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 (TNFα) 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.

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 methotrexate, has been inadequate.

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

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

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.

Crohn's Disease
Cimzia is indicated for reducing signs and symptoms of Crohn's disease and maintaining clinical

response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

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.

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, 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. 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.

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.

Crohn's Disease
After the starting dose, in patients who obtain a clinical response, the recommended maintenance dose is 400 mg every four weeks.

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.

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. 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. Similarly, patients with Crohn's disease that require chronic exposure to immunosuppressant therapies may be at higher risk than the general population for the development of lymphoma, even in the absence of TNF antagonist therapy.

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 ≤ 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 pancytopaenia, including aplastic anaemia, have been rare with TNF-antagonists. Adverse reactions of the haematologic system, including medically significant cytopaenia (e.g. leukopaenia, pancytopaenia, thrombocytopaenia) 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.

Latex-sensitivity
The needle shield inside the removable cap of the CIMZIA pre-filled syringe contains 7% of a derivative of natural rubber latex (see section 6.5). The needle shield does not come into direct contact with the patient or injection administrator. Nevertheless, a potential risk of hypersensitivity reactions cannot be completely excluded in latex-sensitive individuals.

Immunosuppression
Since tumour necrosis factor (TNF) mediates inflammation and modulates cellular immune responses, the possibility exists for TNF-antagonists, including Cimzia, to cause immunosupression, 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 TNFα 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 TNFα, 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 µg/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.

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 (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1000 to < 1/100); Rare (≥ 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

System Organ Class	Frequency	Adverse reactions
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**, lichenoid reactions
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

System Organ Class	Frequency	Adverse reactions
	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.

Crohn's disease

The proportion of patients who discontinued treatment due to adverse reactions in the controlled clinical studies was 8% for Cimzia and 7% for placebo. The most common adverse reactions leading to the discontinuation of Cimzia (for at least 2 patients and with a higher incidence than placebo) were abdominal pain (0.4% Cimzia, 0.2% placebo), diarrhea (0.4% Cimzia, 0% placebo), and intestinal obstruction (0.4% Cimzia, 0% placebo).

The data described below reflect exposure to Cimzia at 400 mg subcutaneous dosing in studies of patients with Crohn's disease. In the safety population in controlled studies, a total of 620 patients with Crohn's disease received Cimzia at a dose of 400 mg, and 614 subjects received placebo (including subjects randomized to placebo in Study CD2 following open label dosing of Cimzia at Weeks 0, 2, 4). In controlled and uncontrolled studies, 1,564 patients received Cimzia at some dose level, of whom 1,350 patients received 400 mg Cimzia. Approximately 55% of subjects were female, 45% were male, and 94% were Caucasian. The majority of patients in the active group were between the ages of 18 and 64.

During controlled clinical studies, the proportion of patients with serious adverse reactions was 10% for Cimzia and 9% for placebo. The most common adverse reactions (occurring in ≥ 5% of Cimzia-treated patients, and with a higher incidence compared to placebo) in controlled clinical studies with Cimzia were upper respiratory infections (e.g. nasopharyngitis, laryngitis, viral infection) in 20% of Cimzia-treated patients and 13% of placebo-treated patients, urinary tract infections (e.g. bladder infection, bacteriuria, cystitis) in 7% of Cimzia-treated patients and in 6% of placebo-treated patients, and arthralgia (6% Cimzia, 4% placebo).

The most commonly occurring adverse reactions in controlled trials of Crohn's disease were described above. Other serious or significant adverse reactions reported in controlled and uncontrolled studies in Crohn's disease and other diseases, occurring in patients receiving Cimzia at doses of 400 mg or other doses include:

Blood and lymphatic system disorders: Anemia, leukopenia, lymphadenopathy, pancytopenia, and thrombophilia.

Cardiac disorders: Angina pectoris, arrhythmias, atrial fibrillation, cardiac failure, hypertensive heart disease, myocardial infarction, myocardial ischemia, pericardial effusion, pericarditis, stroke and transient ischemic attack.

Eye disorders: Optic neuritis, retinal hemorrhage, and uveitis.

General disorders and administration site conditions: Bleeding and injection site reactions.

Hepatobiliary disorders: Elevated liver enzymes and hepatitis.

Immune system disorders: Alopecia totalis.

Psychiatric disorders: Anxiety, bipolar disorder, and suicide attempt.

Renal and urinary disorders: Nephrotic syndrome and renal failure.

Reproductive system and breast disorders: Menstrual disorder.

Skin and subcutaneous tissue disorders: Dermatitis, erythema nodosum, and urticaria.

Vascular disorders: Thrombophlebitis, vasculitis.

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).

The incidence of infections in controlled studies in Crohn's disease was 38% for Cimzia-treated patients and 30% for placebo-treated patients. The infections consisted primarily of upper respiratory infections (20% for Cimzia, 13% for placebo). The incidence of serious infections during the controlled clinical studies was 3% per patient-year for Cimzia-treated patients and 1% for placebo-treated patients. Serious infections observed included bacterial and viral infections, pneumonia, and pyelonephritis.

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.

During controlled and open-labeled portions of Cimzia studies of Crohn's disease and other diseases, malignancies (excluding non-melanoma skin cancer) were observed at a rate (95% confidence interval) of 0.5 (0.4, 0.7) per 100 patient-years among 4,650 Cimzia-treated patients versus a rate of 0.6 (0.1, 1.7) per 100 patient-years among 1,319 placebo-treated patients. The size of the control group and limited duration of the controlled portions of the studies precludes the ability to draw firm conclusions.

In controlled studies of Cimzia for Crohn's disease and other investigational uses, there was one case of lymphoma among 2,657 Cimzia-treated patients and one case of Hodgkin's lymphoma among 1,319 placebo-treated patients.

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.

In clinical studies in Crohn's disease, 4% of patients treated with Cimzia and 2% of patients treated

with placebo that had negative baseline ANA titers developed positive titers during the studies. One of the 1,564 Crohn's disease patients treated with Cimzia developed symptoms of a lupus-like syndrome.

Hypersensitivity Reactions
The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following Cimzia administration to patients: angioedema, dermatitis allergic, dizziness (postural), dyspnea, hot flush, hypotension, injection site reactions, malaise, pyrexia, rash, serum sickness, and (vasovagal) syncope (see section 4.4).

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

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 (TNFα) inhibitors, ATC code: L04AB05

Mechanism of action

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

Cimzia was shown to neutralise membrane associated and soluble human TNFα in a dose-dependent

manner. Incubation of monocytes with Cimzia resulted in a dose-dependent inhibition of lipopolysaccharide (LPS)-induced TNFα and IL1β 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.

Biological activities ascribed to TNFα include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNFα stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNFα have been implicated in the pathology of Crohn's disease and rheumatoid arthritis. Certolizumab pegol binds to TNFα, inhibiting its role as a key mediator of inflammation. TNFα is strongly expressed in the bowel wall in areas involved by Crohn's disease and fecal concentrations of TNFα in patients with Crohn's disease have been shown to reflect clinical severity of the disease. After treatment with certolizumab pegol, patients with Crohn's disease demonstrated a decrease in the levels of C-reactive protein (CRP). Increased TNFα levels are found in the synovial fluid of rheumatoid arthritis patients and play an important role in the joint destruction that is a hallmark of this disease.

Clinical efficacy

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

Table 2 Clinical trial description

Study number	Patient numbers	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.

mTSS: modified Total Sharp Score

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

	Study RA-I Methotrexate combination (24 and 52 weeks)		**Study RA-II Methotrexate combination (24 weeks)**	
Response	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≤0.01, ** p<0.001

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

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

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

Radiographic response

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

Table 4 Changes over 12 months in RA-I

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

p-values were < 0.001 for both mTSS and erosion score and ≤0.01 for JSN score. An ANCOVA was fitted to the ranked change from baseline for each measure with region and treatment as factors and rank baseline as a covariate.

Of the 783 patients initially randomised to active treatment in RA-I, 508 completed 52 weeks of

placebo-controlled treatment and entered the open-label extension study. Sustained inhibition of progression of structural damage was demonstrated in a subset of 449 of these patients who completed at least 2 years of treatment with Cimzia (RA-I and open-label extension study) and had evaluable data at the 2-year timepoint.

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

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 ($p\leq0.001$ 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 signficant 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 5. 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 5 Key efficacy outcomes in AS001 clinical trial (percent of patients)

Parameters	Ankylosing spondylitis		Non-radiographic axial spondyloarthritits		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]	2%	20%**	6%	29%**	4%	24%**
Week 12	7%	28%**	10%	33%**	9%	30%**
Week 24						
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
*$p \leq 0.05$, 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.

Crohn's disease
The efficacy and safety of Cimzia were assessed in two double-blind, randomized, placebo-controlled studies in patients aged 18 years and older with moderately to severely active Crohn's disease, as defined by a Crohn's Disease Activity Index (CDAI[1]) of 220 to 450 points, inclusive. Cimzia was administered subcutaneously at a dose of 400 mg in both studies. Stable concomitant medications for Crohn's disease were permitted.

Study CD1
Study CD1 was a randomized placebo-controlled study in 662 patients with active Crohn's disease. Cimzia or placebo was administered at Weeks 0, 2, and 4 and then every four weeks to Week 24. Assessments were done at Weeks 6 and 26. Clinical response was defined as at least a 100-point reduction in CDAI score compared to baseline, and clinical remission was defined as an absolute CDAI score of 150 points or lower.
The results for Study CD1 are provided in Table 6. At Week 6, the proportion of clinical responders was statistically significantly greater for Cimzia-treated patients compared to controls. The difference in clinical remission rates was not statistically significant at Week 6. The difference in the proportion of patients who were in clinical response at both Weeks 6 and 26 was also statistically significant, demonstrating maintenance of clinical response.

Table 6 Study CD1 – Clinical Response and Remission, Overall Study Population

Timepoint	% Response or Remission (95% CI)	
	Placebo (N = 328)	**Cimzia 400 mg (N = 331)**
Week 6		
Clinical Response[#]	**27%** (22%, 32%)	**35%** (30%, 40%)*
Clinical Remission[#]	**17%** (13%, 22%)	**22%** (17%, 26%)
Week 26		
Clinical Response	**27%** (22%, 31%)	**37%** (32%, 42%)*
Clinical Remission	**18%** (14%, 22%)	**29%** (25%, 34%)*
Both Weeks 6 & 26		
Clinical Response	**16%** (12%, 20%)	**23%** (18%, 28%)*
Clinical Remission	**10%** (7%, 13%)	**14%** (11%, 18%)

* p-value < 0.05 logistic regression test
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Study CD2
Study CD2 was a randomized treatment-withdrawal study in patients with active Crohn's disease.

All patients who entered the study were dosed initially with Cimzia 400 mg at Weeks 0, 2, and 4 and then assessed for clinical response at Week 6 (as defined by at least a 100-point reduction in CDAI score). At Week 6, a group of 428 clinical responders was randomized to receive either Cimzia 400 mg or placebo, every four weeks starting at Week 8, as maintenance therapy through Week 24. Non-responders at Week 6 were withdrawn from the study. Final evaluation was based on the CDAI score at Week 26. Patients who withdrew or who received rescue therapy were considered not to be in clinical response. Three randomized responders received no study injections, and were excluded from the ITT analysis.
The results for clinical response and remission are shown in Table 7. At Week 26, a statistically significantly greater proportion of Week 6 responders were in clinical response and in clinical remission in the Cimzia-treated group compared to the group treated with placebo.

Table 7 Study CD2 – Clinical Response and Clinical Remission

	% Response or Remission (95% CI)	
	Cimzia 400 mg x3 + Placebo N = 210	**Cimzia 400 mg N = 215**
Week 26		
Clinical Response[#]	**36%** (30%, 43%)	**63%** (56%, 69%)*
Clinical Remission[#]	**29%** (22%, 35%)	**48%** (41%, 55%)*

* $p < 0.05$
[#] Clinical response is defined as decrease in CDAI of at least 100 points, and clinical remission is defined as CDAI ≤ 150 points

Baseline use of immunosuppressants or corticosteroids had no impact on the clinical response to Cimzia.

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%.

Crohn's disease
Patients with Crohn's disease were tested at multiple time points for antibodies to certolizumab pegol during Studies CD1 and CD2. In patients continuously exposed to Cimzia, the overall percentage of patients who were antibody positive to Cimzia on at least one occasion was 8%; approximately 6% were neutralizing *in vitro*. No apparent correlation of antibody development to adverse events or efficacy was observed. Patients treated with concomitant immunosuppressants had a lower rate of antibody development than patients not taking immunosuppressants at baseline (3% and 11%, respectively). The following adverse events were reported in Crohn's disease patients who were antibody-positive (N = 100) at an incidence at least 3% higher compared to antibody-negative patients (N = 1,242): abdominal pain, arthralgia, edema peripheral, erythema nodosum, injection site erythema, injection site pain, pain in extremity, and upper respiratory tract infection.
In two long-term (up to 7 years of exposure), open-label Crohn's disease studies, overall 23% (207/903) of patients developed antibodies against certolizumab pegol on at least one occasion. Of the 207 patients who were antibody positive, 152 (73%) had a persistent reduction of drug plasma concentration, which represents 17% (152/903) of the study population. The data from these two studies do not suggest an association between the development of antibodies and adverse events.

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 and Crohn's disease 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 metabolism and 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.

The clearance following IV administration to healthy subjects ranged from 9.21 mL/h to 14.38 mL/h.

The clearance following sc dosing was estimated 17 mL/h in the Crohn's disease population PK analysis with an inter-subject variability of 38% (CV) and an inter-occasion variability of 16%.
Similarly, the clearance following sc dosing was estimated as 21.0 mL/h in the RA population PK analysis, with an inter-subject variability of 30.8% (%CV) and inter-occasion variability 22.0%.
The route of elimination of certolizumab pegol has not been studied in human subjects. Studies in animals indicate that the major route of elimination of the PEG component is via urinary excretion.
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.

Race

A specific clinical study showed no difference in pharmacokinetics between Caucasian and Japanese subjects.

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 TNFα PEGylated Fab' (cTN3 PF) following sustained TNFα 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 chloride
Sodium acetate
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

The expiry date of the product is indicated on the packaging materials**.**
See also section 6.4 for shelf-life related to storage at room temperature up to a maximum of 25°C.

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.
The pre-filled syringes may be stored at room temperature (up to 25°C) for a single period of maximum 10 days with protection from light. At the end of this period the pre-filled syringes **must be used or discarded**.

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. The needle shield is styrene butadiene rubber which contains 7% epoxyprene, a derivative of natural rubber latex (see section 4.4).

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.

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 MANUFACTURER

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8 REGISTRATION HOLDER

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9 REGISTRATION NUMBER

152-53-33883

The content of this leaflet was approved by the Ministry of Health in 04/2018 and updated according to the guidelines of the Ministry of Health in 08/2019.