

1. NAME OF THE MEDICINAL PRODUCT

Simponi 50 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 0.5 ml pre-filled pen contains 50 mg of golimumab*.

* Human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology.

Excipient:

Each pre-filled pen contains 20.5 mg sorbitol per 50mg dose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection), SmartJect

The solution is clear to slightly opalescent, colourless to light yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis (RA)

Simponi, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.

Simponi has also been shown to improve physical function in this patient population.

Psoriatic arthritis (PsA)

Simponi, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate. Simponi has also been shown to improve physical function in this patient population.

Ankylosing spondylitis (AS)

Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

4.2 Posology and method of administration

Simponi treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis. Patients treated with Simponi should be given the Patient Alert Card.

Simponi should be injected subcutaneously. After proper training in subcutaneous injection technique, patients may self-inject with Simponi if their physician determines that this is appropriate, with medical follow-up as necessary. Patients should be instructed to inject the full amount of Simponi according to the comprehensive instructions for administration provided in the package leaflet. For administration instructions, see section 6.6.

Rheumatoid arthritis

Simponi 50 mg given once a month, on the same date each month.
Simponi should be given concomitantly with MTX.

Psoriatic arthritis

Simponi 50 mg given once a month, on the same date each month.

Ankylosing spondylitis

Simponi 50 mg given once a month, on the same date each month.

Available data suggest that clinical response is usually achieved within 12 to 14 weeks of treatment (after 3-4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

In patients weighing more than 100 kg who do not achieve an adequate clinical response after 3 or 4 doses, increasing the dose of golimumab to 100 mg once a month may be considered. Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

Elderly patients (≥ 65 years)

No dose adjustment is required in the elderly.

Paediatric patients (< 18 years)

Simponi is not recommended for use in children and adolescents below age 18 due to a lack of data on efficacy and safety.

Renal and hepatic insufficiency

Simponi has not been studied in these patient populations. No dose recommendations can be made.

Missed dose

If a patient forgets to inject Simponi on the planned date, the forgotten dose should be injected as soon as the patient remembers. Patients should be instructed not to inject a double dose to make up for the forgotten dose.

The next dose should be administered based on the following guidance:

- if the dose is less than 2 weeks late, the patient should inject his/her forgotten dose and stay on his/her original monthly schedule.
- if the dose is more than 2 weeks late, the patient should inject his/her forgotten dose and a new once-monthly schedule should be established from the date of this injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

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

Moderate or severe heart failure (NYHA class III/IV) (see section 4.4).

4.4 Special warnings and precautions for use

Infections

Patients must be monitored closely for infections including tuberculosis before, during and after treatment with Simponi. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. Further treatment with Simponi must not be given if a patient develops a serious infection or sepsis (see section 4.3).

Simponi should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of Simponi in patients with a chronic infection or a history of recurrent infection. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Patients taking TNF-blockers are more susceptible to serious infections.

Bacterial (including sepsis and pneumonia), mycobacterial (including TB), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving Simponi. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease, could predispose them to infections. Patients who develop a new infection while undergoing treatment with Simponi, should be monitored closely and undergo a complete diagnostic evaluation. Administration of Simponi should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled. For patients who have resided in or travelled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of Simponi treatment should be carefully considered before initiation of Simponi therapy.

Tuberculosis

There have been reports of tuberculosis in patients receiving Simponi. It should be noted that in the majority of these reports, tuberculosis was extrapulmonary presenting as either local or disseminated disease.

Before starting treatment with Simponi, all patients must be evaluated for both active and inactive ('latent') tuberculosis. This evaluation should include a detailed medical history with personal history of tuberculosis or possible previous contact with tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests, i.e. tuberculin skin or blood 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, Simponi therapy must not be initiated (see section 4.3).

If 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 Simponi therapy should be very carefully considered.

If inactive ('latent') tuberculosis is diagnosed, treatment for latent tuberculosis must be started with anti-tuberculosis therapy before the initiation of Simponi, and in accordance with local recommendations.

In patients who have several or significant risk factors for tuberculosis and have a negative test for latent tuberculosis, anti-tuberculosis therapy should be considered before the initiation of Simponi. Use of anti-tuberculosis therapy should also be considered before the initiation of Simponi in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

All patients should be informed to seek medical advice if signs/symptoms suggestive of tuberculosis (e.g. persistent cough, wasting/weight loss, low-grade fever) appear during or after Simponi treatment.

Hepatitis B virus reactivation

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

outcome. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Simponi therapy. Carriers of HBV who require treatment with Simponi 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, Simponi should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Malignancies and lymphoproliferative disorders

The potential role of TNF-blocking therapy in the development of malignancies is not known. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy.

Lymphoma

In the controlled portions of clinical trials of all the TNF-blocking agents including Simponi, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Simponi Phase IIb and Phase III clinical trials, the incidence of lymphoma in Simponi-treated patients was higher than expected in the general population. Patients with rheumatoid arthritis and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

Malignancies other than lymphoma

In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, and AS, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the Simponi and the control groups.

In an exploratory clinical trial evaluating the use of Simponi in patients with severe persistent asthma, more malignancies were reported in patients treated with Simponi compared with control patients (see section 4.8). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, 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 (CHF)

In a clinical trial with another TNF-antagonist worsening congestive heart failure and increased mortality due to CHF have been observed. Simponi has not been studied in patients with CHF. Simponi should be used with caution in patients with mild heart failure (NYHA class I/II). Patients should be closely monitored and Simponi must be discontinued in patients who develop new or worsening symptoms of heart failure (see section 4.3).

Neurological events

Use of TNF-blocking agents, including Simponi, has been associated in rare cases with new-onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of Simponi therapy.

Surgery

There is limited safety experience of Simponi treatment in patients who have undergone surgical procedures, including arthroplasty. The long half-life should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Simponi should be closely monitored for infections, and appropriate actions should be taken.

Immunosuppression

The possibility exists for TNF-blocking agents, including Simponi, to affect host defences against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses.

Autoimmune processes

The relative deficiency of TNF $_{\alpha}$ caused by anti-TNF therapy may result in the initiation of an autoimmune process. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Simponi and is positive for antibodies against double-stranded DNA, treatment with Simponi should be discontinued (see section 4.8:).

Haematologic reactions

There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. Cytopenias including pancytopenia, have been infrequently reported with Simponi in clinical trials. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of Simponi therapy should be considered in patients with confirmed significant haematologic abnormalities.

Concurrent administration of TNF-antagonists and anakinra

Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added clinical benefit. Because of the nature of the adverse events seen with this combination therapy, similar toxicities may also result from the combination of anakinra and other TNF-blocking agents. The combination of Simponi and anakinra is not recommended.

Concurrent administration of TNF-antagonists and abatacept

In clinical studies concurrent administration of TNF-antagonists and abatacept has been associated with an increased risk of infections including serious infections compared to TNF-antagonists alone, without increased clinical benefit. The combination of Simponi and abatacept is not recommended.

Vaccinations

Patients treated with Simponi may receive concurrent vaccinations, except for live vaccines (see section 4.5). No data are available on the response to vaccination, risk of infection or transmission of infection with the administration of live vaccines to patients receiving Simponi.

Allergic reactions

Serious allergic adverse reactions have not been reported with subcutaneous administration of Simponi during clinical trials. Non-serious allergic reactions associated with Simponi occurred in clinical trials, and included urticaria, bronchospasm and hypersensitivity. If an anaphylactic reaction or other serious allergic reactions occurs, administration of Simponi should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity

The needle cover on the syringe in the pre-filled pen is manufactured from dry natural rubber containing latex, and may cause allergic reactions in individuals sensitive to latex.

Special populations

Elderly patients (≥ 65 years)

In the Phase III studies in RA, PsA, and AS, no overall differences in Adverse events (AEs), Serious Adverse Events (SAEs), and serious infections in patients age 65 or older (N=155) who received Simponi were observed compared with younger patients. However, caution should be exercised when treating the elderly and particular attention paid with respect to occurrence of infections.

Renal and hepatic insufficiency

Specific studies of Simponi have not been conducted in patients with renal or hepatic impairment. Simponi should be used with caution in subjects with impaired hepatic function (see section 4.2).

Excipients

Simponi contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take Simponi.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with anakinra and abatacept

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

Live vaccines

Live vaccines should not be given concurrently with Simponi (see section 4.4).

Methotrexate

Although concomitant use of MTX results in higher steady-state trough concentrations of Simponi in patients with RA, PsA or AS, the data do not suggest the need for dose adjustment of either Simponi or MTX (see section 5.2).

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of golimumab in pregnant women. Due to its inhibition of TNF, golimumab administered during pregnancy could affect normal immune responses in the newborn. Studies in animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). The use of golimumab in pregnant women is not recommended; golimumab should be given to a pregnant woman only if clearly needed.

Women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least 6 months after the last golimumab treatment.

Lactation

It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Golimumab was shown to pass over to breast milk in monkeys, and because human immunoglobulins are excreted in milk, women must not breast feed during and for at least 6 months after golimumab treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Simponi may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of Simponi (see section 4.8).

4.8 Undesirable effects

Safety data from Phase IIb and Phase III clinical trials are available from 2578 golimumab-treated patients including 1600 with RA, 394 with PsA, 353 with AS, 231 with severe persistent asthma and 751 patients receiving placebo or active comparator.

Adverse drug reactions (ADRs) observed in clinical studies with golimumab are summarised in Table 1. Within the designated system organ classes, the adverse drug reactions are listed under headings of frequency and using the following convention: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1
Summary of ADRs in clinical studies

Infections and infestations	Very common: Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
	Common: Bacterial infections (such as cellulitis), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections,
	Uncommon: Septic shock, sepsis, tuberculosis, lower respiratory tract infection (such as pneumonia), opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), pyelonephritis, abscess, arthritis bacterial, bursitis infective
	Rare: Hepatitis B reactivation
Neoplasms, benign, malignant and unspecified	Uncommon: Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
	Rare: Lymphoma
Blood and lymphatic system disorders	Common: Anemia
	Uncommon: Leukopenia, thrombocytopenia,
	Rare: Pancytopenia
	Not known: Aplastic anemia*
Immune system disorders	Common: Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Endocrine disorders	Uncommon: Thyroid disorder (such as hypothyroidism, hyperthyroidism and goiter)
Metabolism and nutrition disorders	Uncommon: Blood glucose increased, lipids increased
Psychiatric disorders	Common: Depression, insomnia
Nervous system disorders	Common: Dizziness, paresthesia, headache
	Uncommon: Demyelinating disorders, balance disorders, dysguesia
Eye disorders	Uncommon: Visual disorders (such as blurred vision and decreased vision acuity), conjunctivitis, eye allergy (such as pruritis and irritation)
Cardiac disorders	Uncommon: Congestive heart failure (new onset or worsening), arrhythmia,

ischemic coronary artery disorders	
Vascular disorders	Common: Hypertension Uncommon: Thrombosis (such as deep venous and aortic), Raynaud's phenomenon, flushing
Respiratory, thoracic and mediastinal disorders	Uncommon: Asthma and related symptoms (such as wheezing and bronchial hyperactivity) Rare: Interstitial lung disease
Gastrointestinal disorders	Common: Constipation, dyspepsia, gastrointestinal and abdominal pain Uncommon: Gastrointestinal inflammatory disorders (such as gastritis and colitis), gastroesophageal reflux disease, stomatitis
Hepatobiliary disorders	Common: Alanine aminotransferase increased, aspartate aminotransferase increased Uncommon: Cholelithiasis, hepatic disorders
Skin and subcutaneous tissue disorders	Common: Alopecia, dermatitis, pruritus, rash Uncommon: Psoriasis (new onset and pustular), urticaria
Musculoskeletal and connective tissue disorders	Rare: Lupus-like syndrome
Renal and urinary disorders	Uncommon: Bladder disorders Rare: Renal disorders
Reproductive system and breast disorders	Uncommon: Breast disorders, menstrual disorders
General disorders and administration site conditions	Common: Pyrexia, asthenia, injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia), impaired healing, chest discomfort
Injury, poisoning and procedural complications	Uncommon: Bone fractures
*: Observed with other TNF-blocking agents, but not observed in clinical studies with golimumab.	

Infections

Upper respiratory tract infection was the most common adverse reaction reported in the combined Phase III RA, PsA, and AS studies through Week 16, occurring in 7.2% of golimumab-treated patients (incidence per patient-year: 0.26; 95% CI: 0.22, 0.31) as compared with 5.8% of control patients (incidence per patient-year: 0.23; 95% CI: 0.17, 0.31). The incidence per patient year (95% confidence interval; CI) of upper respiratory tract infections through 1 year of follow up was 0.23 events (0.21, 0.25) for golimumab-treated patients and 0.25 events (0.20, 0.31) for control patients.

In controlled Phase III trials through Week 16 in RA, PsA, and AS, infections were observed in 28.3% of golimumab-treated patients (incidence per patient-year: 1.28; 95% CI: 1.18, 1.38) compared with 24.7% of control patients (incidence per patient-year: 1.17; 95% CI: 1.02, 1.33). The incidence per patient year (95% CI) of infections through 1 year of follow up was 1.32 events (1.27, 1.38) for golimumab-treated patients and 1.31 events (1.18, 1.44) for control patients.

In controlled Phase III trials through week 16 in RA, PsA, and AS, serious infections were observed in 1.4% of golimumab-treated patients (incidence per patient-year: 0.06; 95% CI: 0.04, 0.08) and 1.3% of control patients (incidence per patient-year: 0.04; 95% CI: 0.02, 0.08). Serious infections observed in golimumab-treated patients included tuberculosis, bacterial infections including sepsis and pneumonia, invasive fungal infections and other opportunistic infections. Some of these infections have been fatal. The incidence per patient year (95% CI) of serious infections through 1 year of follow up was 0.05 events (0.04, 0.06) for golimumab-treated patients and 0.06 events (0.04, 0.09) for control patients (see section 4.4).

Malignancies

Lymphoma

The incidence of lymphoma in Simponi treated patients with RA, PsA and AS during the controlled portions of phase IIb and III clinical trials and through 1 year of follow up was higher than expected in the general population. Lymphoma was diagnosed in 2 subjects (both in golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow up of 0.10 (0.01, 0.37) events for golimumab and 0.00 (0.00, 0.90) events for placebo. See section 4.4.

Malignancies other than lymphoma

In the controlled portions of the Simponi Phase IIb and Phase III clinical trials in RA, PsA, and AS, and through 1 year of follow up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the Simponi and the control groups.

Through 1 year of follow up, of the Phase IIb and Phase III studies in rheumatologic indications, nonmelanoma skin cancer was diagnosed in 19 subjects (5 in placebo, 6 in golimumab 50 mg and 8 in golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow up of 0.72 (0.39, 1.20) events for golimumab and 1.51 (0.49, 3.52) events for placebo.

Through 1 year of follow up, of the Phase IIb and Phase III studies in rheumatologic indications, malignancies besides nonmelanoma skin cancer and lymphoma were diagnosed in 12 subjects (2 in placebo, 6 in golimumab 50 mg and 4 in golimumab 100 mg treatment groups) with an incidence (95%CI) per 100 subject-years of follow up of 0.51 (0.24, 0.94) events for golimumab and 0.60 (0.07, 2.17) events for placebo. See section 4.4.

Cases reported in clinical studies in asthma

In an exploratory clinical study, patients with severe persistent asthma received a golimumab loading dose (150% of the assigned treatment dose) subcutaneously at Week 0 followed by golimumab 200 mg, golimumab 100 mg or golimumab 50 mg every 4 weeks subcutaneously through Week 52. Eight malignancies in the combined golimumab treatment group (n=230) and none in the placebo treatment group (n=79). Lymphoma was reported in 1 patient, non-melanoma skin cancer in 2 patients, and other malignancies in 5 patients. There was no specific clustering of any type of malignancy.

During the placebo-controlled portion of the study, the incidence (95% CI) of all malignancies per 100 subject-years of follow-up was 3.19 (1.38, 6.28) in the golimumab group. In this study, the incidence (95% CI) per 100 subject-years of follow-up in golimumab-treated subjects was 0.40 (0.01, 2.20) for lymphoma, 0.79 (0.10, 2.86) for non-melanoma skin cancers, and 1.99 (0.64, 4.63) for other malignancies. For placebo subjects, the incidence (95% CI) per 100 subject-years of follow-up of these malignancies was 0.00 (0.00, 2.94). The significance of this finding is unknown.

Liver enzyme elevations

In controlled Phase III trials through week 16, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of golimumab and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS study, more golimumab-treated patients (25.6%) than control patients (3.9 %) had mild ALT elevations. Through 1 year of follow-up the incidence of mild ALT elevations was similar in golimumab-treated and control patients in RA and PsA studies. In the AS population, the incidence of mild ALT elevations was higher in golimumab-treated patients than in control patients.

In the RA and AS studies through Week 16, ALT elevations $\geq 5 \times$ ULN were uncommon and seen in more golimumab-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. Through 1 year of follow-up, the incidence of ALT elevations $\geq 5 \times$ ULN was similar in both golimumab-treated and control patients in the Phase III RA, PsA and AS studies. In general these elevations were asymptomatic and the abnormalities decreased or resolved with either continuation or discontinuation of golimumab or modification of concomitant medications.

Within the Phase II and Phase III programme in RA, PsA and AS, one patient with pre-existing liver abnormalities and confounding medication treated with golimumab developed non-infectious fatal hepatitis with jaundice. The role of golimumab as a contributing or aggravation factor cannot be excluded.

Injection site reactions

In controlled Phase III trials through week 16 in RA, PsA and AS, 5.8% of golimumab-treated patients had injection site reactions compared with 2.2% in control patients. The presence of antibodies to golimumab may increase the risk of injection site reactions. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema. Injection site reactions generally did not necessitate discontinuation of the medicinal product.

In controlled phase IIb and III trials in RA, PsA, AS and severe persistent asthma, no patients treated with golimumab developed anaphylactic reactions.

Autoimmune antibodies

In Phase III trials in RA, PsA, and AS through 1 year of follow up, 4.0% of golimumab-treated patients and 2.6% of control patients were newly ANA-positive (at titers of 1:160 or greater). The frequency of anti-dsDNA antibodies at 1 year of follow up in patients anti-dsDNA negative at baseline was uncommon.

4.9 Overdose

Single doses up to 10 mg/kg intravenously have been administered in a clinical study without dose-limiting toxicity. In case of an overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tumour necrosis factor alpha (TNF- α) inhibitors, ATC code: L04AB06

Mechanism of action

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF- α , which prevents the binding of TNF- α to its receptors.

Pharmacodynamic effects

The binding of human TNF by golimumab was shown to neutralise TNF- α -induced cell-surface expression of the adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 by human endothelial cells. *In vitro*, TNF-induced secretion of interleukin (IL)-6, IL-8 and granulocyte-macrophage colony stimulating factor (GM-CSF) by human endothelial cells was also inhibited by golimumab.

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with Simponi resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and Vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNF- α were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial Simponi administration and were generally maintained through week 24.

Clinical efficacy

Rheumatoid arthritis

The efficacy of Simponi was demonstrated in two multi-centre, randomised, double-blind, placebo-controlled studies in over 900 patients ≥ 18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. Simponi or placebo were subcutaneously administered every 4 weeks. Placebo-controlled efficacy data were collected and analysed through week 24.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomised to receive placebo + MTX, Simponi 50 mg + MTX, Simponi 100 mg + MTX or Simponi 100 mg + placebo.

GO-AFTER evaluated 461 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomised to receive placebo, Simponi 50 mg, or Simponi 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

The (co-)primary endpoint in GO-FORWARD and GO-AFTER was the percentage of patients achieving an ACR 20 response at Week 14. The other co-primary endpoint in GO-FORWARD was the improvement from baseline in Health Assessment Questionnaire (HAQ) at Week 24. In addition to the primary endpoint(s), additional assessments of the impact of Simponi treatment on the signs and symptoms of arthritis, physical function and health-related quality of life were performed.

In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens with concomitant MTX.

Signs and symptoms

Key ACR results for the 50 mg dose are shown in table 2 and are described below. Responses were observed at the first assessment (Week 4) after the initial Simponi administration and were maintained through week 24.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving Simponi than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 2
Key efficacy outcomes from GO-FORWARD and GO-AFTER.

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg
N ^a	133	89	155	153
Responders, % of patients				
ACR 20				
Week 14	33%	55%*	18%	35%*
Week 24	28%	60%*	17%	34%*
ACR 50				
Week 14	10%	35%*	7%	16% p=0.006
Week 24	14%	37%*	5%	18%*
ACR 70				
Week 14	4%	14% p=0.008	2%	11% p=0.002
Week 24	5%	20%*	3%	12% p=0.004
a	N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.			
*	p ≤ 0.001			

In GO-FORWARD and GO-AFTER, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified time point, at week 14 and at week 24 (p ≤ 0.001).

Physical function and health-related quality of life

Physical function and disability were assessed as a separate endpoint in GO-FORWARD and GO-AFTER using the disability index of the HAQ. In these studies, Simponi demonstrated clinically meaningful and statistically significant improvement in HAQ from baseline versus control at week 24.

In GO-FORWARD clinically meaningful and statistically significant improvements were demonstrated in health-related quality of life as measured by the physical component score of the SF-36 in patients treated with Simponi versus placebo. In GO-FORWARD and GO-AFTER, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Psoriatic arthritis

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months and had at least mild psoriatic disease. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). Previous treatment with an anti-TNF agent was not allowed. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg, or Simponi 100 mg.

Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

Key results for the 50 mg dose are shown in table 3 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens.

Table 3
Key efficacy outcomes from GO-REVEAL

	Placebo	Simponi 50 mg*
N ^a	113	146
Responders, % of patients		
ACR 20		
Week 14	9 %	51 %
Week 24	12 %	52 %
ACR 50		
Week 14	2 %	30 %
Week 24	4 %	32 %
ACR 70		
Week 14	1 %	12 %
Week 24	1 %	19 %
PASI^b 75^c		
Week 14	3 %	40 %
Week 24	1 %	56 %
* p < 0.05 for all comparisons; p-value calculations are based on comparisons of median values for continuous variables		
a N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint		
b Psoriasis Area and Severity Index		
c Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Simponi 50mg group.		

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 (p < 0.05). Improvements in key measures of disease activity were observed at the first assessment (Week 4) after the initial Simponi administration and were maintained through Week 24. Similar ACR 20 responses at week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes was too small to allow meaningful assessment. Responses observed in the Simponi treated groups were similar in patients receiving and not receiving concomitant MTX.

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 Simponi-treated patients.

Simponi treatment resulted in significant improvement in physical function as assessed by HAQ, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36.

Ankylosing spondylitis

The safety and efficacy of Simponi were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and a VAS for total back pain of ≥4, on a scale of 0 to 10 cm). Patients enrolled in this study had active disease despite current or previous NSAID or DMARD therapy and had not previously been treated with anti-TNF therapy. Simponi or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Simponi 50 mg and Simponi 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ and/or HCQ). The primary endpoint was the percentage

of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at Week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

Key results for the 50 mg dose are shown in table 4 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the Simponi 50 mg and 100 mg dosing regimens.

Table 4
Key efficacy outcomes from GO-RAISE.

	Placebo	Simponi 50 mg*
N ^a	78	138
Responders, % of patients		
ASAS 20		
Week 14	22%	59%
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%
ASAS 5/6		
Week 14	8%	50%
Week 24	13%	49%
* p ≤ 0.001 for all comparisons		
^a N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint		

Statistically significant responses in BASDAI 50, 70 and 90 (p ≤ 0.017) were also seen at weeks 14 and 24. Improvements in key measures of disease activity were observed at the first assessment (Week 4) after the initial Simponi administration and were maintained through week 24. Consistent efficacy was seen in patients regardless of use of DMARDs (MTX, sulfasalazine and/or hydroxychloroquine), HLA-B27 antigen status or baseline CRP levels as assessed by ASAS 20 responses at week 14.

Simponi treatment resulted in significant improvements in physical function as assessed by changes from baseline in BASFI at Weeks 14 and 24. Health-related quality of life as measured by the physical component score of the SF-36 was also improved significantly at weeks 14 and 24.

Immunogenicity:

Across the Phase 3 RA, PsA and AS studies through week 24, antibodies to golimumab, nearly all neutralising *in vitro*, were detected in 4.3% (57/1322) of golimumab treated patients. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without MTX (approximately 2% [14/719] versus 7% [43/603], respectively).

In combined data from the PsA study and 2 RA studies through week 52, antibodies to golimumab were detected in 5.2% (67/1294) of golimumab treated patients. In patients not given concomitant MTX, the incidence was 8.9% (37/417), compared to 3.4% (30/877) when golimumab was used with concomitant MTX.

The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.4). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

5.2 Pharmacokinetic properties

Following a single subcutaneous administration of golimumab to healthy subjects or patients with RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A subcutaneous injection of 50 mg golimumab to healthy subjects produced a mean \pm standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 $\mu\text{g/ml}$.

Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose. The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 ml/day/kg, and mean volume of distribution was 115 ± 19 ml/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA or AS.

Following a single subcutaneous injection of 100 mg, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since golimumab exhibited approximately dose proportional PK following a subcutaneous administration, the absolute bioavailability of the golimumab 50 mg dose is expected to be similar.

When 50 mg golimumab was administered subcutaneously to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by Week 12. With concomitant use of MTX, treatment with 50 mg golimumab subcutaneous every 4 weeks resulted in a mean (\pm standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 $\mu\text{g/ml}$ in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 $\mu\text{g/ml}$ in patients with active PsA and approximately 0.8 ± 0.4 $\mu\text{g/ml}$ in patients with AS.

Patients with RA, PsA or AS who did not receive concomitant MTX had approximately 30% lower steady-state trough concentrations of golimumab than those who received golimumab with MTX. Population pharmacokinetic analysis in patients with RA also indicated that concomitant use of MTX could reduce the apparent clearance of golimumab by 17.1%. However, concomitant use of NSAIDs, oral corticosteroids or sulfasalazine was not indicated to influence the apparent clearance of golimumab.

Population pharmacokinetic analyses showed there was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

Patients who developed anti-golimumab antibodies generally had low trough steady-state serum concentrations of golimumab (see section 5.1).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction.

No mutagenicity studies, animal fertility studies nor long-term carcinogenic studies have been conducted with golimumab.

In a fertility and general reproductive function study in mouse, using an analogous antibody that selectively inhibits the functional activity of mouse $\text{TNF}\alpha$, the number of pregnant mice was reduced. It is not known whether this finding was due to effects on the males and/or the females. In a developmental toxicity study conducted in mice following administration of the same analogous antibody, and in cynomolgus monkeys using golimumab, there was no indication of maternal toxicity, embryotoxicity or teratogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol(E420)
L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
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

1 year.

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 it from light.

6.5 Nature and contents of container

0.5 ml solution in a pre-filled syringe (1.0 ml Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex) in a pre-filled pen. Simponi is available in packs containing 1 pre-filled pen and multipacks containing 3 (3 packs of 1) pre-filled pens.
Not all pack sizes may be marketed.

Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use prefilled pen called SmartJect. Each Simponi pack is provided with instructions for use that fully describes the use of the pen. After removing the prefilled pen from the refrigerator this should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The pen should not be shaken.

The solution is clear to slightly opalescent, colourless to light yellow and may contain a few small translucent or white particles of protein. This appearance is not unusual for solutions containing protein.

Comprehensive instructions for the preparation and administration of Simponi in a prefilled pen are given in the package leaflet.

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

7. MARKETING AUTHORISATION HOLDER

Centocor B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/001 1 pre-filled pen
EU/1/09/546/002 3 pre-filled pens

9. DATE OF FIRST AUTHORISATION

01/10/ 2009

10. DATE OF REVISION OF THE TEXT

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