afore-mentioned key efficacy outcomes were maintained through Week 204 in the overall population as well as in the subpopulations.

Table 8 Key efficacy outcomes in AS001 clinical trial (percent of patients)

| Parameters | Ankylosing spondylitis | | Non-radiographic axial spondyloarthritis | | Axial spondyloarthritis Overall Population | |
|--|------------------------|--|--|---|--|--|
| | Placebo N=57 | Cimzia all dosing regimens ^(a) N=121 | Placebo N=50 | Cimzia all dosing regimens ^(a) N=97 | Placebo N=107 | Cimzia all dosing regimens ^(a) N=218 |
| ASAS20^(b,c) | | | | | | |
| Week 12 | 37% | 60%* | 40% | 61%* | 38% | 61%** |
| Week 24 | 33% | 69%** | 24% | 68%** | 29% | 68%** |
| ASAS40^(c,d) | | | | | | |
| Week 12 | 19% | 45%** | 16% | 47%** | 18% | 46%** |
| Week 24 | 16% | 53%** | 14% | 51%** | 15% | 52%** |
| ASAS 5/6^(c,d) | | | | | | |
| Week 12 | 9% | 42%** | 8% | 44%** | 8% | 43%** |
| Week 24 | 5% | 40%** | 4% | 45%** | 5% | 42%** |
| Partial remission^(c,d) | | | | | | |
| Week 12 | 2% | 20%** | 6% | 29%** | 4% | 24%** |
| Week 24 | 7% | 28%** | 10% | 33%** | 9% | 30%** |
| BASDAI 50^(c,d) | | | | | | |
| Week 12 | 11% | 41%** | 16% | 49%** | 13% | 45%** |
| Week 24 | 16% | 49%** | 20% | 57%** | 18% | 52%** |

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

^(d) Full Analysis Set

NA = not available

*p≤0.05, Cimzia vs placebo

**p<0.001, Cimzia vs placebo

Spinal mobility

Spinal mobility was assessed in the double-blind, placebo-controlled period by using BASMI at several time points including Baseline, Week 12 and Week 24. Clinically meaningful and statistically significant differences in Cimzia-treated patients compared with placebo-treated patients were demonstrated at each post-baseline visit. The difference from placebo tended to be greater in nr-axSpA than in the AS subpopulation which may be due to less chronic structural damage in nr-axSpA patients.

The improvement in BASMI linear score achieved at Week 24 was maintained through Week 204 for patients who remained in the study.

Physical function response and health-related outcomes

In the AS001 clinical trial, Cimzia-treated patients reported significant improvements in physical function as assessed by the BASFI and in pain as assessed by the Total and Nocturnal Back Pain NRS scales as compared to placebo. Cimzia-treated patients reported significant improvements in tiredness (fatigue) as reported by the BASDAI-fatigue item and in health-related quality of life as measured by the ankylosing spondylitis QoL (ASQoL) and the SF-36 Physical and Mental Component Summaries and all domain scores as compared to placebo. Cimzia-treated patients reported significant improvements in axial spondyloarthritis-related productivity at work and within household, as reported by the Work Productivity Survey as compared to placebo. For patients remaining in the study, improvements in all afore-mentioned outcomes were largely maintained through Week 204.

Inhibition of inflammation in Magnetic Resonance Imaging (MRI)

In an imaging sub-study including 153 patients, 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. At week 12, significant inhibition of inflammatory signs in both sacroiliac joints and the spine was observed in the Cimzia-treated patients (all dose group), in the overall axial spondyloarthritis population as well as in the sub-populations of ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Among patients remaining in the study, who had both baseline values and week 204 values, inhibition of inflammatory signs in both the sacroiliac joints (n=72) and spine (n=82) was largely maintained through Week 204 in the overall axial spondyloarthritis population as well as in both the AS and the nr-axSpA subpopulations.

Psoriatic arthritis

The efficacy and safety of Cimzia were assessed in a multicentre, randomised, 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 ACR 20 response at Week 12 and change from baseline in modified Total Sharp Score (mTSS) at Week 24. Efficacy and safety of Cimzia in patients with PsA whose predominant symptoms were sacroiliitis or axial spondyloarthritis have not been separately analysed.

The 24-week double-blind placebo controlled treatment period of the study was followed by a 24-week dose-blind treatment period and an 168-week open-label treatment period. The maximum duration of the study was 216 weeks. All patients received Cimzia in both the dose-blind and open-label follow-up periods. A total of 264 subjects (64.5%) completed the study through Week 216.

ACR response

Cimzia-treated patients had a statistically significant higher ACR 20 response rate at Week 12 and Week 24 compared with placebo-treated patients ($p < 0.001$). The percentage of ACR 20 responders was clinically relevant 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 (nominal $p \leq 0.001$ at each visit). Cimzia treated patients also had significant improvements in ACR 50 and 70 response rates. At week 12 and 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Cimzia-treated patients (nominal p-value $p < 0.01$).

Key efficacy outcomes from the PsA001 clinical trial are shown in Table 9.

Table 9 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^(c) | | | |
| Week 12 | 14% | 47%*** | 47%*** |
| Week 24 | 15% | 62%*** | 61%*** |
| Week 48 | N/A | 67% | 62% |

^(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) In subjects with at least 3% psoriasis BSA at Baseline

*p<0.01, Cimzia vs placebo

**p<0.001, Cimzia vs placebo

***p<0.001(nominal), 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 test. Non-responder Imputation (NRI) is used for patients who escaped therapy or had missing data.

Among 273 patients initially randomised to Cimzia 200 mg every 2 weeks and Cimzia 400 mg every 4 weeks, 237 (86.8%) were still on this treatment at Week 48. Of the 138 patients randomised to Cimzia 200 mg every 2 weeks, 92, 68 and 48 had an ACR 20/50/70 response, at Week 48, respectively. Of the 135 patients randomised to Cimzia 400 mg every 4 weeks, 89, 62 and 41 patients had an ACR 20/50/70 response, respectively.

Among patients remaining in the study, ACR 20, 50 and 70 response rates were maintained through Week 216. This was also the case for the other parameters of peripheral activity (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis).

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. Cimzia treatment inhibited the radiographic progression compared with placebo treatment at Week 24 as measured by change from baseline in total mTSS Score (LS mean [\pm SE] score was 0.28 [\pm 0.07] in the placebo group compared with 0.06 [\pm 0.06] in the Cimzia all doses group; p=0.007). Inhibition of radiographic progression was maintained with Cimzia treatment up to Week 48 in the subset of patients at higher risk of radiographic progression (patients with a Baseline mTSS score of > 6). Inhibition of radiographic progression was further maintained up to Week 216 for the patients who remained in the study.

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), in pain as assessed by the PAAP and in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) 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 Components and in psoriatic arthritis-related productivity at work and within household, as reported by the Work Productivity Survey compared to placebo. Improvements in all afore-mentioned outcomes were maintained through Week 216.

Immunogenicity

Rheumatoid arthritis

The overall percentage of patients with antibodies to Cimzia detectable on at least 1 occasion was 9.6% in RA placebo-controlled trials. Approximately one-third of antibody-positive patients 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.

In 2 long-term (up to 5 years of exposure) open-label studies, the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 13% (8.4% of the overall patients had transient formation of antibodies and an additional 4.7% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 9.1%. Similar to the placebo-controlled studies, antibody positivity was associated with reduced efficacy in some patients.

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.

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.

Over the course of the entire study (up to 192 weeks), the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 9.6% (4.8% had transient formation and an additional 4.8% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 6.8%.

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.

Over the course of the entire study (up to 4 years of exposure), the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 17.3% (8.7% had transient formation and an additional 8.7% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 11.5%.

For all indications

The data reflect the percentage of patients whose test results were considered positive for antibodies to Cimzia in an ELISA, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors

including sample handling, timing of sample collection, concomitant 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 patients (≥ 65 years old)

Specific clinical trials have not been performed in elderly patients 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. Certolizumab pegol does not bind to the human neonatal Fc receptor (FcRn). Data from a human closed-circuit placental transfer model *ex vivo* suggest low or negligible transfer to the foetal compartment. In addition, experiments of FcRn-mediated transcytosis in cells transfected with human FcRn showed negligible transfer (see section 4.6).

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

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.

Pack size of 2 pre-filled syringes and 2 alcohol wipes.

Multipack containing 6 (3 packs of 2) pre-filled syringes and 6 (3 packs of 2) alcohol wipes.

Multipack containing 10 (5 packs of 2) pre-filled syringes and 10 (5 packs of 2) alcohol wipes.

Pack size of 2 pre-filled syringes with needle guard and 2 alcohol wipes (for use by healthcare professionals only).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

This medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/001
EU/1/09/544/002
EU/1/09/544/003
EU/1/09/544/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 October 2009

Date of latest renewal: 16 May 2014

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection)

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

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 MTX, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate
- the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs.

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 MTX.

Axial spondyloarthritis

Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and /or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs.

Psoriatic arthritis

Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate.

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

For details on therapeutic effects, see section 5.1.

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Cimzia is indicated. Patients should be given the special alert card.

Posology

Loading dose

The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. For rheumatoid arthritis and psoriatic arthritis, MTX should be continued during treatment with Cimzia where appropriate.

Maintenance dose

Rheumatoid arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate.

Axial spondyloarthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.

Psoriatic arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate.

For the above indications, 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 as instructed.

Special populations

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 patients (≥ 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 pen 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 using the pre-filled pen if their physician determines that it is appropriate and with medical follow-up as necessary. The physician should discuss with the patient which injection presentation option is the most appropriate.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Moderate to severe heart failure (NYHA 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 certolizumab pegol 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 or opportunistic 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.

Despite previous or concomitant prophylactic treatment for tuberculosis, cases of active tuberculosis have occurred in patients treated with TNF-antagonists including Cimzia. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Cimzia.

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 certolizumab pegol, 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.

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-antagonists including certolizumab pegol (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

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.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), have been reported in patients treated with TNF-antagonists. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of 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 at or prior to diagnosis. A risk for development of hepatosplenic T-cell lymphoma in patients treated with Cimzia 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 cytopaenia (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. Some of these reactions occurred after the first administration of Cimzia. 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

Patients treated with Cimzia may receive vaccinations, except for live vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving Cimzia. Live vaccines should not be administered concurrently with Cimzia.

In a placebo-controlled clinical trial in patients with rheumatoid arthritis, similar antibody response between Cimzia and placebo treatment were observed when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with Cimzia. Patients receiving Cimzia and concomitant methotrexate had a lower humoral response compared with patients receiving Cimzia alone. The clinical significance of this is unknown.

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 certolizumab pegol 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 patients

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 patients, 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 certolizumab pegol 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

The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Cimzia dose due to its elimination rate (see section 5.2), but the need for treatment of the woman should also be taken into account (see below).

Pregnancy

Data from more than 500 prospectively collected pregnancies exposed to Cimzia with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of Cimzia. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with Cimzia administration during pregnancy.

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.

Cimzia should only be used during pregnancy if clinically needed.

Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol (no Fc region) (see section 5.3).

In a clinical study 16 women were treated with certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) during pregnancy. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 $\mu\text{g/ml}$ with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant concentrations were BLQ. The clinical significance of low levels certolizumab pegol for infants is unknown. It is recommended to wait a minimum of 5 months following the mother's last Cimzia administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants.

Breastfeeding

In a clinical study in 17 lactating women treated with Cimzia, minimal transfer of certolizumab pegol from plasma to breast milk was observed. The percentage of the maternal certolizumab pegol dose reaching an infant during a 24 hour period was estimated to 0.04% to 0.30 %. In addition, since

certolizumab pegol is a protein that is degraded in the gastrointestinal tract after oral administration, the absolute bioavailability is expected to be very low in a breastfed infant.

Consequently, Cimzia can be used during breastfeeding.

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).

In a clinical trial to assess the effect of certolizumab pegol on semen quality parameters, 20 healthy male subjects were randomized to receive a single subcutaneous dose of 400 mg of certolizumab pegol or placebo. During the 14-week follow-up, no treatment effects of certolizumab pegol were seen on semen quality parameters compared to placebo.

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

Summary of the safety profile

Rheumatoid arthritis

Cimzia was studied in 4,049 patients with rheumatoid arthritis in controlled and open label trials for up to 92 months. The data in Table 1 are based primarily on the placebo controlled Studies involving 2,965 patients receiving Cimzia and 1,137 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 4.4% for patients treated with Cimzia and 2.7% for patients treated with placebo.

The most common adverse reactions belonged to the system organ classes Infections and infestations, 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 on Cimzia and 2.4% of patients on placebo.

Axial spondyloarthritis

Cimzia was studied in 325 patients with active axial spondyloarthritis in the AS001 clinical study for up to 4 years, which includes a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 156-week open-label treatment period. The safety profile for axial spondyloarthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

Psoriatic arthritis

Cimzia was studied in 409 patients with psoriatic arthritis in the PsA001 clinical study for up to 4 years which includes a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 168-week open-label treatment period. The safety profile for psoriatic arthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

Tabulated list of adverse reactions

Adverse reactions reported in rheumatoid arthritis clinical trials and postmarketing cases 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 reactions in clinical trials and postmarketing

| System Organ Class | Frequency | Adverse reactions |
|--|-----------|--|
| Infections and infestations | Common | bacterial infections (including abscess), viral infections (including herpes zoster, 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, auto-antibody positive |
| | Rare | angioneurotic oedema, sarcoidosis, serum sickness, panniculitis (including erythema nodosum), worsening of symptoms of dermatomyositis** |
| 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 | tinnitus, vertigo |
| Cardiac disorders | Uncommon | cardiomyopathies (including heart failure), ischaemic coronary artery disorders, arrhythmias (including atrial fibrillation), palpitations |
| | Rare | pericarditis, atrioventricular block |

| System Organ Class | Frequency | Adverse reactions |
|---|------------------|---|
| 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, Stevens-Johnson syndrome**, erythema multiforme** |
| 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 certolizumab pegol is not known.

**These events have been related to the class of TNF-antagonists.

The additional following adverse reactions have been observed uncommonly with Cimzia in other indications: gastrointestinal stenosis and obstructions, general physical health deterioration, abortion spontaneous and azoospermia.

Description of selected adverse reactions

Infections

The incidence rate of new cases of infections in placebo-controlled clinical trials 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, and lower respiratory tract infections and herpes viral 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 (0.07 per patient-year; all doses), compared with placebo (0.02 per patient-year). The most frequent serious infections included pneumonia, tuberculosis infections. Serious infections also included 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, 121 malignancies including 5 cases of lymphoma were observed in the Cimzia RA clinical trials in which a total of 4,049 patients were treated, representing 9,277 patient-years. 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 (see section 4.4). One case of lymphoma was also observed in the Phase III psoriatic arthritis clinical trial.

Autoimmunity

In the pivotal studies, 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, 5.8% of patients treated with Cimzia developed injection site reactions such as erythema, itching, haematoma, pain, swelling or bruising, compared to 4.8% of patients receiving placebo. Injection site pain was observed in 1.5% of patients treated with Cimzia with no cases leading to withdrawal.

Creatine phosphokinase elevations

The frequency of creatine phosphokinase (CPK) elevations was generally higher in patients with axSpA as compared to the RA population. The frequency was increased both in patients treated with placebo (2.8% vs 0.4% in axSpA and RA populations, respectively) as well as in patients treated with Cimzia (4.7% vs 0.8% in axSpA and RA populations, respectively). The CPK elevations in the axSpA study were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

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: immunosuppressants, 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-dependent manner. Incubation of monocytes with Cimzia resulted in a dose-dependent 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

Rheumatoid arthritis

The efficacy and safety of Cimzia have been assessed in 2 randomised, placebo-controlled, double-blind clinical trials in patients \geq 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 \geq 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.

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 \geq 18 years of age and had \geq 4 swollen and tender joints each 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). Patients had a mean time since diagnosis at baseline of 2.9 months and were DMARD naïve (including MTX). 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).

Table 2 Clinical trial description

| Study number | Patient numbers | Active 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. |
| C-EARLY (to 52 weeks) | 879 | 400 mg (0,2,4 weeks) with MTX 200 mg every 2 weeks with MTX | Evaluation for treatment of signs and symptoms and inhibition of structural damage in DMARD naïve patients. Primary endpoint: proportion of subjects in sustained remission* at Week 52 |

mTSS: modified Total Sharp Score

*Sustained remission at Week 52 is defined as DAS28[ESR] <2.6 at both Week 40 and Week 52.

Signs and symptoms

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 ACR 20 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

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

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

| Response | Placebo+MTX N= 213 | Cimzia 200 mg + MTX N= 655 |
|--|-----------------------|-------------------------------|
| Sustained remission* (DAS28(ESR) <2.6 at both Week 40 and Week 52) | 15.0 % | 28.9%** |
| Sustained low disease activity (DAS28(ESR) ≤3.2 at both Week 40 and Week 52) | 28.6 % | 43.8%** |

*Primary endpoint of C-EARLY trial (to Week 52)

Full analysis set, non-responder imputation for missing values.

**Cimzia+MTX vs placebo+MTX: p<0.001

p value was estimated from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months)

Patients in the Cimzia+MTX group had a greater reduction from baseline in DAS 28 (ESR) compared with the placebo+MTX group observed as early as Week 2 and continued through Week 52 (p<0.001 at each visit). Assessments on remission (DAS28(ESR) <2.6), Low Disease Activity (DAS28(ESR) ≤3.2) status, ACR50 and ACR 70 by visit demonstrated that Cimzia+MTX treatment led to faster and greater responses than PBO+MTX treatment. These results were maintained over 52 weeks of treatment in DMARD-naïve subjects.

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 5). In the placebo group, 52% of patients experienced no radiographic progression (mTSS ≤ 0.0) at Week 52 compared to 69% in the Cimzia 200 mg treatment group.

Table 5 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.

In C-EARLY, Cimzia+ MTX inhibited the radiographic progression compared to placebo+MTX at Week 52 (see Table 6). In the placebo+MTX group, 49.7% of patients experienced no radiographic progression (change in mTSS ≤ 0.5) at Week 52 compared to 70.3% in the Cimzia+MTX group ($p < 0.001$).

Table 6 Radiographic change at Week 52 in trial C-EARLY

| | Placebo +MTX N= 163 Mean (SD) | Cimzia 200 mg + MTX N = 528 Mean (SD) | Cimzia 200 mg + MTX – Placebo +MTX Difference* |
|---------------------------------|--|--|--|
| mTSS Week 52 | 1.8 (4.3) | 0.2 (3.2)** | -0.978 (-1.005, -0.500) |
| Erosion score Week 52 | 1.1 (3.0) | 0.1 (2.1)** | -0.500 (-0.508, -0.366) |
| JSN score Week 52 | 0.7 (2.3) | 0.1 (1.7)** | 0.000 (0.000, 0.000) |

Radiographic set with linear extrapolation.

* Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) confidence interval.

**Cimzia+MTX vs placebo+MTX $p < 0.001$. p value 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 a covariate.

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.

In C-EARLY, Cimzia+MTX-treated patients reported significant improvements at Week 52 compared to placebo+MTX in pain as assessed by the Patient Assessment of Arthritis Pain (PAAP) – 48,5 vs - 44,0 (least square mean) ($p < 0.05$).

DoseFlex clinical trial

The efficacy and safety of 2 dose regimens (200 mg every 2 weeks and 400 mg every 4 weeks) of Cimzia versus placebo were assessed in an 18-week, open-label, run-in, and 16-week randomised, double-blind, placebo-controlled clinical trial in adult patients with active rheumatoid arthritis diagnosed according to the ACR criteria who had inadequate response to MTX.

Patients received loading doses of Cimzia 400 mg at weeks 0, 2, and 4 followed by Cimzia 200 mg every 2 weeks during the initial open label period. Responders (achieved ACR 20) at week 16 were randomised at week 18 to Cimzia 200 mg every 2 weeks, Cimzia 400 mg every 4 weeks, or placebo in combination with MTX for an additional 16 weeks (total trial length: 34 weeks). These 3 groups were well balanced with regards to clinical response following the active run-in period (ACR 20: 83-84% at week 18).

The primary endpoint of the study was the ACR 20 responder rate at week 34. The results at week 34 are shown in Table 7. Both Cimzia regimens showed sustained clinical response and were statistically significant compared to placebo at week 34. The ACR 20 endpoint was achieved for both Cimzia 200 mg every 2 weeks and 400 mg every 4 weeks.

Table 7 ACR response in DoseFlex clinical trial at week 34

| Treatment regimen week 0 to 16 | Cimzia 400 mg + MTX at week 0, 2 and 4, followed by Cimzia 200 mg + MTX every 2 weeks | | |
|--|---|-----------------------------------|-----------------------------------|
| Randomised, double-blind treatment regimen week 18 to 34 | Placebo + MTX | Cimzia 200 mg + MTX every 2 weeks | Cimzia 400 mg + MTX every 4 weeks |
| | N=69 | N=70 | N=69 |
| ACR 20 p-value* | 45% N/A | 67% 0.009 | 65% 0.017 |
| ACR 50 p-value* | 30% N/A | 50% 0.020 | 52% 0.010 |
| ACR 70 p-value* | 16% N/A | 30% 0.052 | 38% 0.005 |

N/A: Not Applicable

*Wald p-values for Cimzia 200 mg vs. placebo and Cimzia 400 mg vs. placebo comparisons are estimated from a logistic regression model with factors for treatment

Axial spondyloarthritis

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. The axial spondyloarthritis overall population included subpopulations with and without (non-radiographic axial spondyloarthritis [nr-axSpA]) radiographic evidence for ankylosing spondylitis (AS). 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, 16% of 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. 87.7% of patients received concomitant NSAIDs. The primary efficacy endpoint was the ASAS20 response rate at Week 12. The 24-week double-blind, placebo-controlled treatment period of the study was followed by a 24-week dose-blind treatment period, and a 156-week open-label treatment period. The maximum duration of the study was 204 weeks. All patients received Cimzia in both the dose-blind and open-label follow-up periods. A total of 199 subjects (61.2% of randomized subjects) completed the study through Week 204.

Key efficacy outcomes

In AS001 clinical trial, at Week 12 ASAS20 responses were achieved by 58% of patients receiving Cimzia 200 mg every 2 weeks and 64% of patients receiving Cimzia 400 mg every 4 weeks as compared to 38% of patients receiving placebo ($p < 0.01$). In the overall population, 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 from Week 1 through Week 24 ($p \leq 0.001$ at each visit). At Weeks 12 and 24, the percentage of subjects with an ASAS40 response was greater in the Cimzia-treated groups compared to placebo.

Similar results were achieved in both the ankylosing spondylitis and non-radiographic axial spondyloarthritis subpopulations. In women, ASAS20 responses were not statistically significantly different from placebo until after the Week 12 time point.

Improvements in ASAS5/6, Partial Remission and BASDAI-50 were statistically significant at Week 12 and Week 24 and were sustained up to Week 48 in the overall population as well as in the subpopulations. Key efficacy outcomes from the AS001 clinical trial are shown in Table -8.

Among patients remaining in the study, improvements in all afore-mentioned key efficacy outcomes were maintained through Week 204 in the overall population as well as in the subpopulations.

Table 8 Key efficacy outcomes in AS001 clinical trial (percent of patients)

| Parameters | Ankylosing spondylitis | | Non-radiographic axial spondyloarthritis | | Axial spondyloarthritis Overall Population | |
|--|------------------------|--|--|---|--|--|
| | Placebo N=57 | Cimzia all dosing regimens ^(a) N=121 | Placebo N=50 | Cimzia all dosing regimens ^(a) N=97 | Placebo N=107 | Cimzia all dosing regimens ^(a) N=218 |
| ASAS20^(b,c) | | | | | | |
| Week 12 | 37% | 60%* | 40% | 61%* | 38% | 61%** |
| Week 24 | 33% | 69%** | 24% | 68%** | 29% | 68%** |
| ASAS40^(c,d) | | | | | | |
| Week 12 | 19% | 45%** | 16% | 47%** | 18% | 46%** |
| Week 24 | 16% | 53%** | 14% | 51%** | 15% | 52%** |
| ASAS 5/6^(c,d) | | | | | | |
| Week 12 | 9% | 42%** | 8% | 44%** | 8% | 43%** |
| Week 24 | 5% | 40%** | 4% | 45%** | 5% | 42%** |
| Partial remission^(c,d) | | | | | | |
| Week 12 | 2% | 20%** | 6% | 29%** | 4% | 24%** |
| Week 24 | 7% | 28%** | 10% | 33%** | 9% | 30%** |
| BASDAI 50^(c,d) | | | | | | |
| Week 12 | 11% | 41%** | 16% | 49%** | 13% | 45%** |
| Week 24 | 16% | 49%** | 20% | 57%** | 18% | 52%** |

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

^(d) Full Analysis Set

NA = not available

*p≤0.05, Cimzia vs placebo

**p<0.001, Cimzia vs placebo

Spinal mobility

Spinal mobility was assessed in the double-blind, placebo-controlled period by using BASMI at several time points including Baseline, Week 12 and Week 24. Clinically meaningful and statistically significant differences in Cimzia-treated patients compared with placebo-treated patients were demonstrated at each post-baseline visit. The difference from placebo tended to be greater in nr-axSpA than in the AS subpopulation which may be due to less chronic structural damage in nr-axSpA patients.

The improvement in BASMI linear score achieved at Week 24 was maintained through Week 204 for patients who remained in the study.

Physical function response and health-related outcomes

In the AS001 clinical trial, Cimzia-treated patients reported significant improvements in physical function as assessed by the BASFI and in pain as assessed by the Total and Nocturnal Back Pain NRS scales as compared to placebo. Cimzia-treated patients reported significant improvements in tiredness (fatigue) as reported by the BASDAI-fatigue item and in health-related quality of life as measured by the ankylosing spondylitis QoL (ASQoL) and the SF-36 Physical and Mental Component Summaries and all domain scores as compared to placebo. Cimzia-treated patients reported significant improvements in axial spondyloarthritis-related productivity at work and within household, as reported by the Work Productivity Survey as compared to placebo. For patients remaining in the study, improvements in all afore-mentioned outcomes were largely maintained through Week 204.

Inhibition of inflammation in Magnetic Resonance Imaging (MRI)

In an imaging sub-study including 153 patients, 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. At week 12 significant inhibition of inflammatory signs in both sacroiliac joints and the spine was observed in the Cimzia-treated patients (all dose group), in the overall axial spondyloarthritis population as well as in the sub-populations of ankylosing spondylitis and non-radiographic axial spondyloarthritis. Among patients remaining in the study, who had both baseline values and week 204 values, inhibition of inflammatory signs in both the sacroiliac joints (n=72) and spine (n=82) was largely maintained through Week 204 in the overall axial spondyloarthritis population as well as in both the AS and the nr-axSpA subpopulations.

Psoriatic arthritis

The efficacy and safety of Cimzia were assessed in a multicentre, randomised, double-blind, placebo controlled clinical trial (PsA001) in 409 patients \geq 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 \geq 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 ACR 20 response at Week 12 and change from baseline in modified Total Sharp Score (mTSS) at Week 24. Efficacy and safety of Cimzia in patients with PsA whose predominant symptoms were sacroiliitis or axial spondyloarthritis have not been separately analysed.

The 24-week double-blind placebo controlled treatment period of the study was followed by a 24-week dose-blind treatment period and an 168-week open-label treatment period. The maximum duration of the study was 216 weeks. All patients received Cimzia in both the dose-blind and open-label follow-up periods. A total of 264 subjects (64.5%) completed the study through Week 216.

ACR response

Cimzia-treated patients had a statistically significant higher ACR 20 response rate at Week 12 and Week 24 compared with placebo-treated patients ($p < 0.001$). The percentage of ACR 20 responders was clinically relevant 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 (nominal $p \leq 0.001$ at each visit). Cimzia treated patients also had significant improvements in ACR 50 and 70 response rates. At week 12 and 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Cimzia-treated patients (nominal p-value $p < 0.01$).

Key efficacy outcomes from the PsA001 clinical trial are shown in Table 9.

Table 9 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^(c) | | | |
| Week 12 | 14% | 47%*** | 47%*** |
| Week 24 | 15% | 62%*** | 61%*** |
| Week 48 | N/A | 67% | 62% |

^(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) In subjects with at least 3% psoriasis BSA at Baseline

*p<0.01, Cimzia vs placebo

**p<0.001, Cimzia vs placebo

***p<0.001(nominal), 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 test. Non-responder Imputation (NRI) is used for patients who escaped therapy or had missing data.

Among 273 patients initially randomised to Cimzia 200 mg every 2 weeks and Cimzia 400 mg every 4 weeks, 237 (86.8%) were still on this treatment at Week 48. Of the 138 patients randomised to Cimzia 200 mg every 2 weeks, 92, 68 and 48 had an ACR 20/50/70 response, at Week 48, respectively. Of the 135 patients randomised to Cimzia 400 mg every 4 weeks, 89, 62 and 41 patients had an ACR 20/50/70 response, respectively.

Among patients remaining in the study, ACR 20, 50 and 70 response rates were maintained through Week 216. This was also the case for the other parameters of peripheral activity (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis).

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. Cimzia treatment inhibited the radiographic progression compared with placebo treatment at Week 24 as measured by change from baseline in total mTSS Score (LS mean [\pm SE] score was 0.28 [\pm 0.07] in the placebo group compared with 0.06 [\pm 0.06] in the Cimzia all doses group; p=0.007). Inhibition of radiographic progression was maintained with Cimzia treatment up to Week 48 in the subset of patients at higher risk of radiographic progression (patients with a Baseline mTSS score of > 6). Inhibition of radiographic progression was further maintained up to Week 216 for the patients who remained in the study.

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), in pain as assessed by the PAAP and in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) 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 Components and in psoriatic arthritis-related productivity at work and within household, as reported by the Work Productivity Survey compared to placebo. Improvements in all afore-mentioned outcomes were maintained through Week 216.

Immunogenicity

Rheumatoid arthritis

The overall percentage of patients with antibodies to Cimzia detectable on at least 1 occasion was 9.6% in RA placebo-controlled trials. Approximately one-third of antibody-positive patients 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.

In 2 long-term (up to 5 years of exposure) open-label studies, the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 13% (8.4% of the overall patients had transient formation of antibodies and an additional 4.7% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 9.1%. Similar to the placebo-controlled studies, antibody positivity was associated with reduced efficacy in some patients.

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.

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.

Over the course of the entire study (up to 192 weeks), the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 9.6% (4.8% had transient formation and an additional 4.8% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 6.8%.

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.

Over the course of the entire study (up to 4 years of exposure), the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 17.3% (8.7% had transient formation and an additional 8.7% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 11.5%.

For all indications

The data reflect the percentage of patients whose test results were considered positive for antibodies to Cimzia in an ELISA, and are highly dependent on the sensitivity and specificity of the assay.

Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant 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 patients (≥ 65 years old)

Specific clinical trials have not been performed in elderly patients 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 µg/ml (95% CI: 10-23 µg/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. Certolizumab pegol does not bind to the human neonatal Fc receptor (FcRn). Data from a human closed-circuit placental transfer model *ex vivo* suggest low or negligible transfer to the foetal compartment. In addition, experiments of FcRn-mediated transcytosis in cells transfected with human FcRn showed negligible transfer (see section 4.6).

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

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 pen in the outer carton in order to protect from light.

6.5 Nature and contents of container

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

Pack size of 2 pre-filled pens and 2 alcohol wipes, a multipack containing 6 (3 packs of 2) pre-filled pens and 6 (3 packs of 2) alcohol wipes, a multipack of 10 (5 packs of 2) pre-filled pens and 10 (5 packs of 2) alcohol wipes

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

This medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/005

EU/1/09/544/006

EU/1/09/544/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 October 2009

Date of latest renewal: 16 May 2014

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in dose-dispenser cartridge

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose-dispenser cartridge 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 the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis

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 MTX, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate
- the treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs.

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 MTX.

Axial spondyloarthritis

Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising:

Ankylosing spondylitis (AS)

Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Axial spondyloarthritis without radiographic evidence of AS

Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein (CRP) and /or magnetic resonance imaging (MRI), who have had an inadequate response to, or are intolerant to NSAIDs.

Psoriatic arthritis

Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate.

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

For details on therapeutic effects, see section 5.1.

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which Cimzia is indicated. Patients should be given the special alert card.

Posology

Loading dose

The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. For rheumatoid arthritis and psoriatic arthritis, MTX should be continued during treatment with Cimzia where appropriate.

Maintenance dose

Rheumatoid arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate.

Axial spondyloarthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with axial spondyloarthritis is 200 mg every 2 weeks or 400 mg every 4 weeks.

Psoriatic arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate.

For the above indications, 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 as instructed.

Special populations

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 patients (≥ 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 dose-dispenser cartridge should be administered using the electromechanical injection device ava for a subcutaneous injection only. Suitable sites for injection would include the thigh or abdomen.

Cimzia solution for injection in a dose-dispenser cartridge is intended for single-use in conjunction with the electromechanical injection device named ava. After proper training in the injection technique, patients may self-inject using the electromechanical injection device ava with the single-use dose-dispenser cartridge if their physician determines that it is appropriate and with medical follow-up as necessary. The physician should discuss with the patient which injection presentation option is the most appropriate.

For administration, the instructions for use at the end of the package leaflet and in the user manual provided with the electromechanical injection device ava should be followed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Moderate to severe heart failure (NYHA 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 certolizumab pegol 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 or opportunistic 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.

Despite previous or concomitant prophylactic treatment for tuberculosis, cases of active tuberculosis have occurred in patients treated with TNF-antagonists including Cimzia. Some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with Cimzia.

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 certolizumab pegol, 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.

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-antagonists including certolizumab pegol (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

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.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), have been reported in patients treated with TNF-antagonists. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. The majority of 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 at or prior to diagnosis. A risk for development of hepatosplenic T-cell lymphoma in patients treated with Cimzia 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. Some of these reactions occurred after the first administration of Cimzia. 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

Patients treated with Cimzia may receive vaccinations, except for live vaccines. No data are available on the response to live vaccinations or the secondary transmission of infection by live vaccines in patients receiving Cimzia. Live vaccines should not be administered concurrently with Cimzia.

In a placebo-controlled clinical trial in patients with rheumatoid arthritis, similar antibody response between Cimzia and placebo treatment were observed when the pneumococcal polysaccharide vaccine and influenza vaccine were administered concurrently with Cimzia. Patients receiving Cimzia and concomitant methotrexate had a lower humoral response compared with patients receiving Cimzia alone. The clinical significance of this is unknown.

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 certolizumab pegol 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 patients

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 patients, 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 certolizumab pegol 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

The use of adequate contraception should be considered for women of childbearing potential. For women planning pregnancy, continued contraception may be considered for 5 months after the last Cimzia dose due to its elimination rate (see section 5.2), but the need for treatment of the woman should also be taken into account (see below).

Pregnancy

Data from more than 500 prospectively collected pregnancies exposed to Cimzia with known pregnancy outcomes, including more than 400 pregnancies exposed during the first trimester, does not indicate a malformative effect of Cimzia. However, the available clinical experience is too limited to, with a reasonable certainty, conclude that there is no increased risk associated with Cimzia administration during pregnancy.

Animal studies using a rodent anti-rat TNF α did not reveal evidence of impaired fertility or harm to the foetus. However, the value of these data may be limited 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.

Cimzia should only be used during pregnancy if clinically needed.

Non-clinical studies suggest low or negligible level of placental transfer of a homologue Fab-fragment of certolizumab pegol (no Fc region) (see section 5.3).

In a clinical study 16 women were treated with certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) during pregnancy. Certolizumab pegol plasma concentrations measured in 14 infants at birth were Below the Limit of Quantification (BLQ) in 13 samples; one was 0.042 $\mu\text{g/ml}$ with an infant/mother plasma ratio at birth of 0.09%. At Week 4 and Week 8, all infant concentrations were BLQ. The clinical significance of low levels certolizumab pegol for infants is unknown. It is recommended to wait a minimum of 5 months following the mother's last Cimzia administration during pregnancy before administration of live or live-attenuated vaccines (e.g. BCG vaccine), unless the benefit of the vaccination clearly outweighs the theoretical risk of administration of live or live-attenuated vaccines to the infants.

Breastfeeding

In a clinical study in 17 lactating women treated with Cimzia, minimal transfer of certolizumab pegol from the plasma to breast milk was observed. The percentage of the maternal certolizumab pegol dose reaching an infant during a 24 hour period was estimated to 0.04% to 0.30 %. In addition, since certolizumab pegol is a protein that is degraded in the gastrointestinal tract after oral administration, the absolute bioavailability is expected to be very low in a breastfed infant.

Consequently, Cimzia can be used during breastfeeding.

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).

In a clinical trial to assess the effect of certolizumab pegol on semen quality parameters, 20 healthy male subjects were randomized to receive a single subcutaneous dose of 400 mg of certolizumab pegol or placebo. During the 14-week follow-up, no treatment effects of certolizumab pegol were seen on semen quality parameters compared to placebo.

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

Summary of the safety profile

Rheumatoid arthritis

Cimzia was studied in 4,049 patients with rheumatoid arthritis in controlled and open label trials for up to 92 months. The data in Table 1 are based primarily on the placebo controlled Studies involving 2,965 patients receiving Cimzia and 1,137 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 4.4% for patients treated with Cimzia and 2.7% for patients treated with placebo.

The most common adverse reactions belonged to the system organ classes Infections and infestations, 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 on Cimzia and 2.4% of patients on placebo.

Axial spondyloarthritis

Cimzia was studied in 325 patients with active axial spondyloarthritis in the AS001 clinical study for up to 4 years, which includes a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 156-week open-label treatment period. The safety profile for axial spondyloarthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

Psoriatic arthritis

Cimzia was studied in 409 patients with psoriatic arthritis in the PsA001 clinical study for up to 4 years which includes a 24-week placebo-controlled phase followed by a 24-week dose-blind period and a 168-week open-label treatment period. The safety profile for psoriatic arthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

Tabulated list of adverse reactions

Adverse reactions reported in rheumatoid arthritis clinical trials and postmarketing cases 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 2 Adverse reactions in clinical trials and postmarketing

| System Organ Class | Frequency | Adverse reactions |
|--|------------------|--|
| Infections and infestations | Common | bacterial infections (including abscess), viral infections (including herpes zoster, 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, auto-antibody positive |
| | Rare | angioneurotic oedema, sarcoidosis, serum sickness, panniculitis (including erythema nodosum), worsening of symptoms of dermatomyositis** |
| 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 |

| System Organ Class | Frequency | Adverse reactions |
|---|------------------|---|
| 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, Stevens-Johnson syndrome**, erythema multiforme** |
| 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, 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 certolizumab pegol is not known.

**These events have been related to the class of TNF-antagonists.

The additional following adverse reactions have been observed uncommonly with Cimzia in other indications: gastrointestinal stenosis and obstructions, general physical health deterioration, abortion spontaneous and azoospermia.

Description of selected adverse reactions

Infections

The incidence rate of new cases of infections in placebo-controlled clinical trials 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, and lower respiratory tract infections and herpes viral 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 (0.07 per patient-year; all doses), compared with placebo (0.02 per patient-year). The most frequent serious infections included pneumonia, tuberculosis infections. Serious infections also included 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, 121 malignancies including 5 cases of lymphoma were observed in the Cimzia RA clinical trials in which a total of 4,049 patients were treated, representing 9,277 patient-years. 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 (see section 4.4). One case of lymphoma was also observed in the Phase III psoriatic arthritis clinical trial.

Autoimmunity

In the pivotal studies, 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, 5.8% of patients treated with Cimzia developed injection site reactions such as erythema, itching, haematoma, pain, swelling or bruising, compared to 4.8% of patients receiving placebo. Injection site pain was observed in 1.5% of patients treated with Cimzia with no cases leading to withdrawal.

Creatine phosphokinase elevations

The frequency of creatine phosphokinase (CPK) elevations was generally higher in patients with axSpA as compared to the RA population. The frequency was increased both in patients treated with placebo (2.8% vs 0.4% in axSpA and RA populations, respectively) as well as in patients treated with Cimzia (4.7% vs 0.8% in axSpA and RA populations, respectively). The CPK elevations in the axSpA study were mostly mild to moderate, transient in nature and of unknown clinical significance with no cases leading to withdrawal.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

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: immunosuppressants, 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-dependent manner. Incubation of monocytes with Cimzia resulted in a dose-dependent 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

Rheumatoid arthritis

The efficacy and safety of Cimzia have been assessed in 2 randomised, placebo-controlled, double-blind clinical trials in patients \geq 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 \geq 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.

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 \geq 18 years of age and had \geq 4 swollen and tender joints each 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). Patients had a mean time since diagnosis at baseline of 2.9 months and were DMARD naïve (including MTX). 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).

Table 2 Clinical trial description

| Study number | Patient numbers | Active 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. |
| C-EARLY (to 52 weeks) | 879 | 400 mg (0,2,4 weeks) with MTX 200 mg every 2 weeks with MTX | Evaluation for treatment of signs and symptoms and inhibition of structural damage in DMARD naïve patients. Primary endpoint: proportion of subjects in sustained remission* at Week 52 |

mTSS: modified Total Sharp Score

*Sustained remission at Week 52 is defined as DAS28[ESR] <2.6 at both Week 40 and Week 52.

Signs and symptoms

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 ACR 20 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

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

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

| Response | Placebo+MTX N= 213 | Cimzia 200 mg + MTX N= 655 |
|--|-----------------------|-------------------------------|
| Sustained remission* (DAS28(ESR) <2.6 at both Week 40 and Week 52) | 15.0 % | 28.9%** |
| Sustained low disease activity (DAS28(ESR) ≤3.2 at both Week 40 and Week 52) | 28.6 % | 43.8%** |

*Primary endpoint of C-EARLY trial (to Week 52)

Full analysis set, non-responder imputation for missing values.

**Cimzia+MTX vs placebo+MTX: p<0.001

p value was estimated from a logistic regression model with factors for treatment, region, and time since RA diagnosis at Baseline (≤4 months vs >4 months)

Patients in the Cimzia+MTX group had a greater reduction from baseline in DAS 28 (ESR) compared with the placebo+MTX group observed as early as Week 2 and continued through Week 52 (p<0.001 at each visit). Assessments on remission (DAS28(ESR) <2.6), Low Disease Activity (DAS28(ESR) ≤3.2) status, ACR50 and ACR 70 by visit demonstrated that Cimzia+MTX treatment led to faster and greater responses than PBO+MTX treatment. These results were maintained over 52 weeks of treatment in DMARD-naïve subjects.

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 5). In the placebo group, 52% of patients experienced no radiographic progression (mTSS ≤ 0.0) at Week 52 compared to 69% in the Cimzia 200 mg treatment group.

Table 5 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.

In C-EARLY, Cimzia+ MTX inhibited the radiographic progression compared to placebo+MTX at Week 52 (see Table 6). In the placebo+MTX group, 49.7% of patients experienced no radiographic progression (change in mTSS ≤ 0.5) at Week 52 compared to 70.3% in the Cimzia+MTX group ($p < 0.001$).

Table 6 Radiographic change at Week 52 in trial C-EARLY

| | Placebo +MTX N= 163 Mean (SD) | Cimzia 200 mg + MTX N = 528 Mean (SD) | Cimzia 200 mg + MTX – Placebo +MTX Difference* |
|---------------------------------|--|--|--|
| mTSS Week 52 | 1.8 (4.3) | 0.2 (3.2)** | -0.978 (-1.005, -0.500) |
| Erosion score Week 52 | 1.1 (3.0) | 0.1 (2.1)** | -0.500 (-0.508, -0.366) |
| JSN score Week 52 | 0.7 (2.3) | 0.1 (1.7)** | 0.000 (0.000, 0.000) |

Radiographic set with linear extrapolation.

* Hodges-Lehmann point estimate of shift and 95% asymptotic (Moses) confidence interval.

**Cimzia+MTX vs placebo+MTX $p < 0.001$. p value 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 a covariate.

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.

In C-EARLY, Cimzia+MTX-treated patients reported significant improvements at Week 52 compared to placebo+MTX in pain as assessed by the Patient Assessment of Arthritis Pain (PAAP) – 48,5 vs - 44,0 (least square mean) ($p < 0.05$).

DoseFlex clinical trial

The efficacy and safety of 2 dose regimens (200 mg every 2 weeks and 400 mg every 4 weeks) of Cimzia versus placebo were assessed in an 18-week, open-label, run-in, and 16-week randomised, double-blind, placebo-controlled clinical trial in adult patients with active rheumatoid arthritis diagnosed according to the ACR criteria who had inadequate response to MTX.

Patients received loading doses of Cimzia 400 mg at weeks 0, 2, and 4 followed by Cimzia 200 mg every 2 weeks during the initial open label period. Responders (achieved ACR 20) at week 16 were randomised at week 18 to Cimzia 200 mg every 2 weeks, Cimzia 400 mg every 4 weeks, or placebo in combination with MTX for an additional 16 weeks (total trial length: 34 weeks). These 3 groups were well balanced with regards to clinical response following the active run-in period (ACR 20: 83-84% at week 18).

The primary endpoint of the study was the ACR 20 responder rate at week 34. The results at week 34 are shown in Table 7. Both Cimzia regimens showed sustained clinical response and were statistically significant compared to placebo at week 34. The ACR 20 endpoint was achieved for both Cimzia 200 mg every 2 weeks and 400 mg every 4 weeks.

Table 7 ACR response in DoseFlex clinical trial at week 34

| Treatment regimen week 0 to 16 | Cimzia 400 mg + MTX at week 0, 2 and 4, followed by Cimzia 200 mg + MTX every 2 weeks | | |
|--|---|-----------------------------------|-----------------------------------|
| Randomised, double-blind treatment regimen week 18 to 34 | Placebo + MTX | Cimzia 200 mg + MTX every 2 weeks | Cimzia 400 mg + MTX every 4 weeks |
| | N=69 | N=70 | N=69 |
| ACR 20 p-value* | 45% N/A | 67% 0.009 | 65% 0.017 |
| ACR 50 p-value* | 30% N/A | 50% 0.020 | 52% 0.010 |
| ACR 70 p-value* | 16% N/A | 30% 0.052 | 38% 0.005 |

N/A: Not Applicable

*Wald p-values for Cimzia 200 mg vs. placebo and Cimzia 400 mg vs. placebo comparisons are estimated from a logistic regression model with factors for treatment

Axial spondyloarthritis

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. The axial spondyloarthritis overall population included subpopulations with and without (non-radiographic axial spondyloarthritis [nr-axSpA]) radiographic evidence for ankylosing spondylitis (AS). 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, 16% of 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. 87.7% of patients received concomitant NSAIDs. The primary efficacy endpoint was the ASAS20 response rate at Week 12. The 24-week double-blind, placebo-controlled treatment period of the study was followed by a 24-week dose-blind treatment period, and a 156-week open-label treatment period. The maximum duration of the study was 204 weeks. All patients received Cimzia in both the dose-blind and open-label follow-up periods. A total of 199 subjects (61.2% of randomized subjects) completed the study through Week 204.

Key efficacy outcomes

In AS001 clinical trial, at Week 12 ASAS20 responses were achieved by 58% of patients receiving Cimzia 200 mg every 2 weeks and 64% of patients receiving Cimzia 400 mg every 4 weeks as compared to 38% of patients receiving placebo ($p < 0.01$). In the overall population, 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 from Week 1 through Week 24 ($p \leq 0.001$ at each visit). At Weeks 12 and 24, the percentage of subjects with an ASAS40 response was greater in the Cimzia-treated groups compared to placebo.

Similar results were achieved in both the ankylosing spondylitis and non-radiographic axial spondyloarthritis subpopulations. In women, ASAS20 responses were not statistically significantly different from placebo until after the Week 12 time point.

Improvements in ASAS5/6, Partial Remission and BASDAI-50 were statistically significant at Week 12 and Week 24 and were sustained up to Week 48 in the overall population as well as in the subpopulations. Key efficacy outcomes from the AS001 clinical trial are shown in Table -8.

Among patients remaining in the study, improvements in all afore-mentioned key efficacy outcomes were maintained through Week 204 in the overall population as well as in the subpopulations.

Table 8 Key efficacy outcomes in AS001 clinical trial (percent of patients)

| Parameters | Ankylosing spondylitis | | Non-radiographic axial spondyloarthritis | | Axial spondyloarthritis Overall Population | |
|--|------------------------|--|--|---|--|--|
| | Placebo N=57 | Cimzia all dosing regimens ^(a) N=121 | Placebo N=50 | Cimzia all dosing regimens ^(a) N=97 | Placebo N=107 | Cimzia all dosing regimens ^(a) N=218 |
| ASAS20^(b,c) | | | | | | |
| Week 12 | 37% | 60%* | 40% | 61%* | 38% | 61%** |
| Week 24 | 33% | 69%** | 24% | 68%** | 29% | 68%** |
| ASAS40^(c,d) | | | | | | |
| Week 12 | 19% | 45%** | 16% | 47%** | 18% | 46%** |
| Week 24 | 16% | 53%** | 14% | 51%** | 15% | 52%** |
| ASAS 5/6^(c,d) | | | | | | |
| Week 12 | 9% | 42%** | 8% | 44%** | 8% | 43%** |
| Week 24 | 5% | 40%** | 4% | 45%** | 5% | 42%** |
| Partial remission^(c,d) | | | | | | |
| Week 12 | 2% | 20%** | 6% | 29%** | 4% | 24%** |
| Week 24 | 7% | 28%** | 10% | 33%** | 9% | 30%** |
| BASDAI 50^(c,d) | | | | | | |
| Week 12 | 11% | 41%** | 16% | 49%** | 13% | 45%** |
| Week 24 | 16% | 49%** | 20% | 57%** | 18% | 52%** |

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

(d) Full Analysis Set

NA = not available

*p≤0.05, Cimzia vs placebo

**p<0.001, Cimzia vs placebo

Spinal mobility

Spinal mobility was assessed in the double-blind, placebo-controlled period by using BASMI at several time points including Baseline, Week 12 and Week 24. Clinically meaningful and statistically significant differences in Cimzia-treated patients compared with placebo-treated patients were demonstrated at each post-baseline visit. The difference from placebo tended to be greater in nr-axSpA than in the AS subpopulation which may be due to less chronic structural damage in nr-axSpA patients.

The improvement in BASMI linear score achieved at Week 24 was maintained through Week 204 for patients who remained in the study.

Physical function response and health-related outcomes

In the AS001 clinical trial, Cimzia-treated patients reported significant improvements in physical function as assessed by the BASFI and in pain as assessed by the Total and Nocturnal Back Pain NRS scales as compared to placebo. Cimzia-treated patients reported significant improvements in tiredness (fatigue) as reported by the BASDAI-fatigue item and in health-related quality of life as measured by the ankylosing spondylitis QoL (ASQoL) and the SF-36 Physical and Mental Component Summaries and all domain scores as compared to placebo. Cimzia-treated patients reported significant improvements in axial spondyloarthritis-related productivity at work and within household, as reported by the Work Productivity Survey as compared to placebo. For patients remaining in the study, improvements in all afore-mentioned outcomes were largely maintained through Week 204.

Inhibition of inflammation in Magnetic Resonance Imaging (MRI)

In an imaging sub-study including 153 patients, 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. At week 12, significant inhibition of inflammatory signs in both sacroiliac joints and the spine was observed in the Cimzia-treated patients (all dose group), in the overall axial spondyloarthritis population as well as in the sub-populations of ankylosing spondylitis and non-radiographic axial spondyloarthritis.

Among patients remaining in the study, who had both baseline values and week 204 values, inhibition of inflammatory signs in both the sacroiliac joints (n=72) and spine (n=82) was largely maintained through Week 204 in the overall axial spondyloarthritis population as well as in both the AS and the nr-axSpA subpopulations.

Psoriatic arthritis

The efficacy and safety of Cimzia were assessed in a multicentre, randomised, 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 ACR 20 response at Week 12 and change from baseline in modified Total Sharp Score (mTSS) at Week 24. Efficacy and safety of Cimzia in patients with PsA whose predominant symptoms were sacroiliitis or axial spondyloarthritis have not been separately analysed.

The 24-week double-blind placebo controlled treatment period of the study was followed by a 24-week dose-blind treatment period and an 168-week open-label treatment period. The maximum duration of the study was 216 weeks. All patients received Cimzia in both the dose-blind and open-label follow-up periods. A total of 264 subjects (64.5%) completed the study through Week 216.

ACR response

Cimzia-treated patients had a statistically significant higher ACR 20 response rate at Week 12 and Week 24 compared with placebo-treated patients ($p < 0.001$). The percentage of ACR 20 responders was clinically relevant 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 (nominal $p \leq 0.001$ at each visit). Cimzia treated patients also had significant improvements in ACR 50 and 70 response rates. At week 12 and 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Cimzia-treated patients (nominal p-value $p < 0.01$).

Key efficacy outcomes from the PsA001 clinical trial are shown in Table 9.

Table 9 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^(c) | | | |
| Week 12 | 14% | 47%*** | 47%*** |
| Week 24 | 15% | 62%*** | 61%*** |
| Week 48 | N/A | 67% | 62% |

^(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) In subjects with at least 3% psoriasis BSA at Baseline

*p<0.01, Cimzia vs placebo

**p<0.001, Cimzia vs placebo

***p<0.001(nominal), 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 test. Non-responder Imputation (NRI) is used for patients who escaped therapy or had missing data.

Among 273 patients initially randomised to Cimzia 200 mg every 2 weeks and Cimzia 400 mg every 4 weeks, 237 (86.8%) were still on this treatment at Week 48. Of the 138 patients randomised to Cimzia 200 mg every 2 weeks, 92, 68 and 48 had an ACR 20/50/70 response, at Week 48 respectively. Of the 135 patients randomised to Cimzia 400 mg every 4 weeks, 89, 62 and 41 patients had an ACR 20/50/70 response, respectively.

Among patients remaining in the study, ACR 20, 50 and 70 response rates were maintained through Week 216. This was also the case for the other parameters of peripheral activity (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis).

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. Cimzia treatment inhibited the radiographic progression compared with placebo treatment at Week 24 as measured by change from baseline in total mTSS Score (LS mean [\pm SE] score was 0.28 [\pm 0.07] in the placebo group compared with 0.06 [\pm 0.06] in the Cimzia all doses group; p=0.007). Inhibition of radiographic progression was maintained with Cimzia treatment up to Week 48 in the subset of patients at higher risk of radiographic progression (patients with a Baseline mTSS score of > 6). Inhibition of radiographic progression was further maintained up to Week 216 for the patients who remained in the study.

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), in pain as assessed by the PAAP and in tiredness (fatigue) as reported by the Fatigue Assessment Scale (FAS) 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 Components and in psoriatic arthritis-related productivity at work and within household, as reported by the Work Productivity Survey compared to placebo. Improvements in all afore-mentioned outcomes were maintained through Week 216.

Immunogenicity

Rheumatoid arthritis

The overall percentage of patients with antibodies to Cimzia detectable on at least 1 occasion was 9.6% in RA placebo-controlled trials. Approximately one-third of antibody-positive patients 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.

In 2 long-term (up to 5 years of exposure) open-label studies, the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 13% (8.4% of the overall patients had transient formation of antibodies and an additional 4.7% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 9.1%. Similar to the placebo-controlled studies, antibody positivity was associated with reduced efficacy in some patients.

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.

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.

Over the course of the entire study (up to 192 weeks), the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 9.6% (4.8% had transient formation and an additional 4.8% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 6.8%.

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.

Over the course of the entire study (up to 4 years of exposure), the overall percentage of patients with antibodies to Cimzia detectable on at least one occasion was 17.3% (8.7% had transient formation and an additional 8.7% had persistent formation of antibodies to Cimzia). The overall percentage of patients that were antibody positive with a persistent reduction of drug plasma concentration was estimated to be 11.5%.

For all indications

The data reflect the percentage of patients whose test results were considered positive for antibodies to Cimzia in an ELISA, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors

including sample handling, timing of sample collection, concomitant 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 patients (≥ 65 years old)

Specific clinical trials have not been performed in elderly patients 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 µg/ml (95% CI: 10-23 µg/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. Certolizumab pegol does not bind to the human neonatal Fc receptor (FcRn). Data from a human closed-circuit placental transfer model *ex vivo* suggest low or negligible transfer to the foetal compartment. In addition, experiments of FcRn-mediated transcytosis in cells transfected with human FcRn showed negligible transfer (see section 4.6).

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

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 dose-dispenser cartridge in the outer carton in order to protect from light.

6.5 Nature and contents of container

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

Pack size of 2 dose-dispenser cartridges and 2 alcohol wipes.

Multipack containing 6 (3 packs of 2) dose-dispenser cartridge and 6 (3 packs of 2) alcohol wipes.

Multipack containing 10 (5 packs of 2) dose-dispenser cartridge and 10 (5 packs of 2) alcohol wipes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the preparation and administration of Cimzia in a dose-dispenser cartridge are given in the package leaflet and in the user manual provided with the electromechanical injection device ava.

This medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

UCB Pharma S.A.
Allée de la Recherche 60
B-1070 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/008

EU/1/09/544/009

EU/1/09/544/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 October 2009

Date of latest renewal: 16 May 2014

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

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

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR
BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE
SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Sandoz GmbH
Biochemiestraße 10
A-6250 Kundl
Austria

Lonza AG
Lonzastraße
CH-3930 Visp
Switzerland

UCB Farchim SA
Zone Industrielle de Planchy d'Avau
Chemin de Croix Blanche 10
CH-1630 Bulle
Switzerland

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 OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

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.

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 in pre-filled syringe
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 in pre-filled syringe
2 single-use pre-filled syringes
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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Multipack of 6 (3 packs of 2 pre-filled syringes and 2 alcohol wipes)
(with bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled syringe
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 in pre-filled syringe
Multipack: 6 (3 x 2) single-use pre-filled syringes and 6 (3 x 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Multipack of 10 (5 packs of 2 pre-filled syringes and 2 alcohol wipes)
(with bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled syringe
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 in pre-filled syringe
Multipack: 10 (5 x 2) single-use pre-filled syringes and 10 (5 x 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/004

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

Intermediate carton within Multipack of 6 (for 2 pre-filled syringes and 2 alcohol wipes) (without bluebox)

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled syringe
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 in pre-filled syringe
2 single-use pre-filled syringes
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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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 S.A.
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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

Intermediate carton within Multipack of 10 (for 2 pre-filled syringes and 2 alcohol wipes) (without bluebox)

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled syringe
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 in pre-filled syringe
2 single-use pre-filled syringes
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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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**

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/004

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14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Cimzia 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled syringe
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 in pre-filled syringe
2 single-use pre-filled syringes with needle guard
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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For healthcare professionals only.

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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/003

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

TRAY BACKING TEXT

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled syringe
certolizumab pegol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

UCB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Read the package leaflet before use

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

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

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled pen
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen 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 in a pre-filled pen (AutoClicks)
2 single-use AutoClicks pre-filled pens
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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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 pen 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/005

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Carton Multipack of 6 (3 packs of 2 pre-filled pens and 2 alcohol wipes)
(with bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled pen
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen 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 in a pre-filled pen (AutoClicks)
Multipack: 6 (3 x 2) single-use AutoClicks pre-filled pens and 6 (3 x 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 pen 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/006

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Carton Multipack of 10 (5 packs of 2 pre-filled pens and 2 alcohol wipes)
(with bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled pen
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen 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 in a pre-filled pen (AutoClicks)
Multipack: 10 (5 x 2) single-use AutoClicks pre-filled pens and 10 (5 x 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 pen 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/007

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

**Intermediate carton within Multipack of 6 (for 2 pre-filled pens and 2 alcohol wipes)
(without blue box)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled pen
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen 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 in a pre-filled pen (AutoClicks)
2 single-use AutoClicks pre-filled pens
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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 pen 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/006

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

**Intermediate carton within Multipack of 10 (for 2 pre-filled pens and 2 alcohol wipes)
(without bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in pre-filled pen
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen 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 in a pre-filled pen (AutoClicks)
2 AutoClicks pre-filled pens
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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 pen 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/007

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton (for packs of 2 dose-dispenser cartridges and 2 alcohol wipes)

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in dose-dispenser cartridge
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose-dispenser cartridge 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 in dose-dispenser cartridge
2 single-use dose-dispenser cartridges
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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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 dose-dispenser cartridge 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/008

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Carton Multipack of 6 (3 packs of 2 dose-dispenser cartridges and 2 alcohol wipes)
(with bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in dose-dispenser cartridge
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose-dispenser cartridge 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 in dose-dispenser cartridge
Multipack: 6 (3 x 2) single-use dose-dispenser cartridges and 6 (3 x 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 dose-dispenser cartridge 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/009

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**Carton Multipack of 10 (5 packs of 2 dose-dispenser cartridges and 2 alcohol wipes)
(with bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in dose-dispenser cartridge
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose-dispenser cartridge 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 in dose-dispenser cartridge
Multipack: 10 (5 x 2) single-use dose-dispenser cartridge and 10 (5 x 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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 dose-dispenser cartridge 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/010

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

**Intermediate carton within Multipack of 6 (for 2 dose-dispenser cartridges and 2 alcohol wipes)
(without bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in dose-dispenser cartridge
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose-dispenser cartridge 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 in dose-dispenser cartridge
2 single-use dose-dispenser cartridges
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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 dose-dispenser cartridge 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/009

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

**Intermediate carton within Multipack of 10 (for 2 dose-dispenser cartridges and 2 alcohol wipes)
(without bluebox)**

1. NAME OF THE MEDICINAL PRODUCT

Cimzia 200 mg solution for injection in dose-dispenser cartridge
certolizumab pegol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One dose-dispenser cartridge 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 in dose-dispenser cartridge
2 single-use dose-dispenser cartridges
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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach 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 dose-dispenser cartridge 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 S.A.
Allée de la Recherche 60
1070 Brussels
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/544/010

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

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
SYRINGE/PEN/DOSE-DISPENSER CARTRIDGE LABEL**

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

Cimzia 200 mg injection
certolizumab pegol
SC

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 in pre-filled syringe certolizumab pegol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cimzia is and what it is used for
2. What you need to know before you use Cimzia
3. How to use Cimzia
4. Possible side effects
5. How to store Cimzia
6. Contents of the pack and other 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, axial spondyloarthritis and psoriatic arthritis. Medicines that bind to TNF α are also called TNF blockers.

Cimzia is used in adults for the following inflammatory diseases:

- **rheumatoid arthritis,**
- **axial spondyloarthritis** (including ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis),
- **psoriatic arthritis**

Rheumatoid arthritis

Cimzia is used to treat rheumatoid arthritis. Rheumatoid arthritis is an inflammatory disease of the joints. If you have moderate to severe active rheumatoid arthritis, you may first be given other medicines usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to treat your rheumatoid arthritis. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Cimzia in combination with methotrexate can also be used to treat severe, active and progressive rheumatoid arthritis without previous use of methotrexate or other medicines.

Cimzia, which you will take in combination with methotrexate, is used to:

- reduce the signs and symptoms of your disease,
- slow down the damage to the cartilage and bone of the joints caused by the disease,

- improve your physical function and performance of daily tasks.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Cimzia is used to treat severe active ankylosing spondylitis and axial spondyloarthritis-without radiographic evidence of ankylosing spondylitis (sometimes referred to as non-radiographic axial spondyloarthritis). These diseases are inflammatory diseases of the spine. If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Cimzia to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

Psoriatic arthritis

Cimzia is used to treat active psoriatic arthritis. Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines, usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

2. What you need to know before you use Cimzia

Do NOT use Cimzia

- If you are **ALLERGIC** (hypersensitive) to certolizumab pegol or any of the other ingredients of this medicine (listed in section 6)
- 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.

Warnings and precautions

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**. Some of these reactions could occur after the first administration of Cimzia.

Infections

- If you have had **RECURRENT or OPPORTUNISTIC 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. In rare occasions tuberculosis can develop during therapy even if you have received preventive treatment for tuberculosis. 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.
- 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 and adolescents”).

Other disorders

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

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 and adolescents

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

Other medicines and Cimzia

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).

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is limited experience with Cimzia in pregnant women.

Cimzia should be used during pregnancy only if clearly needed. If you are a woman of childbearing potential, discuss with your doctor regarding use of adequate contraception while using Cimzia. For women planning pregnancy, contraception may be considered for 5 months after the last Cimzia dose.

If you received Cimzia during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Cimzia use before the baby receives any vaccine (for more information see section on vaccinations).

Cimzia can be used during breastfeeding.

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.

Cimzia contains sodium acetate and sodium chloride

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 this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Rheumatoid arthritis

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 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. Methotrexate is continued while using Cimzia. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Axial spondyloarthritis

The **starting dose** for adults with axial spondyloarthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks (from week 6) or 400 mg every 4 weeks (from week 8) as instructed by your physician.

Psoriatic arthritis

The **starting dose** for adults with psoriatic arthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. 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, abbreviation: SC). 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 as 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, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine 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)
- serious skin rashes. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. (Stevens-Johnson syndrome)

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:

Common (may affect up to 1 in 10 people):

- 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
- nausea

Uncommon (may affect up to 1 in 100 people):

- allergic conditions including allergic rhinitis and allergic reactions to the medicine (including anaphylactic shock)
- antibody directed against normal tissue
- blood and lymphatic system cancers like lymphoma and leukaemia
- solid organ cancers
- skin cancers, pre-cancerous skin lesions
- 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
- ringing in the ears
- 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, inflammation of the skin (such as eczema), 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
- some blood parameters increased (blood alkaline phosphatase increased)
- prolonged coagulation (clotting) test times

Rare (may affect up to 1 in 1,000 people):

- gastrointestinal cancer, melanoma
- lung inflammation (interstitial lung disease, pneumonitis)
- stroke, blockage in blood vessels (arteriosclerosis), 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
- pericardial inflammation
- cardiac arrhythmia
- enlarged spleen
- increase of red cell mass
- white blood cell morphology abnormal
- formation of stones in the gall bladder
- kidney problems (including nephritis)
- 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)
- increased iron levels in the body
- increased blood levels of uric acid
- suicide attempt, mental impairment, delirium
- inflammation of the nerves for hearing, seeing, or of the face, impaired coordination or balance
- 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
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Stevens-Johnson syndrome (a serious skin condition which early symptoms include malaise, fever, headache and rash)
- inflammatory skin rash (erythema multiforme)

Not known (frequency cannot be estimated from the available data):

- multiple sclerosis*
- Guillain-Barré syndrome*
- Merkel cell carcinoma (a type of skin cancer)*

*These events have been related to this class of medicines but the incidence with Cimzia is not known.

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).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cimzia

Keep this medicine out of the sight and reach of children.

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

Do not use this medicine if the solution is discoloured, cloudy or if you can see particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other 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 (see “Cimzia contains sodium acetate and sodium chloride” in section 2).

What Cimzia looks like and contents of the pack

Cimzia is provided as a solution for injection (injection) in a ready to use pre-filled syringe. The solution is clear to opalescent, colourless to yellow.

One Cimzia pack contains:

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

Packs of 2 pre-filled syringes and 2 alcohol wipes, a multipack containing 6 (3 packs of 2) pre-filled syringes and 6 (3 packs of 2) alcohol wipes, and a multipack containing 10 (5 packs of 2) pre-filled syringes and 10 (5 packs of 2) alcohol wipes are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

UCB Pharma S.A.
Chemin du Foriest
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

INSTRUCTIONS FOR USE FOR CIMZIA INJECTION BY MEANS OF A PRE-FILLED SYRINGE

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.

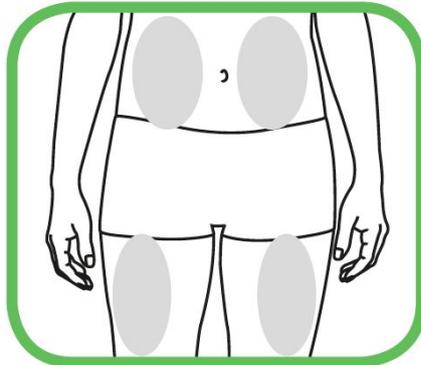
1. Setting up

- Remove the Cimzia pack from the refrigerator.
 - If the seal(s) is missing or broken – do not use and contact your pharmacist.
- Remove the following items from the Cimzia pack and set them up on a clean flat surface:
 - One or two pre-filled syringe(s), depending on your prescribed dose
 - One or two alcohol wipe(s)
- 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 30 minutes. This will help reduce discomfort when injecting.
 - Do not heat the pre-filled syringe – let it warm on its own.

- Do not remove the cap until you are ready to inject.
- Wash your hands thoroughly.

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.



Check the medicine in the body of the syringe.

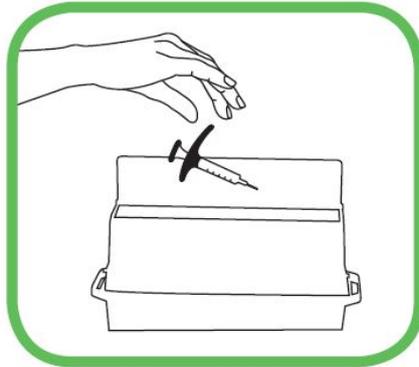
- Do not use if the solution is discoloured, cloudy or if you can see particles in it.
- You may see air bubbles - this is normal. Injecting a solution subcutaneously which contains air bubbles is harmless.
- Remove the cap from the needle in a straight direction, being careful not to touch the needle or let the needle touch any surface. Do not bend the needle.
- Inject within 5 minutes of removing the needle cap.
- Gently grasp the cleaned area of skin with one hand and hold firmly.



- With the other hand, hold the syringe at a 45-degree angle to the skin.
- With one quick, short motion, push the needle all the way into the skin.
- Push the 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. After Use

- Do not re-use the syringe or re-cap the needle.
- After injection, immediately throw away the used syringe(s) in a special container as instructed by your doctor, nurse or pharmacist.



- Keep the container out of the sight and reach of children.
- If you need to have a second injection as prescribed by your doctor repeat the injection process starting at Step 2.

Package leaflet: Information for the user

Cimzia 200 mg solution for injection in pre-filled syringe

Pre-filled syringe with needle guard
certolizumab pegol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cimzia is and what it is used for
2. What you need to know before you use Cimzia
3. How Cimzia will be given
4. Possible side effects
5. How to store Cimzia
6. Contents of the pack and other 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, axial spondyloarthritis and psoriatic arthritis. Medicines that bind to TNF α are also called TNF blockers.

Cimzia is used in adults for the following inflammatory diseases:

- **rheumatoid arthritis,**
- **axial spondyloarthritis** (including ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis)
- **psoriatic arthritis.**

Rheumatoid arthritis

Cimzia is used to treat rheumatoid arthritis. Rheumatoid arthritis is an inflammatory disease of the joints. If you have moderate to severe active rheumatoid arthritis, you may first be given other medicines usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to treat your rheumatoid arthritis. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Cimzia in combination with methotrexate can also be used to treat severe, active and progressive rheumatoid arthritis without previous use of methotrexate or other medicines.

Cimzia, which you will take in combination with methotrexate, is used to:

- reduce the signs and symptoms of your disease,
- slow down the damage to the cartilage and bone of the joints caused by the disease,
- improve your physical function and performance of daily tasks.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Cimzia is used to treat severe active ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (sometimes referred to as non-radiographic axial spondyloarthritis). These diseases are inflammatory diseases of the spine. If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Cimzia to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

Psoriatic arthritis

Cimzia is used to treat active psoriatic arthritis. Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines, usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

2. What you need to know before you use Cimzia

Do NOT use Cimzia

- If you are **ALLERGIC** (hypersensitive) to certolizumab pegol or any of the other ingredients of this medicine (listed in section 6)
- 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.

Warnings and precautions

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**. Some of these reactions could occur after the first administration of Cimzia.

Infections

- If you have had **RECURRENT or OPPORTUNISTIC 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. In rare occasions tuberculosis can develop during therapy even if you have received preventive treatment for tuberculosis. 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.
- 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 and adolescents”).

Other disorders

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

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 and adolescents

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

Other medicines and Cimzia

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).

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is limited experience with Cimzia in pregnant women.

Cimzia should be used during pregnancy only if clearly needed. If you are a woman of childbearing potential discuss with your doctor regarding use of adequate contraception while using Cimzia. For women planning pregnancy, contraception may be considered for 5 months after the last Cimzia dose.

If you received Cimzia during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Cimzia use before the baby receives any vaccine (for more information see section on vaccinations).

Cimzia can be used during breastfeeding.

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.

Cimzia contains sodium acetate and sodium chloride

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

3. How Cimzia will be given

Cimzia will be given to you by your doctor or nurse, in hospital or clinic.

Rheumatoid arthritis

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 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. Methotrexate is continued while using Cimzia. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Axial spondyloarthritis

The **starting dose** for adults with axial spondyloarthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks (from week 6) or 400 mg every 4 weeks (from week 8) as instructed by your physician.

Psoriatic arthritis

The **starting dose** for adults with psoriatic arthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. Methotrexate is continued while using Cimzia. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Cimzia will 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, abbreviation: SC). It is usually injected into the thigh or tummy.

If you are given too much Cimzia

As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. Always take the Patient Alert Card with you.

If you forget to use Cimzia

If you forget or miss an appointment to receive Cimzia, make another appointment as soon as possible.

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

4. Possible side effects

Like all medicines, this medicine 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)
- serious skin rashes. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. (Stevens-Johnson syndrome)

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:

Common (may affect up to 1 in 10 people):

- 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
- nausea

Uncommon (may affect up to 1 in 100 people):

- allergic conditions including allergic rhinitis and allergic reactions to the medicine (including anaphylactic shock)
- antibody directed against normal tissue
- blood and lymphatic system cancers like lymphoma and leukaemia
- solid organ cancers
- skin cancers, pre-cancerous skin lesions
- 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
- ringing in the ears
- 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, inflammation of the skin (such as eczema), 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
- some blood parameters increased (blood alkaline phosphatase increased)
- prolonged coagulation (clotting) test times

Rare (may affect up to 1 in 1,000 people):

- gastrointestinal cancer, melanoma
- lung inflammation (interstitial lung disease, pneumonitis)
- stroke, blockage in blood vessels (arteriosclerosis), 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
- pericardial inflammation
- cardiac arrhythmia
- enlarged spleen
- increase of red cell mass
- white blood cell morphology abnormal
- formation of stones in the gall bladder
- kidney problems (including nephritis)
- 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)
- increased iron levels in the body
- increased blood levels of uric acid
- suicide attempt, mental impairment, delirium
- inflammation of the nerves for hearing, seeing, or of the face, impaired coordination or balance
- 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
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Stevens-Johnson syndrome (a serious skin condition which early symptoms include malaise, fever, headache and rash)
- inflammatory skin rash (erythema multiforme)

Not known (frequency cannot be estimated from the available data):

- multiple sclerosis*
- Guillain-Barré syndrome*
- Merkel cell carcinoma (a type of skin cancer)*

*These events have been related to this class of medicines but the incidence with Cimzia is not known.

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).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#)

listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cimzia

Keep this medicine out of the sight and reach of children.

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

Do not use this medicine if the solution is discoloured, cloudy or if you can see particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other 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 (see “Cimzia contains sodium acetate and sodium chloride” in section 2).

What Cimzia looks like and contents of the pack

Cimzia is provided as a solution for injection (injection) in a ready to use pre-filled syringe. The solution is clear to opalescent, colourless to yellow.

One Cimzia pack contains:

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

Pack of 2 pre-filled syringes and 2 alcohol wipes.

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Manufacturer

UCB Pharma S.A.
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

The following information is intended for medical or healthcare professionals only:

INSTRUCTIONS FOR USE FOR THE CIMZIA INJECTION BY MEANS OF A PRE-FILLED SYRINGE WITH NEEDLE GUARD

The following instructions explain how to inject Cimzia. Please read the instructions carefully and follow them step by step.

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

Below is a diagram of the pre-filled syringe with needle guard.

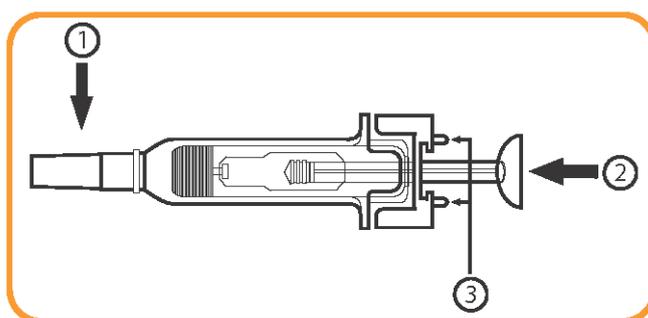


Figure 1

- 1: Needle cap
- 2: Plunger head
- 3: Needle guard activation clips

For each injection you will need:

- 1 pre-filled syringe with needle guard
- 1 alcohol wipe

1. Setting up

- Remove the Cimzia pack from the refrigerator.
 - If the seal(s) is missing or broken – do not use and contact your pharmacist.
- Remove the following items from the Cimzia pack and set them up on a clean flat surface:
 - One or two pre-filled syringe(s), depending on your prescriber dose
 - One or two alcohol wipe(s)
- Look at the expiry date on the pack and dose tray. Do not use Cimzia after the expiry date which is stated on the pack and dose tray 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 30 minutes. This will help reduce discomfort when injecting.
 - Do not heat the medication - let it warm up on its own.
- Remove the prefilled syringe from the dose tray by grasping the syringe body as shown in Figure 2. **Do NOT touch the needle guard activation clips (labelled as 3 in Figure 1) during removal (as shown in Figure 3) in order to prevent prematurely covering the needle with the needle guard.**



Figure 2



Figure 3

- Do not use the syringe if it has been dropped without its packaging.
- Do not remove the cap until you are ready to inject.
- Wash your hands thoroughly.

2. Choosing and preparing an injection site

- Choose a site on the thigh or abdomen.
- 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 this area again before injection.
 - Do not inject until the skin is dry.

3. Injection

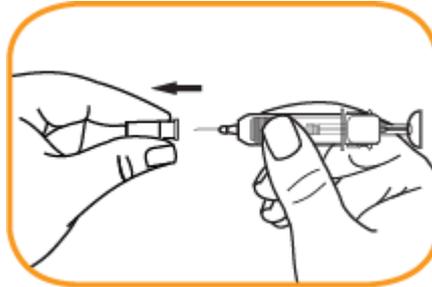
- Do not shake the syringe.



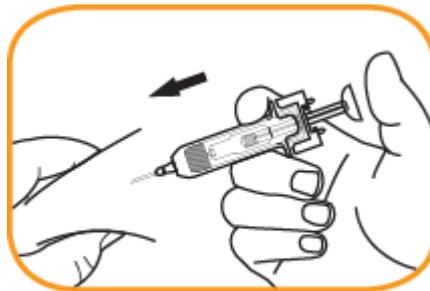
Check the medicine in the body of the syringe.

- Do not use if the solution is discoloured, cloudy or if you can see particles in it.

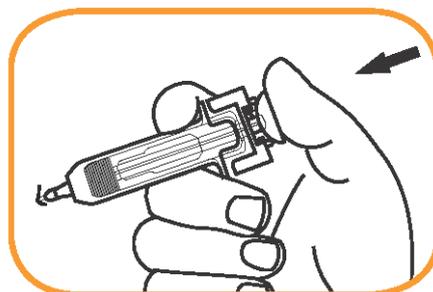
- You may see some air bubbles - this is normal. Injecting the solution subcutaneously with air bubbles is harmless.
- Remove the needle cap from the needle by pulling off in a straight line. Take care not to touch the needle or let the needle touch any surface. **Do NOT touch the needle guard activation clips (labelled as 3 in Figure 1) during removal in order to prevent prematurely covering the needle with the needle guard.** Inject within 5 minutes of removing the needle cap.



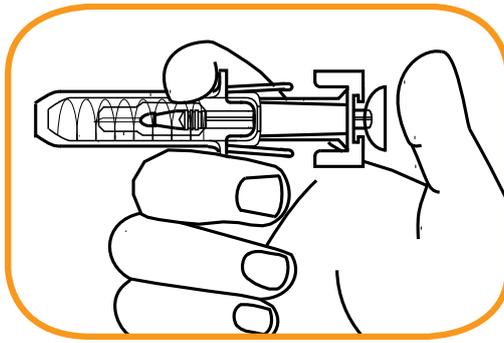
- Gently grasp the cleaned area of skin with one hand and hold firmly.
- With the other hand, hold syringe at a 45-degree angle to skin.
- With one quick, short motion, push the needle all the way into the skin.



- Release the skin with the first hand.
- Push plunger head all the way down until the **entire dose** has been given and the plunger head is between the needle guard activation clips. 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.
- Take your thumb off the plunger head. The empty syringe and needle will **automatically move back into the barrel** and lock in place.
- The needle safety device will not activate unless the entire dose is given.



- Use a piece of gauze to 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. After Use

- Do not re-use the syringe.
- Any unused product(s) or waste material should be disposed of in accordance with local requirements.
- If a second injection is needed as prescribed by the doctor repeat the injection process starting at Step 2.

Package leaflet: Information for the user

Cimzia 200 mg solution for injection in pre-filled pen certolizumab pegol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cimzia is and ~~for~~ what it is used for
2. What you need to know before you use Cimzia
3. How to use Cimzia
4. Possible side effects
5. How to store Cimzia
6. Contents of the pack and other 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, axial spondyloarthritis and psoriatic arthritis. Medicines that bind to TNF α are also called TNF blockers.

Cimzia is used in adults for the following inflammatory diseases:

- **rheumatoid arthritis,**
- **axial spondyloarthritis** (including ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis),
- **psoriatic arthritis**

Rheumatoid arthritis

Cimzia is used to treat rheumatoid arthritis. Rheumatoid arthritis is an inflammatory disease of the joints. If you have moderate to severe active rheumatoid arthritis, you may first be given other medicines usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to treat your rheumatoid arthritis. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Cimzia in combination with methotrexate can also be used to treat severe, active and progressive rheumatoid arthritis without previous use of methotrexate or other medicines.

Cimzia, which you will take in combination with methotrexate, is used to:

- reduce the signs and symptoms of your disease,
- slow down the damage to the cartilage and bone of the joints caused by the disease,

- improve your physical function and performance of daily tasks.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Cimzia is used to treat severe active ankylosing spondylitis and axial spondyloarthritis-without radiographic evidence of ankylosing spondylitis (sometimes referred to as non-radiographic axial spondyloarthritis). These diseases are inflammatory diseases of the spine. If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Cimzia to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

Psoriatic arthritis

Cimzia is used to treat active psoriatic arthritis. Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines, usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

2. What you need to know before you use Cimzia

Do NOT use Cimzia

- If you are **ALLERGIC** (hypersensitive) to certolizumab pegol or any of the other ingredients of this medicine (listed in section 6)
- 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.

Warnings and precautions

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**. Some of these reactions could occur after the first administration of Cimzia.

Infections

- If you have had **RECURRENT or OPPORTUNISTIC 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. In rare occasions tuberculosis can develop during therapy even if you have received preventive treatment for tuberculosis. 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.
- 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 and adolescents”).

Other disorders

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

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 and adolescents

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

Other medicines and Cimzia

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).

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is limited experience with Cimzia in pregnant women.

Cimzia should be used during pregnancy only if clearly needed. If you are a woman of childbearing potential discuss with your doctor regarding use of adequate contraception while using Cimzia. For women planning pregnancy, contraception may be considered for 5 months after the last Cimzia dose.

If you received Cimzia during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Cimzia use before the baby receives any vaccine (for more information see section on vaccinations).

Cimzia can be used during breastfeeding.

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.

Cimzia contains sodium acetate and sodium chloride

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 this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Rheumatoid arthritis

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 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. Methotrexate is continued while using Cimzia. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Axial spondyloarthritis

The **starting dose** for adults with axial spondyloarthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks (from week 6) or 400 mg every 4 weeks (from week 8) as instructed by your physician.

Psoriatic arthritis

The **starting dose** for adults with psoriatic arthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. 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, abbreviation: SC). 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 as 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, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine 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)
- serious skin rashes. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. (Stevens-Johnson syndrome)

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:

Common (may affect up to 1 in 10 people):

- 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
- nausea

Uncommon (may affect up to 1 in 100 people):

- allergic conditions including allergic rhinitis and allergic reactions to the medicine (including anaphylactic shock)
- antibody directed against normal tissue
- blood and lymphatic system cancers like lymphoma and leukaemia
- solid organ cancers
- skin cancers, pre-cancerous skin lesions
- 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
- ringing in the ears
- 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, inflammation of the skin (such as eczema), 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
- some blood parameters increased (blood alkaline phosphatase increased)
- prolonged coagulation (clotting) test times

Rare (may affect up to 1 in 1,000 people):

- gastrointestinal cancer, melanoma
- lung inflammation (interstitial lung disease, pneumonitis)
- stroke, blockage in blood vessels (arteriosclerosis), 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
- pericardial inflammation
- cardiac arrhythmia
- enlarged spleen
- increase of red cell mass
- white blood cell morphology abnormal
- formation of stones in the gall bladder
- kidney problems (including nephritis)
- 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)
- increased iron levels in the body
- increased blood levels of uric acid
- suicide attempt, mental impairment, delirium
- inflammation of the nerves for hearing, seeing, or of the face, impaired coordination or balance
- 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
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Stevens-Johnson syndrome (a serious skin condition which early symptoms include malaise, fever, headache and rash)
- inflammatory skin rash (erythema multiforme)

Not known (frequency cannot be estimated from the available data):

- multiple sclerosis*
- Guillain-Barré syndrome*
- Merkel cell carcinoma (a type of skin cancer)*

*These events have been related to this class of medicines but the incidence with Cimzia is not known.

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).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cimzia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack and pen after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Do not freeze.

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

Do not use this medicine if the solution is discoloured, cloudy or if you can see particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cimzia contains

- The active substance is certolizumab pegol. Each pre-filled pen contains 200 mg of certolizumab pegol in one ml.
- The other ingredients are: sodium acetate, sodium chloride and water for injections (see “Cimzia contains sodium acetate and sodium chloride” in section 2).

What Cimzia looks like and contents of the pack

Cimzia is provided as a solution for injection (injection) in a ready to use pre-filled pen (AutoClicks). The solution is clear to opalescent, colourless to yellow.

One Cimzia pack contains:

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

Packs of 2 pre-filled pens and 2 alcohol wipes, a multipack containing 6 (3 packs of 2) pre-filled pens and 6 (3 packs of 2) alcohol wipes, and a multipack containing 10 (5 packs of 2) pre-filled pens and 10 (5 packs of 2) alcohol wipes are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Belgium

Manufacturer

UCB Pharma S.A.
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Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in {MM/YYYY}

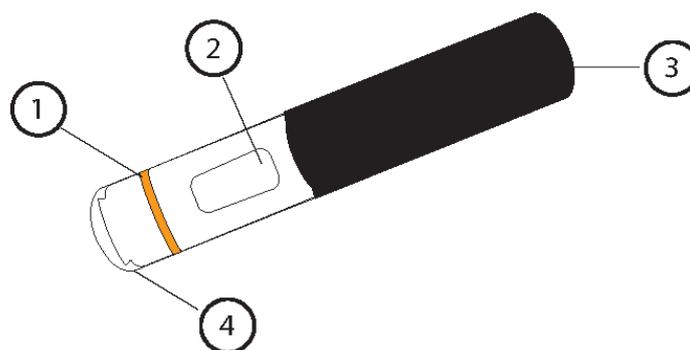
Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

INSTRUCTIONS FOR USE FOR THE CIMZIA INJECTION BY MEANS OF PRE-FILLED PEN

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 use the pre-filled pen (AutoClicks) 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.

Below is a diagram of the AutoClicks pre-filled pen.



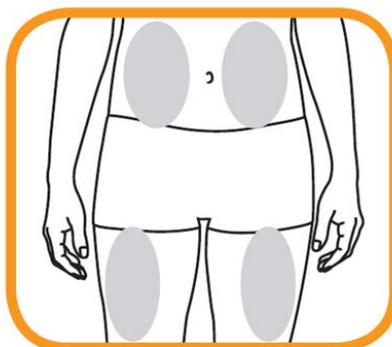
- 1: Orange band
- 2: Viewing window
- 3: Black handle
- 4: Clear cap

1. Setting up

- Remove the Cimzia pack from the refrigerator.
 - If the seal(s) is missing or broken – do not use and contact your pharmacist.
- Remove the following items from the Cimzia pack and set them up on a clean flat surface:
 - One or two AutoClicks pre-filled pen(s), depending on your prescribed dose
 - One or two alcohol wipe(s)
- Look at the expiry date on the pre-filled pen and pack. Do not use Cimzia after the expiry date which is stated on the pack and pre-filled pen after EXP. The expiry date refers to the last day of the month shown.
- Allow the AutoClicks pre filled pen(s) to reach room temperature. This will take 30 to 45 minutes. This will help to reduce discomfort when injecting.
 - Do not heat the medication - let it warm up on its own
 - Do not remove the cap until you are ready to inject.
- Wash your hands thoroughly.

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.

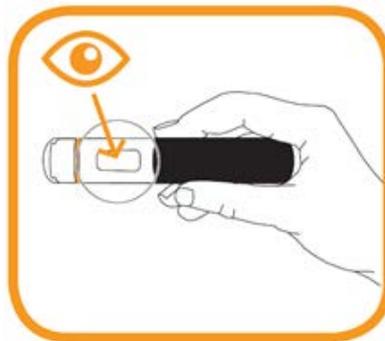
3. Injection

- AutoClicks pre-filled pen is designed to work accurately and safely. However, if any of the following steps go wrong and/or if you feel unsure about the injection process, contact your doctor or pharmacist.
- Do not shake the pre-filled pen.

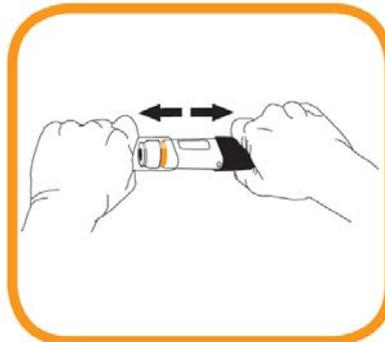


Check the medicine through the viewing window.

- Do not use the pre-filled pen if the solution is discoloured, cloudy or if you can see particles in it.
- You may see air bubbles - this is normal. Injecting the solution subcutaneously which contains air bubbles is harmless.



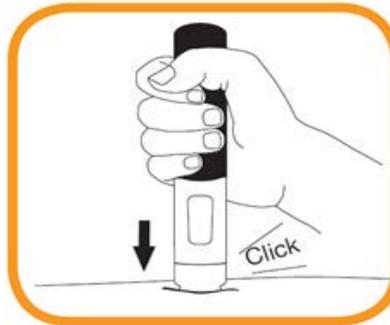
- Hold the pre-filled pen firmly with one hand around the black handle.
- Grasp the clear cap with the other hand and remove it.



- Inject within 5 minutes of removing the cap. **Do not replace the cap.**
- Although hidden from view the needle tip is now uncovered. Do not try to touch the needle as it could activate the pre-filled pen. Hold the pre-filled pen straight (at a 90° degree angle) against the skin, that previously has been cleaned (the “injection site”).



- Press the pre-filled pen firmly against the skin. The injection begins when a first “click” is heard and the orange band at the bottom of the pre-filled pen disappears.



- Continue to hold the pre-filled pen in place firmly against the skin until a second “click” is heard and the viewing window turns orange. This can take up to 15 seconds. At this time, the injection will be complete. If the viewing window turns orange and you hear a second click this means the injection has been completed. If you feel unsure about the injection process, please contact your doctor or pharmacist. Do not try to repeat the injection process without speaking to your doctor or your pharmacist.



- The needle will automatically move back into the empty pen. Do not try to touch the needle.
- You can now remove the used pen by pulling the pen straight up carefully from the skin.
- 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. After Use

- Do not re-use the pen. There is no need to replace the cap.

- After injection, immediately throw away the used pen(s) in a special container as instructed by your doctor, nurse or pharmacist.



- Keep the container out of the sight and reach of children.
- If you need to have a second injection as prescribed by your doctor repeat the injection process starting at Step 2.

Package leaflet: Information for the user

Cimzia 200 mg solution for injection in dose-dispenser cartridge certolizumab pegol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, please ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to you doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cimzia is and what it is used for
2. What you need to know before you use Cimzia
3. How to use Cimzia
4. Possible side effects
5. How to store Cimzia
6. Contents of the pack and other 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, axial spondyloarthritis and psoriatic arthritis. Medicines that bind to TNF α are also called TNF blockers.

Cimzia is used in adults for the following inflammatory diseases:

- **rheumatoid arthritis**
- **axial spondyloarthritis** (including ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis)
- **psoriatic arthritis**

Rheumatoid arthritis

Cimzia is used to treat rheumatoid arthritis. Rheumatoid arthritis is an inflammatory disease of the joints. If you have moderate to severe active rheumatoid arthritis, you may first be given other medicines usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to treat your rheumatoid arthritis. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Cimzia in combination with methotrexate can also be used to treat severe, active and progressive rheumatoid arthritis without previous use of methotrexate or other medicines treatment.

Cimzia, which you will take in combination with methotrexate, is used to:

- reduce the signs and symptoms of your disease,
- slow down the damage to the cartilage and bone of the joints caused by the disease,
- improve your physical function and performance of daily tasks.

Ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis

Cimzia is used to treat severe active ankylosing spondylitis and axial spondyloarthritis without radiographic evidence of ankylosing spondylitis (sometimes referred to as non-radiographic axial spondyloarthritis). These diseases are inflammatory diseases of the spine.

If you have ankylosing spondylitis or non-radiographic axial spondyloarthritis you will first be given other medicines. If you do not respond well enough to these medicines, you will be given Cimzia to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

Psoriatic arthritis

Cimzia is used to treat active psoriatic arthritis. Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis. If you have active psoriatic arthritis you will first be given other medicines, usually methotrexate. If you do not respond well enough to these medicines, you will be given Cimzia in combination with methotrexate to:

- reduce the signs and symptoms of your disease,
- improve your physical function and performance of daily tasks.

If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

2. What you need to know before you use Cimzia

Do NOT use Cimzia:

- If you are **ALLERGIC** (hypersensitive) to certolizumab pegol or any of the other ingredients of this medicine (listed in section 6)
- 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.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using 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**. Some of these reactions could occur after the first administration of Cimzia.

Infections

- If you have had **RECURRENT or OPPORTUNISTIC 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. In rare occasions tuberculosis can develop during therapy even if you have received preventive treatment for tuberculosis. 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.
- 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 and adolescents”).

Other disorders

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

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 and adolescents

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

Other medicines and Cimzia

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).

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

There is limited experience with Cimzia in pregnant women.

Cimzia should only be used during pregnancy if clearly needed. If you are a woman of childbearing potential discuss with your doctor regarding use of adequate contraception while using Cimzia. For women planning pregnancy, contraception may be considered for 5 months after the last Cimzia dose.

If you received Cimzia during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Cimzia use before the baby receives any vaccine (for more information see section on vaccinations).

Cimzia can be used during breastfeeding.

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.

Cimzia contains sodium acetate and sodium chloride

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 this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Rheumatoid arthritis

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 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. Methotrexate is continued while using Cimzia. If your doctor determines that methotrexate is inappropriate, Cimzia can be given alone.

Axial spondyloarthritis

The **starting dose** for adults with axial spondyloarthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks (from week 6) or 400 mg every 4 weeks (from week 8) as instructed by your physician.

Psoriatic arthritis

The **starting dose** for adults with psoriatic arthritis is 400 mg given at **weeks 0, 2 and 4**. This is followed by a **maintenance dose** of 200 mg every 2 weeks. If you respond to the medicine, your doctor may prescribe an **alternative maintenance** dosing of 400 mg every 4 weeks. 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, abbreviation: SC). It is usually injected into the thigh or tummy.

Instructions for preparing and giving an injection of Cimzia

Cimzia solution for injection in a dose-dispenser cartridge (also referred to as “medication”) is intended for single-use in conjunction with the electromechanical injection device called ava. After suitable training, your doctor may allow you to inject Cimzia yourself. Please read the instructions at the end of this leaflet on how to inject Cimzia and in the user manual provided with the injection device ava. Please follow these carefully.

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 yourself as soon as you remember and contact your doctor for information. Then inject the following dose as 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, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine 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)
- serious skin rashes. These can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes and can be preceded by fever and flu-like symptoms. (Stevens-Johnson syndrome)

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:

Common (may affect up to 1 in 10 people):

- 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
- nausea

Uncommon (may affect up to 1 in 100 people):

- allergic conditions including allergic rhinitis and allergic reactions to the medicine (including anaphylactic shock)
- antibody directed against normal tissue
- blood and lymphatic system cancers like lymphoma and leukaemia
- solid organ cancers
- skin cancers, pre-cancerous skin lesions
- 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
- ringing in the ears
- 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, inflammation of the skin (such as eczema), 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
- some blood parameters increased (blood alkaline phosphatase increased)
- prolonged coagulation (clotting) test times

Rare (may affect up to 1 in 1,000 people):

- gastrointestinal cancer, melanoma
- lung inflammation (interstitial lung disease, pneumonitis)
- stroke, blockage in blood vessels (arteriosclerosis), 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
- pericardial inflammation
- cardiac arrhythmia
- enlarged spleen
- increase of red cell mass
- white blood cell morphology abnormal
- formation of stones in the gall bladder
- kidney problems (including nephritis)
- 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)
- increased iron levels in the body
- increased blood levels of uric acid
- suicide attempt, mental impairment, delirium
- inflammation of the nerves for hearing, seeing, or of the face, impaired coordination or balance
- 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
- worsening of a condition called dermatomyositis (seen as a skin rash accompanying muscle weakness)
- Stevens-Johnson syndrome (a serious skin condition which early symptoms include malaise, fever, headache and rash)
- inflammatory skin rash (erythema multiforme)

Not known (frequency cannot be estimated from the available data):

- multiple sclerosis*

- Guillain Barré syndrome*
- Merkel cell carcinoma (a type of skin cancer)*

*These events have been related to this class of medicines but the incidence with Cimzia is not known.

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).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cimzia

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack and dose-dispenser cartridge after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Keep the dose-dispenser cartridge in the outer carton in order to protect from light.

Do not use this medicine if the solution is discoloured, cloudy or if you can see particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cimzia contains

- The active substance is certolizumab pegol. Each dose-dispenser cartridge contains 200 mg of certolizumab pegol in one ml.
- The other ingredients are: sodium acetate, sodium chloride and water for injections (see “Cimzia contains sodium acetate and sodium chloride” in section 2).

What Cimzia looks like and contents of the pack

Cimzia is provided as a solution for injection (injection) in a ready to use dose-dispenser cartridge. The dose-dispenser cartridge is to be used with the electromechanical injection device ava. The device is provided separately. The solution is clear to opalescent, colourless to yellow.

One Cimzia pack contains:

- two dose-dispenser cartridges of solution, and
- two alcohol wipes (for cleansing the areas chosen for injection).

Packs of 2 dose-dispenser cartridges and 2 alcohol wipes, a multipack containing 6 (3 packs of 2) dose-dispenser cartridges and 6 (3 packs of 2) alcohol wipes, and a multipack containing 10 (5 packs of 2) dose-dispenser cartridges and 10 (5 packs of 2) alcohol wipes are available.

Not all pack sizes may be marketed.

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Manufacturer

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

INSTRUCTIONS FOR USE FOR THE CIMZIA INJECTION BY MEANS OF A DOSE-DISPENSER CARTRIDGE

Important information

Read the instructions below carefully – this explains how to inject Cimzia by means of a dose-dispenser cartridge. The dose-dispenser cartridge is also referred to as “medication”.

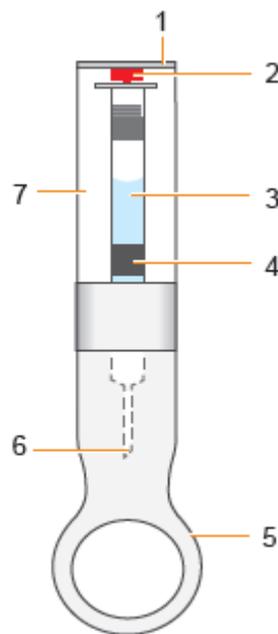
- The medication is to be used with the electromechanical injection device called “ava” which is provided separately.
- **You must also carefully read the full instructions in the ava User Manual.**

You can inject yourself or the injection can be given by someone else (caregiver).

If your doctor says you can inject yourself, you need to be fully trained first.

- You will be instructed by your doctor or healthcare giver how to inject the medicine.
- If something is not clear – please ask your doctor or pharmacist.

Medication: dose-dispenser cartridge



1. End cap
2. Medication level indicator
3. Syringe
4. Medication information chip
5. Needle cap
6. Needle (inside cap)
7. Medication body

Injection device: ava



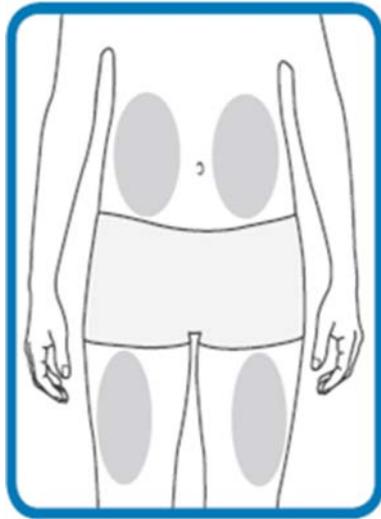
1.  On/Off Button
2.  Start/Pause button
3. Cartridge/Injection port
4. Skin sensor (the skin sensor detects when the injection port is fully in contact with your skin).
5. Scroll wheel (to adjust the speed of injection)
6. Information screen
7. Micro-USB Port

1. Setting up

- Remove the Cimzia carton from the refrigerator.
 - If the seal(s) is missing or broken – do not use and contact your pharmacist.
- Remove the following items from the Cimzia pack and set them up on a clean flat surface:
 - One or two medication cartridge(s), depending on your prescribed dose
 - One or two alcohol wipe(s)
- Look at the expiry date on the medication and pack. Do not use Cimzia after the expiry date which is stated on the pack and medication after EXP. The expiry date refers to the last day of the month shown.
- Allow the medication to reach room temperature. This will take from 30 to 45 minutes. This will help reduce discomfort when injecting.
 - Do not heat the medication - let it warm up on its own.
 - Use a clean dry cloth to wipe off any condensation on the outside of the cartridge.
- Do not remove the needle cap until ava instructs you to do so.
- Wash your hands thoroughly.

2. Choosing and preparing an injection site

- Choose a site on your thighs or tummy.



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

3. Injection

- If you feel unsure about the injection process, contact your doctor or pharmacist.
- Do not shake the medication.
- Do not use the medication if it has been dropped after taking it out of the pack.
- Turn on ava:
 - Press the  (On/Off button) for 1 second, or until the screen lights up and you hear sound
 - “Hello” is displayed for 2 seconds - this means ava is switched on.
- ava then shows:
 - Your current dose and how often you need to inject it,
 - This is then followed by the message, “Inspect and then insert medication”.



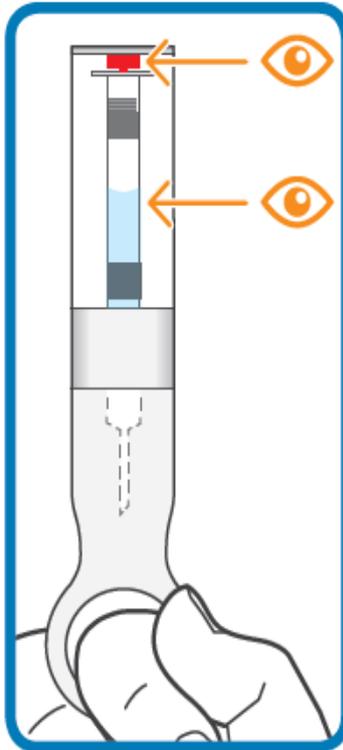
Check the medicine through the medication body.

- Do not use if the solution is discoloured, cloudy or there are particles in it.
- You may see air bubbles - this is normal. Injecting a solution subcutaneously which contains air bubbles is harmless.

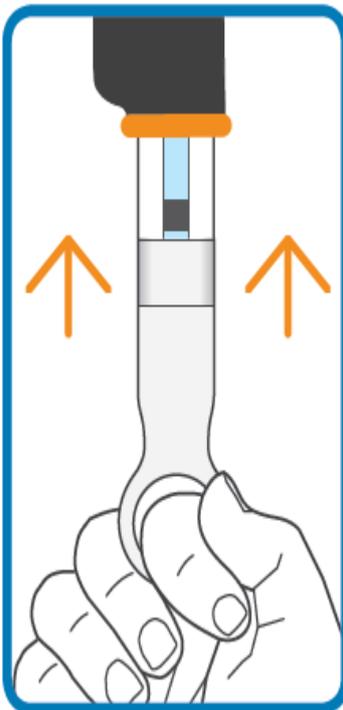


Check that the red “medication level indicator” is at the top of the cartridge.

- The medication contains 1ml of Cimzia and is not completely full - this is normal.
- Do not remove the needle cap from the medication yet.

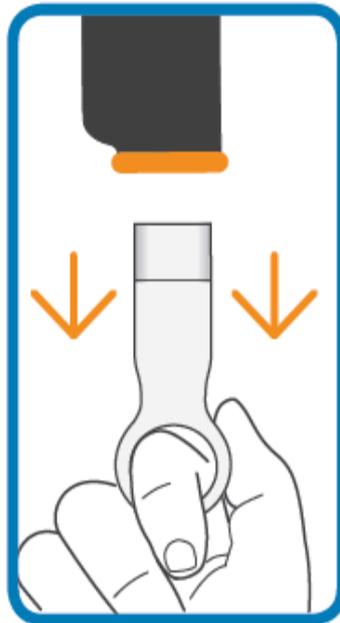


- Firmly push the flat end cap into the medication/injection port at the bottom of ava – push until you hear a click.
 - Do not twist the dose-dispenser cartridge - it is a special shape so that it fits correctly.



- Let go of the needle cap – this allows ava to check if the medication is usable. Do not remove the needle cap.
 - “Medication accepted” is shown if it is correct.
 - After a short pause, ava will automatically pull the cartridge in further.
- The current injection speed (medication flow rate) is shown.
 - You can change this speed using the “scroll wheel” on the side of your ava.
 - You can choose “slowest”, “slow”, “fast” or “fastest” - this controls how fast the medicine will be injected and should be selected (and adjusted) as per your personal comfort preference. Your doctor can provide advice.

- “Remove and save needle cap” is shown.
 - Only remove the needle cap when you are ready to inject.
- When ready, remove the needle cap by pulling it firmly downwards.
 - Once the needle cap has been removed, you must give the injection within 5 minutes. There is no need to rush your injection - 5 minutes gives you enough time. The time left is shown on screen.
 - **Keep the needle cap** - you will need it to remove the used medication from ava later.



- Find a comfortable position and sit down for your injection.
 - Try to relax as this will make the injection more comfortable.
- Place the orange skin sensor against the injection site where you are going to inject.
 - Position ava at a right angle on your skin with the screen facing you. This will make sure you are giving the injection correctly.
 - Position ava as shown so that you can comfortably reach the  (Start/Pause button) without moving ava.

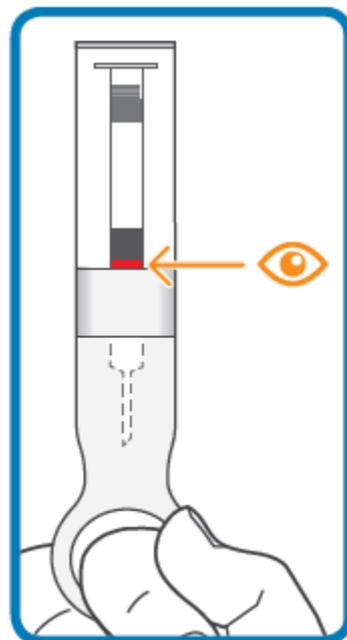


- Once ava is placed firmly against your skin “When ready press > once” is shown.
- Press the  (Start/Pause button).
 - As the injection is being given, keep holding ava firmly against your skin.
 - Avoid removing ava from the skin during the injection to ensure that you receive the full dose.
 - If ava is accidentally removed from your skin during the injection, the injection will automatically stop and the needle will go back into ava. To complete your injection:
 - Repeat Step 2 (Choosing and preparing an injection site), using a different injection site
 - Press ava firmly against the skin to begin the injection again, then
 - Press the  (Start/Pause button).

- If you feel unsure about the injection process, please contact your doctor or pharmacist. Do not try to repeat the injection process without speaking to your doctor or your pharmacist.
- When the injection is complete, a message is shown on ava's screen saying "Injection complete. Please remove from skin" - you can then remove ava from you skin.



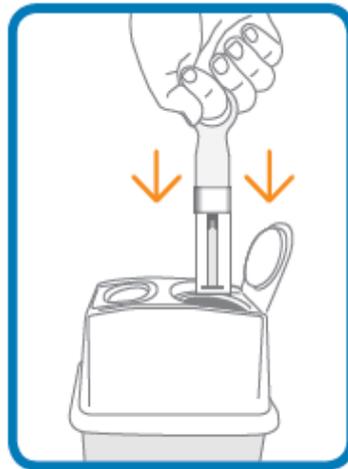
- Use a piece of gauze, apply pressure over the injection site for a few seconds:
 - Do not rub the injection site.
 - You may cover the injection site with a small adhesive bandage, if necessary.
- The messages “Needle uncapped! Handle with care!” and “Please replace needle cap” are shown until the needle cap is put back on.
- Replace the needle cap.
- Let go of the needle cap so that ava can push out the used medication.
- When “Remove and discard used medication” is shown, pull out the medication using the needle cap.
-  Check the red medication level indicator is at the bottom of the cartridge - this shows you have had all of your injection. If the indicator is not at the bottom, contact your pharmacist.



4. After Use

- Do not re-use the cartridge
- After injection, immediately throw away the used cartridge(s) in a special container as instructed by your doctor, nurse or pharmacist.
- Keep the container out of the sight and reach of children.
- If you need to have a second injection as prescribed by your doctor:

- The message “You have 1 injection left” will be shown on screen.
- Repeat the injection process starting at Step 2.



- Store ava in the storage case after use.