ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml pre-filled pen contains 100 mg of golimumab*.

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

Excipient with known effect:
Each pre-filled pen contains 41 mg sorbitol per 100 mg dose.

For the 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 adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

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

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 been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adults 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.

Posology

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.

Patients with bodyweight greater than 100 kg
In patients with RA, PsA or AS with a body weight of 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, taking into account the increased risk of certain serious adverse drug reactions with the 100 mg dose compared with the 50 mg dose (see section 4.8). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

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.

Elderly patients (≥ 65 years)
No dose adjustment is required in the elderly.

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

Paediatric population
The safety and efficacy of Simponi in patients aged less than 18 have not yet been established. No data are available.

Method of administration
For subcutaneous use. 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.

4.3 Contraindications

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

Cases of active tuberculosis have occurred in patients treated with Simponi during and after treatment for latent tuberculosis. Patients receiving Simponi should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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 should be tested for HBV infection before initiating treatment with Simponi. 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 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. Based on 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. 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.

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

Lymphoma and leukaemia
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. 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 risk estimation.

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 an increased risk of malignancy due to heavy smoking.

Skin cancers
Melanoma has been reported in patients treated with TNF-blocking agents, including Simponi. Merkel cell carcinoma has been reported in patients treated with other TNF-blocking agents (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including Simponi. 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 with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. 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. Discontinuation of Simponi should be considered if these disorders develop (see section 4.8).

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_{α} 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 pancytopaenia, leucopaenia, neutropaenia, aplastic anaemia, and thrombocytopaenia in patients receiving TNF-blockers. Cytopaenias including pancytopaenia 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 and neutropenia 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.

Concurrent administration with other biological therapeutics
There is insufficient information regarding the concomitant use of Simponi with other biological therapeutics used to treat the same conditions as Simponi. The concomitant use of Simponi with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations
Patients treated with Simponi may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). 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
In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following Simponi administration. Some of these reactions occurred after the first administration of Simponi. If an anaphylactic reaction or other serious allergic reactions occur, administration of Simponi should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity
The needle cover on 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 impairment
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.

Potential for Medication errors

Simponi is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics
The combination of Simponi with other biological therapeutics used to treat the same conditions as Simponi, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines
Live vaccines should not be given concurrently with Simponi (see sections 4.4 and 4.6).

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 Fertility, pregnancy and lactation

Women of childbearing potential
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.

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.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab in utero is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding
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.

Fertility
No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

Summary of the safety profile

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in the controlled Phase III RA, PsA, and AS studies through week 16, occurring in 7.2% of golimumab-treated patients as compared with 5.8% of control patients. The most serious ADRs that have been reported for Simponi include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome) and haematologic reactions (see section 4.4).

Tabulated list of adverse reactions

ADRs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed 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 (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data).

Table 1
Tabulated list of ADRs

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, bacterial arthritis, infective bursitis
Rare:	Hepatitis B reactivation
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma
Not known:	Merkel cell carcinoma*
Blood and lymphatic system disorders	
Common:	Anaemia
Uncommon:	Leucopaenia, thrombocytopaenia
Rare:	Pancytopaenia
Not known:	Aplastic anaemia *
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis
Endocrine disorders	
Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders	
Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders	
Common:	Depression, insomnia
Nervous system disorders	

	Common: Dizziness, paraesthesia, headache Uncommon: Demyelinating disorders (central and peripheral), balance disorders, dysguesia
Eye disorders	
	Uncommon: Visual disorders (such as blurred vision and decreased visual 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, nausea Uncommon: Gastrointestinal inflammatory disorders (such as gastritis and colitis), gastro-oesophageal 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 or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria, vasculitis (cutaneous) Rare: Skin exfoliation
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.

Description of selected adverse drug reactions

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 100 subject-years: 26.3; 95% CI: 22.1, 31.2) as compared with 5.8% of control patients (incidence per 100 subject-years: 22.9; 95% CI: 16.6, 30.7. In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per 100 subject-years of upper respiratory tract infections was 17.4 events; 95% CI: 16.4, 18.6 for golimumab treated 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 100 subject-years: 128.0; 95% CI: 118.3, 138.2) compared with 24.7% of control patients (incidence per 100 subject-years: 116.6; 95% CI: 101.8, 132.9). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per 100 subject-years of infections was 96.0 events; 95% CI: 93.5, 98.6 for golimumab treated patients.

In controlled Phase III trials through week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of golimumab-treated patients and 1.3% of control-treated patients. Through Week 16, the incidence of serious infections per 100 subject-years of follow-up was 7.4; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 3.3; 95% CI: 1.3, 6.9 for the golimumab 50 mg group and 4.2; 95% CI: 1.8 , 8.2 for the placebo group. 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. In the controlled and uncontrolled portions of the Phase II and Phase III trials in RA, PsA, and AS with a median follow-up of approximately 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mgcompared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 5.1; 95% CI: 4.4, 5.9, in patients receiving golimumab 100 mg and 3.0; 95% CI: 2.4, 3.8, in patients receiving golimumab 50 mg.

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 approximately 3 years of follow up was higher than expected in the general population. In the controlled and uncontrolled portions of these trials through a median follow-up of approximately 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 7 subjects (1 in the golimumab 50 mg treatment groups and 6 in the golimumab 100 mg treatment groups) with an incidence (95%, CI) per 100 subject-years of follow up of 0.04 (0.00, 0.24) and 0.18 (0.06, 0.38) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.84) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease. 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 approximately 3 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the Simponi and the control groups.

Through approximately 3 years of follow-up, of the Phase IIb and Phase III studies in rheumatologic indications, nonmelanoma skin cancer was diagnosed in 33 subjects (5 in placebo, 10 in golimumab 50 mg and 18 in golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow up of 0.49 (0.33, 0.71) for combined golimumab and 1.40 (0.46, 3.28) for placebo.

Through approximately 3 years of follow-up, of the Phase IIb and Phase III studies in rheumatologic indications, malignancies besides nonmelanoma skin cancer and lymphoma were diagnosed in 34 subjects (2 in placebo, 18 in golimumab 50 mg and 14 in golimumab 100 mg treatment groups)

with an incidence (95%CI) per 100 subject-years of follow-up of 0.56 (0.38, 0.79) for combined golimumab and 0.56 (0.07, 2.02) 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.

Neurological events
In the controlled and uncontrolled portions of the Phase II RA and the Phase III RA, PsA, and AS trials with a median follow-up of approximately 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. See section 4.4.

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 approximately 3 years 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 ≥ 5 x 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 approximately 3 years of follow-up, the incidence of ALT elevations ≥ 5 x 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 titres 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.

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

4.9 Overdose

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: Immunosuppressants, 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 three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 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.

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. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 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).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been 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. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

In GO-FORWARD, the (co-)primary endpoints were the percentage of patients achieving an ACR 20 response at week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at week 24. In GO-AFTER, the primary endpoint was the percentage of patients achieving an ACR 20 response at week 14. In GO-BEFORE, the co-primary endpoints were the percentage of patients achieving ACR 50 response at week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at week 52. 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 Simponi 50 mg dose at weeks 14, 24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 2 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104.

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 the controlled portions of GO-FORWARD, GO-AFTER and GO-BEFORE.

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg	Placebo + MTX	Simponi 50 mg + MTX
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA

Week 24	28%	60%*	16%	31% p = 0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p = 0.008	2%	10% p = 0.005	NA	NA
Week 24	5%	20%*	2%	9% p = 0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.

* $p \leq 0.001$

NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 ($p = 0.053$). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 2). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

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 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group ($p = 0.018$). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104.

Radiographic Response:

In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 3.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group ($p = 0.003$). The radiographic effects observed at week 52 were maintained through week 104.

Table 3
Radiographic Mean (SD) Changes from Baseline in Total vdH-S Score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n [a]	**160**	**159**
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		

Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomized patients

* p = 0.015

** p = 0.044

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. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ was maintained through week 104.

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 at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. 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. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at Week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at Week 14 and change from baseline in total PsA modified vdH-S score at Week 24.

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

Signs and symptoms

Key results for the 50 mg dose at weeks 14 and 24 are shown in table 4 and described below.

Table 4
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;

[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 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. 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. Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

At Week 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the 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. Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ responses were maintained through week 104.

Radiographic Response:
Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean + SD score was 0.27 + 1.3 in the placebo group compared with -0.16 + 1.3 in the Simponi group; $p = 0.011$). Out of 146 patients who were randomized to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline.

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 5 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 5
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%

* $p \leq 0.001$ 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 ($p \leq 0.017$) 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 III RA, PsA and AS studies through week 52, antibodies to golimumab were detected in 5% (105/2115) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. 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 3% [41/1262] versus 8% [64/853], respectively).

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.

Paediatric population
The European Medicines Agency has waived the obligation to conduct studies with Simponi in all subsets of the paediatric population in ankylosing spondylitis and rheumatoid arthritis (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Simponi in one or more subsets of the paediatric population in juvenile idiopathic arthritis and psoriatic arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
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 ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/ml.

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.

Distribution
Following a single IV administration, the mean volume of distribution was 115 ± 19 ml/kg.

Elimination
The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 ml/day/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.

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 (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/ml in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/ml in patients with active PsA and approximately 0.8 ± 0.4 μg/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. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

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

Linearity
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.

Effect of weight on pharmacokinetics
There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

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 and development.

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 TNFα, 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

1 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.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use pre-filled pen called SmartJect. Each Simponi pack is provided with instructions for use that fully describes the use of the pen. After removing the pre-filled 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. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

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

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

7. MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/005 1 pre-filled pen
EU/1/09/546/006 3 pre-filled pens

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: 1 October 2009

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled syringe.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml pre-filled syringe contains 100 mg of golimumab*.

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

Excipient with known effect:
Each pre-filled syringe contains 41 mg sorbitol per 100 mg dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled syringe (injection)

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 adults when the response to disease-modifying anti-rheumatic drug (DMARD) therapy including MTX has been inadequate.
- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX.

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

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 been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease (see section 5.1) and to improve physical function.

Ankylosing spondylitis (AS)
Simponi is indicated for the treatment of severe, active ankylosing spondylitis in adults 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.

Posology

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.

Patients with bodyweight greater than 100 kg
In patients with RA, PsA or AS with a body weight of 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, taking into account the increased risk of certain serious adverse drug reactions with the 100 mg dose compared with the 50 mg dose (see section 4.8). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit after receiving 3 to 4 additional doses of 100 mg.

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.

Elderly patients(≥ 65 years)
No dose adjustment is required in the elderly.

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

Paediatric population
The safety and efficacy of Simponi in patients aged less than 18 have not yet been established. No data are available.

Method of administration
For subcutaneous use. 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.

4.3 Contraindications

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

Cases of active tuberculosis have occurred in patients treated with Simponi during and after treatment for latent tuberculosis. Patients receiving Simponi should be monitored closely for signs and symptoms of active tuberculosis, including patients who tested negative for latent tuberculosis, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

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 should be tested for HBV infection before initiating treatment with Simponi. 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 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. Based on 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. 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.

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

Lymphoma and leukaemia
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. 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 risk estimation.

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 an increased risk of malignancy due to heavy smoking.

Skin cancers
Melanoma has been reported in patients treated with TNF-blocking agents, including Simponi. Merkel cell carcinoma has been reported in patients treated with other TNF-blocking agents (see section 4.8). Periodic skin examination is recommended, particularly for patients with risk factors for skin cancer.

Congestive heart failure (CHF)
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including Simponi. 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 with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and peripheral demyelinating disorders. 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. Discontinuation of Simponi should be considered if these disorders develop (see section 4.8).

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_{α} 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 pancytopaenia, leucopaenia, neutropaenia, aplastic anaemia, and thrombocytopaenia in patients receiving TNF-blockers. Cytopaenias including pancytopaenia 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 and neutropenia 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.

Concurrent administration with other biological therapeutics
There is insufficient information regarding the concomitant use of Simponi with other biological therapeutics used to treat the same conditions as Simponi. The concomitant use of Simponi with these biologics is not recommended because of the possibility of an increased risk of infection, and other potential pharmacological interactions.

Switching between biological DMARDs
Care should be taken and patients should continue to be monitored when switching from one biologic to another, since overlapping biological activity may further increase the risk for adverse events, including infection.

Vaccinations
Patients treated with Simponi may receive concurrent vaccinations, except for live vaccines (see sections 4.5 and 4.6). 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
In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following Simponi administration. Some of these reactions occurred after the first administration of Simponi. If an anaphylactic reaction or other serious allergic reactions occur, administration of Simponi should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity
The needle cover on the pre-filled syringe 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 impairment
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.

Potential for Medication errors

Simponi is registered in 50 mg and 100 mg strengths for subcutaneous administration. It is important that the right strength is used to administer the correct dose as indicated in the posology (see section 4.2). Care should be taken to provide the right strength to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Concurrent use with other biological therapeutics
The combination of Simponi with other biological therapeutics used to treat the same conditions as Simponi, including anakinra and abatacept is not recommended (see section 4.4).

Live vaccines
Live vaccines should not be given concurrently with Simponi (see sections 4.4 and 4.6).

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 Fertility, pregnancy and lactation

Women of childbearing potential
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.

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.

Golimumab crosses the placenta. Following treatment with a TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infant born by the treated woman. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab in utero is not recommended for 6 months following the mother’s last golimumab injection during pregnancy (see sections 4.4 and 4.5).

Breast-feeding
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.

Fertility
No animal fertility studies have been conducted with golimumab. A fertility study in mice, using an analogous antibody that selectively inhibits the functional activity of mouse TNFα, showed no relevant effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

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

Summary of the safety profile

Upper respiratory tract infection was the most common adverse drug reaction (ADR) reported in the controlled Phase III RA, PsA, and AS studies through week 16, occurring in 7.2% of golimumab-treated patients as compared with 5.8% of control patients. The most serious ADRs that have been reported for Simponi include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome) and haematologic reactions (see section 4.4).

Tabulated list of adverse reactions

ADRs observed in clinical studies and reported from world-wide post-marketing use of golimumab are listed 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 (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000); Not known (cannot be estimated from the available data).

Table 1
Tabulated list of ADRs

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, bacterial arthritis, infective bursitis
Rare:	Hepatitis B reactivation
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia, melanoma
Not known:	Merkel cell carcinoma*
Blood and lymphatic system disorders	
Common:	Anaemia
Uncommon:	Leucopaenia, thrombocytopaenia
Rare:	Pancytopaenia
Not known:	Aplastic anaemia *
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction), vasculitis (systemic), sarcoidosis
Endocrine disorders	
Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders	
Uncommon:	Blood glucose increased, lipids increased
Psychiatric disorders	
Common:	Depression, insomnia
Nervous system disorders	

	Common:	Dizziness, paraesthesia, headache
	Uncommon:	Demyelinating disorders (central and peripheral), balance disorders, dysguesia
Eye disorders		
	Uncommon:	Visual disorders (such as blurred vision and decreased visual 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, nausea
	Uncommon:	Gastrointestinal inflammatory disorders (such as gastritis and colitis), gastro-oesophageal 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 or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria, vasculitis (cutaneous)
	Rare:	Skin exfoliation
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.

Description of selected adverse drug reactions

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 100 subject-years: 26.3; 95% CI: 22.1, 31.2) as compared with 5.8% of control patients (incidence per 100 subject-years: 22.9; 95% CI: 16.6, 30.7. In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per 100 subject-years of upper respiratory tract infections was 17.4 events; 95% CI: 16.4, 18.6 for golimumab treated 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 100 subject-years: 128.0; 95% CI: 118.3, 138.2) compared with 24.7% of control patients (incidence per 100 subject-years: 116.6; 95% CI: 101.8, 132.9). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per 100 subject-years of infections was 96.0 events; 95% CI: 93.5, 98.6 for golimumab treated patients.

In controlled Phase III trials through week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of golimumab-treated patients and 1.3% of control-treated patients. Through Week 16, the incidence of serious infections per 100 subject-years of follow-up was 7.4; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 3.3; 95% CI: 1.3, 6.9 for the golimumab 50 mg group and 4.2; 95% CI: 1.8 , 8.2 for the placebo group. 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. In the controlled and uncontrolled portions of the Phase II and Phase III trials in RA, PsA, and AS with a median follow-up of approximately 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving golimumab 100 mgcompared with patients receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 5.1; 95% CI: 4.4, 5.9, in patients receiving golimumab 100 mg and 3.0; 95% CI: 2.4, 3.8, in patients receiving golimumab 50 mg.

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 approximately 3 years of follow up was higher than expected in the general population. In the controlled and uncontrolled portions of these trials through a median follow-up of approximately 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. Lymphoma was diagnosed in 7 subjects (1 in the golimumab 50 mg treatment groups and 6 in the golimumab 100 mg treatment groups) with an incidence (95%, CI) per 100 subject-years of follow-up of 0.04 (0.00, 0.24) and 0.18 (0.06, 0.38) events for golimumab 50 mg and 100 mg respectively and 0.00 (0.00, 0.84) events for the placebo. The majority of lymphomas occurred in study GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease. 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 approximately 3 years of follow-up, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the Simponi and the control groups.

Through approximately 3 years of follow-up, of the Phase IIb and Phase III studies in rheumatologic indications, nonmelanoma skin cancer was diagnosed in 33 subjects (5 in placebo, 10 in golimumab 50 mg and 18 in golimumab 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow up of 0.49 (0.33, 0.71) for combined golimumab and 1.40 (0.46, 3.28) for placebo.

Through approximately 3 years of follow-up, of the Phase IIb and Phase III studies in rheumatologic indications, malignancies besides nonmelanoma skin cancer and lymphoma were diagnosed in 34 subjects (2 in placebo, 18 in golimumab 50 mg and 14 in golimumab 100 mg treatment groups)

with an incidence (95%CI) per 100 subject-years of follow up of 0.56 (0.38, 0.79) for combined golimumab and 0.56 (0.07, 2.02) 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.

Neurological events
In the controlled and uncontrolled portions of the Phase II RA and the Phase III RA, PsA, and AS trials with a median follow-up of approximately 3 years, a greater incidence of demyelination was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. See section 4.4.

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 approximately 3 years 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 ≥ 5 x 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 approximately 3 years of follow-up, the incidence of ALT elevations ≥ 5 x 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 titres 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.

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

4.9 Overdose

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: Immunosuppressants, 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 three multi-centre, randomised, double-blind, placebo-controlled studies in over 1500 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.

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. Patients receiving placebo + MTX were switched to Simponi 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

GO-AFTER evaluated 445 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).

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve and had not previously been 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. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Simponi 50 mg + MTX.

In GO-FORWARD, the (co-)primary endpoints were the percentage of patients achieving an ACR 20 response at week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at week 24. In GO-AFTER, the primary endpoint was the percentage of patients achieving an ACR 20 response at week 14. In GO-BEFORE, the co-primary endpoints were the percentage of patients achieving ACR 50 response at week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at week 52. 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 Simponi 50 mg dose at weeks 14,24 and 52 for GO-FORWARD, GO-AFTER and GO-BEFORE are shown in Table 2 and are described below. Responses were observed at the first assessment (week 4) after the initial Simponi administration.

In GO-FORWARD, among 89 subjects randomised to Simponi 50 mg + MTX, 48 were still on this treatment at week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at week 104.

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 the controlled portions of GO-FORWARD, GO-AFTER and GO-BEFORE.

	GO-FORWARD Active RA despite MTX		GO-AFTER Active RA, previously treated with one or more anti-TNF agent(s)		GO-BEFORE Active RA, MTX Naïve	
	Placebo + MTX	Simponi 50 mg + MTX	Placebo	Simponi 50 mg	Placebo + MTX	Simponi 50 mg + MTX
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA

Week 24	28%	60%*	16%	31% p = 0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p = 0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p = 0.008	2%	10% p = 0.005	NA	NA
Week 24	5%	20%*	2%	9% p = 0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

[a] n reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.

* $p \leq 0.001$

NA: Not Applicable

In GO-BEFORE the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Simponi 50 and 100 mg + MTX groups vs MTX alone for ACR50) was not statistically significant at week 24 (p = 0.053). At week 52 in the overall population, the percentage of patients in the Simponi 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 2). Additional analyses were performed in subsets representative of the indicated population of patients with severe, active and progressive RA. A generally greater effect of Simponi 50 mg + MTX versus MTX alone was demonstrated in the indicated population compared with the overall population.

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 ($p \leq 0.001$). Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 responses were maintained through week 104.

In GO-BEFORE, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At week 52, 15% of patients in the Simponi 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group (p = 0.018). Among 159 subjects randomised to Simponi 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104.

Radiographic Response:

In GO-BEFORE the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Simponi 50 mg dose at week 52 are presented in Table 3.

The number of patients with no new erosions or a change from baseline in total vdH-S Score ≤ 0 was significantly higher in the Simponi treatment group than in the control group (p = 0.003). The radiographic effects observed at week 52 were maintained through week 104.

Table 3
Radiographic Mean (SD) Changes from Baseline in Total vdH-S Score at week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Simponi 50 mg + MTX**
n [a]	**160**	**159**
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		

Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomized patients

* p = 0.015

** p = 0.044

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. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement in HAQ was maintained through week 104.

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 at week 24. Among patients who remained on the Simponi treatment to which they were randomised at study start, improvement of the SF-36 physical component was maintained through week 104. 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. Patients receiving placebo were switched to Simponi 50 mg after week 24. Patients entered an open label long-term extension at Week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at Week 14 and change from baseline in total PsA modified vdH-S score at Week 24.

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

Signs and symptoms

Key results for the 50 mg dose at weeks 14 and 24 are shown in table 4 and described below.

Table 4
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;

[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 50 mg group.

Responses were observed at the first assessment (week 4) after the initial Simponi administration. Similar ACR 2 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. Among 146 patients randomised to Simponi 50 mg, 70 were still on this treatment at week 104. Of these 70 patients, 64, 46 and 31 patients had an ACR 20/50/70 response, respectively.

Statistically significant responses in DAS28 were also observed at weeks 14 and 24 ($p < 0.05$).

At Week 24 improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the 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. Among patients who remained on the Simponi treatment to which they were randomised at study start, DAS28 and HAQ responses were maintained through week 104.

Radiographic Response:
Structural damage in both hands and feet was assessed radiographically by the change from baseline in the vdH-S score, modified for PsA by addition of hand distal interphalangeal (DIP) joints.

Simponi 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean + SD score was 0.27 + 1.3 in the placebo group compared with -0.16 + 1.3 in the Simponi group; $p = 0.011$). Out of 146 patients who were randomized to Simponi 50 mg, 52 week X-ray data were available for 126 patients, of whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline.

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 5 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 5
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%

* $p \leq 0.001$ 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 ($p \leq 0.017$) 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 III RA, PsA and AS studies through week 52, antibodies to golimumab were detected in 5% (105/2115) of golimumab treated patients and, where tested, nearly all antibodies were neutralising *in vitro*. 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 3% [41/1262] versus 8% [64/853], respectively).

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.

Paediatric population
The European Medicines Agency has waived the obligation to conduct studies with Simponi in all subsets of the paediatric population in ankylosing spondylitis and rheumatoid arthritis (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Simponi in one or more subsets of the paediatric population in juvenile idiopathic arthritis and psoriatic arthritis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
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 ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 μg/ml.

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.

Distribution
Following a single IV administration, the mean volume of distribution was 115 ± 19 ml/kg.

Elimination
The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 ml/day/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.

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 (± standard deviation) steady-state trough serum concentration of approximately 0.6 ± 0.4 μg/ml in RA patients with active RA despite MTX therapy, and approximately 0.5 ± 0.4 μg/ml in patients with active PsA and approximately 0.8 ± 0.4 μg/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. In a limited number of RA patients treated with subcutaneous golimumab over a 6-month period, concomitant use of MTX reduced the apparent clearance of golimumab by approximately 36%. However, population pharmacokinetic analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of golimumab.

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

Linearity
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.

Effect of weight on pharmacokinetics
There was a trend toward higher apparent clearance of golimumab with increasing weight (see section 4.2).

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 and development.

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 TNFα, 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 syringe in the outer carton in order to protect it from light.

6.5 Nature and contents of container

1 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 syringe. Simponi is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Simponi is supplied in a single use pre-filled syringe. Each Simponi pack is provided with instructions for use that fully describes the use of the syringe. After removing the pre-filled syringe from the refrigerator the pre-filled syringe should be allowed to reach room temperature by waiting for 30 minutes, before injecting Simponi. The syringe 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. Simponi should not be used if the solution is discoloured, cloudy or containing visible foreign particles.

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

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

7. MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/007 1 pre-filled syringe
EU/1/09/546/008 3 pre-filled syringes

9. DATE OF FIRST AUTHORISATION

Date of first authorisation: 1 October 2009

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturer of the biological active substance

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

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

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

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

- **Additional risk minimisation measures**

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

- The Summary of Product Characteristics
- Physician information

- Patient Alert Card

The physician information should contain the following key messages:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED PEN CARTON

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

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

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
Read the package leaflet before use
Subcutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

Do not freeze
Keep the pre-filled pen in the outer carton in order to protect from light

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 PRE-FILLED PEN AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (Smartject)
1 pre-filled pen
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
Read the package leaflet before use
Subcutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/006

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR MULTIPACK COMPRISING 3 PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg
solution for injection in pre-filled pen
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled pen contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen (SmartJect)
Multipack: 3 packs, each containing 1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
Read the package leaflet before use
Subcutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the pen to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/006 (3 packs, each containing 1 pre-filled pen)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE OF CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiration date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

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

Simponi 100 mg solution for injection
golimumab
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

PRE-FILLED SYRINGE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
Read the package leaflet before use
Subcutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/007

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 PRE-FILLED SYRINGE AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
1 pre-filled syringe
Component of a multipack, can't be sold separately

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
Read the package leaflet before use
Subcutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/008

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR MULTIPACK COMPRISING 3 PACKS (INCLUDING BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Simponi 100 mg
solution for injection in pre-filled syringe
golimumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml pre-filled syringe contains 100 mg golimumab

3. LIST OF EXCIPIENTS

Excipients: sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled syringe
Multipack: 3 packs, each containing 1 pre-filled syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Do not shake
Read the package leaflet before use
Subcutaneous use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The needle cover contains latex rubber. See the package leaflet for further information.
Allow the syringe to sit at room temperature outside the box for 30 minutes before use.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/546/008 (3 packs, each containing 1 pre-filled syringe)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Simponi 100 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INSIDE Of CARTON

Before you start using Simponi:

- Please read the enclosed package leaflet
- Do not shake the product
- Check the expiration date and the security seal
- Wait 30 minutes to allow the product to reach room temperature

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

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

Simponi 100 mg
injection
golimumab
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER

Simponi Patient Alert Card

This patient alert card contains important safety information that you need to be aware of before and during treatment with Simponi.

Show this card to any doctor involved in your treatment.

1. Infections

When you are treated with Simponi, you might get infections more easily. Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

1.1 Prior to Simponi treatment:

- Tell your doctor if you have an infection. You must not be treated with Simponi if you have tuberculosis (TB) or any other severe infection.
- You should be screened for TB. It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had TB. Ask your doctor to record the type and date of the last screening(s) for TB below:
  Test _____ Date _____
  Test _____ Date _____
- Tell your doctor if you know or suspect you are a carrier of the hepatitis B virus.

1.2 During and after Simponi treatment:

- Seek medical attention immediately if you develop symptoms of an infection, such as fever, tiredness, (persistent) cough, shortness of breath, or flu-like signs, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.

2. Heart failure

2.1 Prior to Simponi treatment:

- Tell your doctor if you have a history of heart failure. You must not be treated with Simponi if you have moderate to severe heart failure.

2.2 During and after Simponi treatment

- If you develop symptoms of heart failure (e.g. shortness of breath or swelling of the feet) seek medical attention immediately.

3. Dates of Simponi treatment:

1st administration: _____

Subsequent administrations: _____
_____

4. Other information

Patient's Name: _____
Doctor's Name: _____
Doctor's Phone: _____

- Please make sure you also have a list of all other medicines that you are using with you at any visit to a health care professional.

- Keep this card with you for 6 months after the last Simponi dose, since side effects may occur a long time after your last dose of Simponi.

- Read the Simponi package leaflet carefully before you start using this medicine.

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Simponi 100 mg solution for injection in a pre-filled pen
golimumab

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

Your doctor will also give you a Patient Alert Card, which contains important safety information you need to be aware of before and during your treatment with Simponi.

What is in this leaflet

1. What Simponi is and what it is used for

Simponi contains the active substance called golimumab.

Simponi belongs to a group of medicines called 'TNF blockers'. It is used in adults for the treatment of the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis.

Simponi works by blocking the action of a protein called 'tumour necrosis factor alpha' (TNF-α). This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body.

Rheumatoid arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi which you will take in combination with another medicine called methotrexate to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis, an inflammatory disease of the skin. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Ankylosing spondylitis
Ankylosing spondylitis is an inflammatory disease of the spine. If you have ankylosing spondylitis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.

2. What you need to know before you use Simponi

Do not use Simponi:
- if you are allergic (hypersensitive) to golimumab or any of the other ingredients of this medicine (listed in Section 6).
- if you have tuberculosis (TB) or any other severe infection.
- if you have moderate or severe heart failure.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Simponi.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Simponi.

Infections
Tell your doctor straight away if you already have or get any symptoms of infection, during or after your treatment with Simponi. Symptoms of infection include fever, cough, shortness of breath, flu-like symptoms, diarrhoea, wounds, dental problems or a burning feeling when urinating.
- You may get infections more easily while using Simponi.
- Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

Tuberculosis (TB)
Tell your doctor straight away if symptoms of TB appear during or after your treatment. Symptoms of TB include persistent cough, weight loss, tiredness, fever or night sweats.
- Cases of TB have been reported in patients treated with Simponi, in rare occasions even in patients who have been treated with medications for TB. Your doctor will test you to see if you have TB. Your doctor will record these tests on your Patient Alert Card.
- It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had or has TB.
- If your doctor feels that you are at risk of TB, you may be treated with medicines for TB before you begin using Simponi.

Hepatitis B virus (HBV)
- Tell your doctor if you are a carrier or if you have or have had HBV before you are given Simponi.
- Tell your doctor if you think you might be at risk of contracting HBV
- Your doctor should test you for HBV
- Treatment with TNF blockers such as Simponi may result in reactivation of HBV in patients who carry this virus, which can be life-threatening in some cases.

Invasive fungal infections
If you have lived in or travelled to an area where infections caused by specific type of fungi that can affect the lungs or other parts of the body (called histoplasmosis, coccidioidomycosis, or blastomycosis), are common, tell your doctor straight away. Ask your doctor if you don't know if these fungal infections are common in the area in which you have lived or travelled.

Cancer and lymphoma

Tell your doctor if you have ever been diagnosed with lymphoma (a type of blood cancer) or any other cancer before you use Simponi.

- If you use Simponi or other TNF blockers, your risk for developing lymphoma or another cancer may increase.
- Patients with severe rheumatoid arthritis and other inflammatory diseases, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death.
- Patients with severe persistent asthma, chronic obstructive pulmonary disease (COPD), or are heavy smokers may be at increased risk for cancer with Simponi treatment. If you have severe persistent asthma, COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- Some patients treated with golimumab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Heart failure

Tell your doctor straight away if you get new or worsening symptoms of heart failure. Symptoms of heart failure include shortness of breath or swelling of your feet.

- New and worsening congestive heart failure has been reported with TNF blockers.
- If you have mild heart failure and you are being treated with Simponi, you must be closely monitored by your doctor.

Nervous system disease

Tell your doctor straight away if you have ever been diagnosed with or develop symptoms of a demyelinating disease such as multiple sclerosis. Symptoms may include changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body. Your doctor will decide if you should receive Simponi.

Operations or dental procedures

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

Autoimmune disease

Tell your doctor if you develop symptoms of a disease called lupus. Symptoms include persistent rash, fever, joint pain and tiredness.

- On rare occasions, people treated with TNF blockers have developed lupus.

Blood disease

In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Vaccinations

Talk to your doctor if you have had, or are due to have a vaccine.

- You should not receive certain (live) vaccines while using Simponi.
- Certain vaccinations may cause infections. If you received Simponi while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Simponi use so they can decide when your baby should receive any vaccine.

Allergic reactions
Tell your doctor straight away if you develop symptoms of an allergic reaction after your treatment with Simponi. Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles.

- Some of these reactions may be serious or, rarely, life-threatening.
- Some of these reactions occurred after the first administration of Simponi.

Children and adolescents
Simponi is not recommended for children and adolescents (younger than 18 years) because it has not been studied in this age group.

Other medicines and Simponi

- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including any other medicines to treat rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.
- You should not take Simponi with medicines containing the active substance anakinra or abatacept. These medicines are used for the treatment of rheumatic diseases.
- Tell your doctor or pharmacist if you are taking any other medicines that affect your immune system.
- You should not receive certain (live) vaccines while using Simponi.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Pregnancy and breast-feeding
Talk to your doctor before using Simponi if:

- You are pregnant or are planning to become pregnant while using Simponi. The effects of this medicine in pregnant women are not known. The use of Simponi in pregnant women is not recommended. If you are being treated with Simponi, you must avoid becoming pregnant by using adequate contraception during your treatment and for at least 6 months after the last Simponi injection.
- You are a (potential) nursing mother. Before starting breast-feeding, your last treatment with Simponi must be at least 6 months ago. You must stop breast-feeding if you are to be given Simponi.
- If you received Simponi during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Simponi use before the baby receives any vaccine (for more information see section on vaccination).

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

Driving and using machines
Simponi may have a minor influence on your ability to drive and use tools or machines. Dizziness may occur after you take Simponi. If this happens, do not drive or use any tools or machines.

Simponi contains latex and sorbitol
Latex sensitivity
A part of the pre-filled pen, the needle cover, contains latex. Because latex may cause severe allergic reactions, talk to your doctor before using Simponi if you or your carer are allergic to latex.

Sorbitol intolerance
Simponi contains sorbitol (E420). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to use Simponi

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

How much Simponi is given
- The recommended dose is 50 mg given once a month, on the same date each month.
- Talk to your doctor before taking your fourth dose. Your doctor will determine if you should continue Simponi treatment.
    - If you weigh more than 100 kg, the dose might be increased to 100 mg (the content of 1 pre-filled pen) given once a month, on the same date each month.

How Simponi is given
- Simponi is given by injection under the skin (subcutaneously).
- At the start, your doctor or nurse may inject Simponi. However, you and your doctor may decide that you may inject Simponi yourself. In this case you will get training on how to inject Simponi yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed "Instructions for administration" at the end of this leaflet.

If you use more Simponi than you should
If you have used or been given too much Simponi (either by injecting too much on a single occasion, or by using it too often), talk to your doctor or pharmacist straight away. Always take the outer carton with you, even if it is empty.

If you forget to use Simponi
If you forget to use Simponi on your planned date, inject the forgotten dose as soon as you remember.

Do not use a double dose to make up for a forgotten dose.

When to inject your next dose:
- If you were less than 2 weeks late, inject the forgotten dose as soon as you remember and stay on your original schedule.
- If you were more than 2 weeks late, inject the forgotten dose as soon as you remember and talk to your doctor or pharmacist to ask when you need to take the next dose.

If you are not sure what to do, talk to your doctor or pharmacist.

If you stop using Simponi
If you are considering stopping Simponi, talk to your doctor or pharmacist first.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some patients may experience serious side effects and may require treatment. The risk of certain side effects is greater with the 100 mg dose compared with the 50 mg dose. Side effects may appear up to several months after the last injection.

Tell your doctor straight away if you notice any of the following serious side effects of Simponi which include:
- **allergic reactions which may be serious, or rarely, life-threatening (rare).** Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions occurred after the first administration of Simponi.

- **serious infections (including TB, bacterial infections including serious blood infections and pneumonia, severe fungal infections and other opportunistic infections) (uncommon).** Symptoms of an infection can include fever, tiredness, (persistent) cough, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.
- **reactivation of hepatitis B virus if you are a carrier or have had hepatitis B before (rare).** Symptoms can include yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever, feeling sick, being sick, and feeling very tired.
- **nervous system disease such as multiple sclerosis (uncommon).** Symptoms of nervous system disease can include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.
- **cancer of the lymph nodes (lymphoma) (rare).** Symptoms of lymphoma can include swelling of the lymph nodes, weight loss, or fever.
- **heart failure (uncommon).** Symptoms of heart failure can include shortness of breath or swelling of your feet.
- **signs of an immune system disorder called lupus (rare).** Symptoms can include joint pain or a rash on cheeks or arms that is sensitive to the sun.
- **blood disease.** Symptoms of blood disease can include a fever that does not go away, bruising or bleeding very easily or looking very pale.

Tell your doctor straight away if you notice any of the above symptoms.

The following additional side effects have been observed with Simponi:

Very common side effects (may affect more than 1 in 10 people):

- Upper respiratory tract infections, sore throat or hoarseness, runny nose

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

- Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor
- Feeling dizzy
- Headache
- Superficial fungal infections
- Bacterial infections (such as cellulitis)
- Low red blood cell counts
- Positive blood lupus test
- Difficulty sleeping
- Depression
- Constipation
- Hair loss
- Allergic reactions
- Rash and itching of the skin
- Indigestion
- Stomach pain
- Feeling sick (nausea)
- Feeling numb or having a tingling feeling
- Flu
- Bronchitis
- Sinus infection
- Cold sores
- High blood pressure
- Fever
- Injection site reactions (including redness, hardness, pain, bruising, itching, tingling and irritation)
- Feeling weak
- Impaired healing
- Chest discomfort

Uncommon side effects (may affect up to 1 in 100 people):
- Infection of the joints or the tissue around them
- Kidney infection
- Abscess
- cancers, including skin cancer and non-cancerous growths or lumps, including skin moles
- Psoriasis (including on the palms of your hand and/or the soles of your feet and/or in the form of skin blisters)
- Low platelet count
- Low white blood cell counts
- Combined low platelet, red, and white blood cell count
- Thyroid disorders
- Increase in blood sugar levels
- Increase in blood cholesterol levels
- Balance disorders
- Taste disturbances
- Vision disturbances
- Sensation of heart beating irregularly
- Narrowing of the blood vessels in the heart
- Blood clots
- Pain and discoloration in the fingers or toes
- Flushing
- Asthma, shortness of breath, wheezing
- Stomach and bowel disorders which include inflammation of the stomach lining and colon which may cause fever
- Acid reflux
- Pain and ulcers in the mouth
- Gall stones
- Liver disorders
- Bladder disorders
- Breast disorders
- Menstrual disorders
- Bone fractures
- Inflammation of the blood vessels in your skin which results in rash

Rare side effects (may affect up to 1 in 1,000 people):
- Chronic inflammatory condition of the lungs
- Kidney disorders
- Inflammation of blood vessels in internal organs
- Leukaemia
- Melanoma (a type of skin cancer)
- Scaly, peeling skin
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)

Side effects of which the frequency is not known:
- Failure of the bone marrow to produce blood cells
- Merkel cell carcinoma (a type of skin cancer)

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

5. How to store Simponi

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C). Do not freeze.
- Keep the pre-filled pen in the outer carton in order to protect it from light.
- Do not use this medicine if you notice that the liquid is not a clear to light yellow colour, cloudy, or contains foreign particles.
- Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Simponi contains
The active substance is golimumab. One 1 ml pre-filled pen contains 100 mg of golimumab.

The other ingredients are sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 and water for injections.

What Simponi looks like and contents of the pack
Simponi is supplied as solution for injection in a single-use 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.

The solution is clear to slightly opalescent (having a pearl-like shine), colourless to light yellow and may contain a few small translucent or white particles of protein. Do not use Simponi if the solution is discoloured, cloudy or you can see foreign particles in it.

Marketing Authorisation Holder and Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

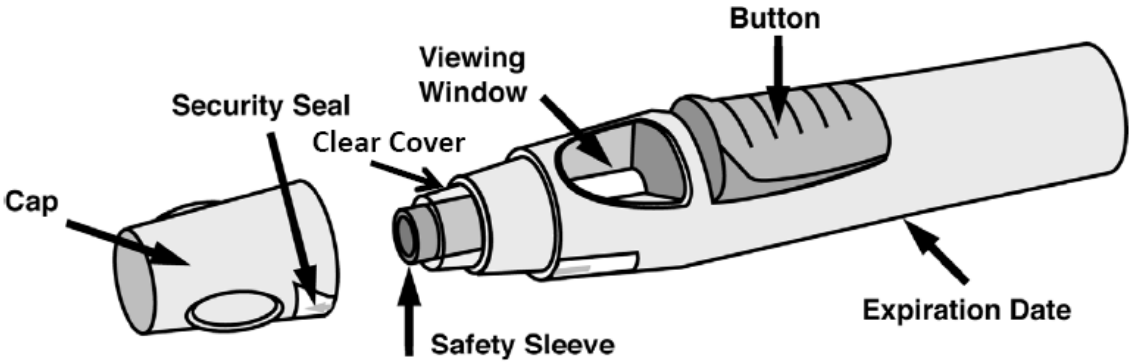
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

INSTRUCTIONS FOR ADMINISTRATION

If you would like to self inject Simponi, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your doctor, nurse or pharmacist to schedule a training session.

In these instructions:
1. Preparing for use of the pen
2. Choosing and preparing the injection site
3. Injecting the medicine
4. After the injection

The diagram below (see figure 1) shows what the ”SmartJect” pre-filled pen looks like. In this leaflet “SmartJect” pre-filled pen may sometimes be shortened to “pen”.



1. Preparing for use of the pen
- Do not shake the pen at any time.
- Do not remove the cap from the pen until instructed to do so.

Check the number of pre-filled pens
Check the pre-filled pens to make sure
- the number of pre-filled pens and strength is correct
  - If your dose is 100 mg, you will get one 100 mg pre-filled pen

Check expiry date
- Check the expiration date (as indicated as “EXP”) on the pen.
- You can also check the expiration date printed on the carton.

Do not use the pen if the expiration date has passed. The expiration date refers to the last day of the month. Please contact your doctor or pharmacist for assistance.

Check security seal
- Check the security seal around the cap of the pen.

Do not use the pen if the seal is broken. Please contact your doctor or pharmacist.

Wait 30 minutes to allow pen to reach room temperature
- To ensure proper injection, allow the pen to sit at room temperature outside the box for 30 minutes out of the reach of children.

Do not warm the pen in any other way (for example, do not warm it in a microwave or in hot water). Do not remove the pen’s cap while allowing it to reach room temperature.

Get the rest of your equipment ready
While you are waiting you can get the rest of your equipment ready, including an alcohol swab, a cotton ball or gauze and a sharps container.

Check the liquid in the pen

- Look through the viewing window to make sure that the liquid in the pen is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow. The solution can be used if it contains a few small translucent or white particles of protein.
- You will also notice an air bubble, which is normal.

Do not use the pen if the liquid is the wrong colour, cloudy, or contains larger particles. If this happens, talk to your doctor or pharmacist.

2. Choosing and preparing the injection site (see figure 2)

- You usually inject the medicine into the front of the middle thighs.
- You can also use the stomach (abdomen) below the belly button, except for approximately the 5 cm area directly underneath the belly button.
- Do not inject into areas where the skin is tender, bruised, red, scaly, hard or has scars or stretch marks.
- If multiple injections are required, the injections should be administered at different sites on the body.

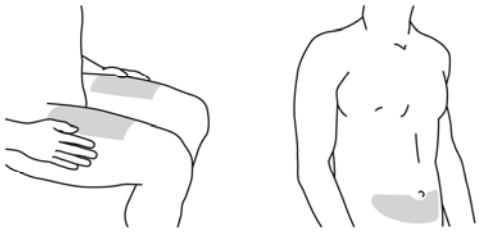


Figure 2

Injection site selection for caregivers (see figure 3)

- If a caregiver is giving you the injection, they can also use the outer area of the upper arms
- Again, all sites mentioned can be used regardless of your body type or size.

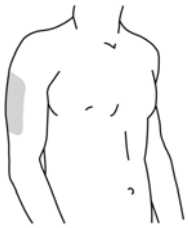


Figure 3

Preparing injection site

- Wash your hands thoroughly with soap and warm water.
- Wipe the injection site with an alcohol swab.
- Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Do not touch this area again before giving the injection.

3. Injecting the medicine

The cap should not be removed until you are ready to inject the medication. The medication should be injected within 5 minutes after the cap has been removed.

Remove the cap (figure 4)

- When you are ready to inject, twist the cap slightly to break the security seal.
- Pull the cap off and throw it away after your injection.

Do not put the cap back on because it may damage the needle inside the pen. Do not use the pen if it is dropped without the cap in place. If this happens please contact your doctor or pharmacist.

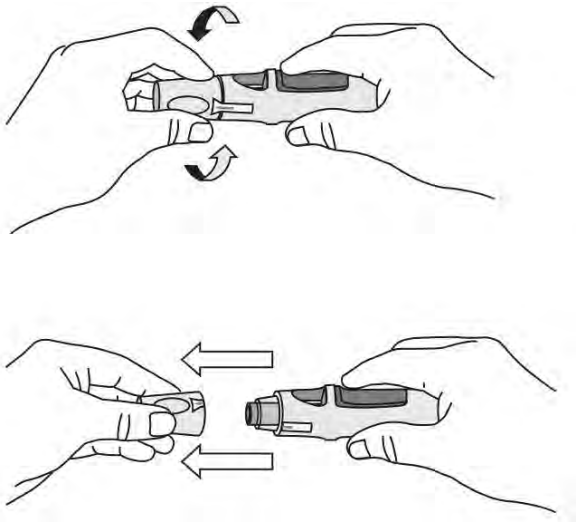


Figure 4

Push the pen firmly against the skin (see figures 5 and 6)

- Hold the pen comfortably in your hand. **DO NOT** press the button at this time.
- You will choose from 2 injection methods. Injecting without pinching the skin is recommended (Figure 5a). However, if you prefer, you may pinch the skin to create a firmer surface for your injection (Figure 5b).
- Push the open end of the pen firmly against the skin at a 90-degree angle until the Safety Sleeve slides fully into the Clear Cover (Figure 6).

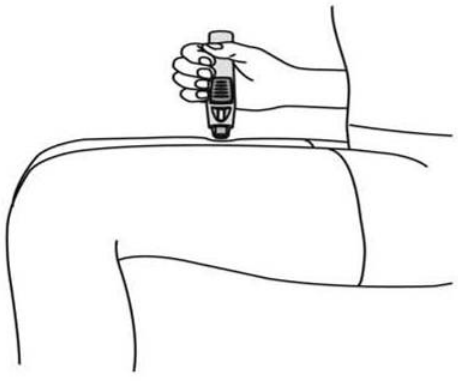


Figure 5a

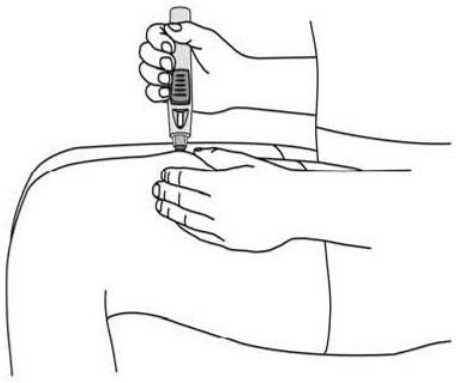


Figure 5b

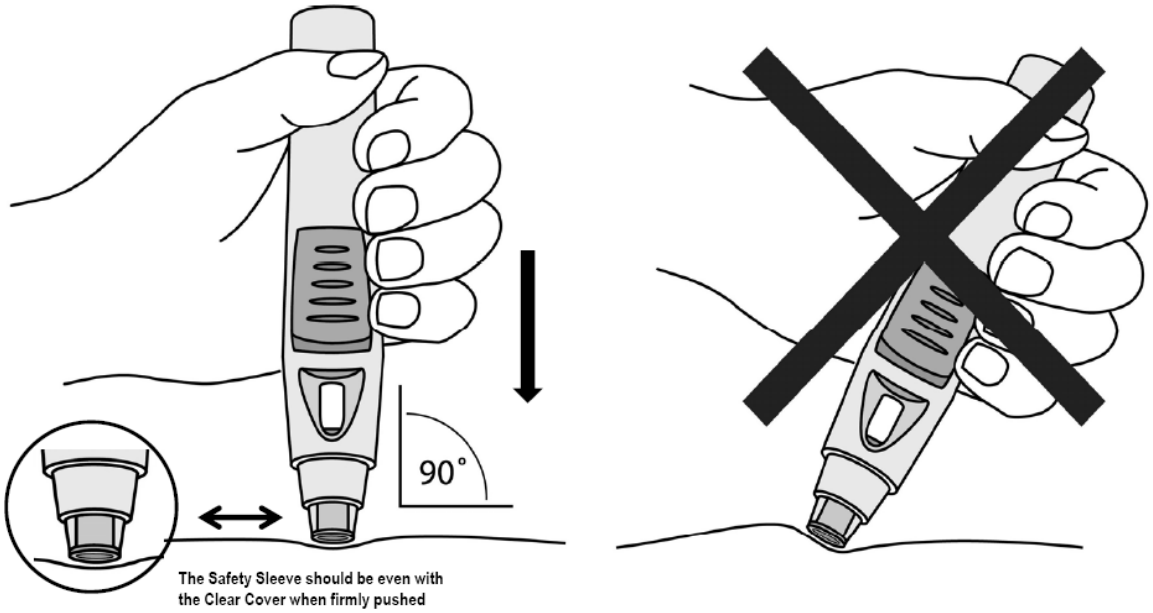


Figure 6

Press button to inject (see figure 7)

- **Continue to push the pen firmly against your skin and press the raised part of the button with your fingers or thumb**. You will not be able to press in the button unless the pen is **pushed firmly against your skin** and the Safety Sleeve slides into the Clear Cover.
- Once the button is pressed, it will remain pressed in so you do not need to keep pressure on it.

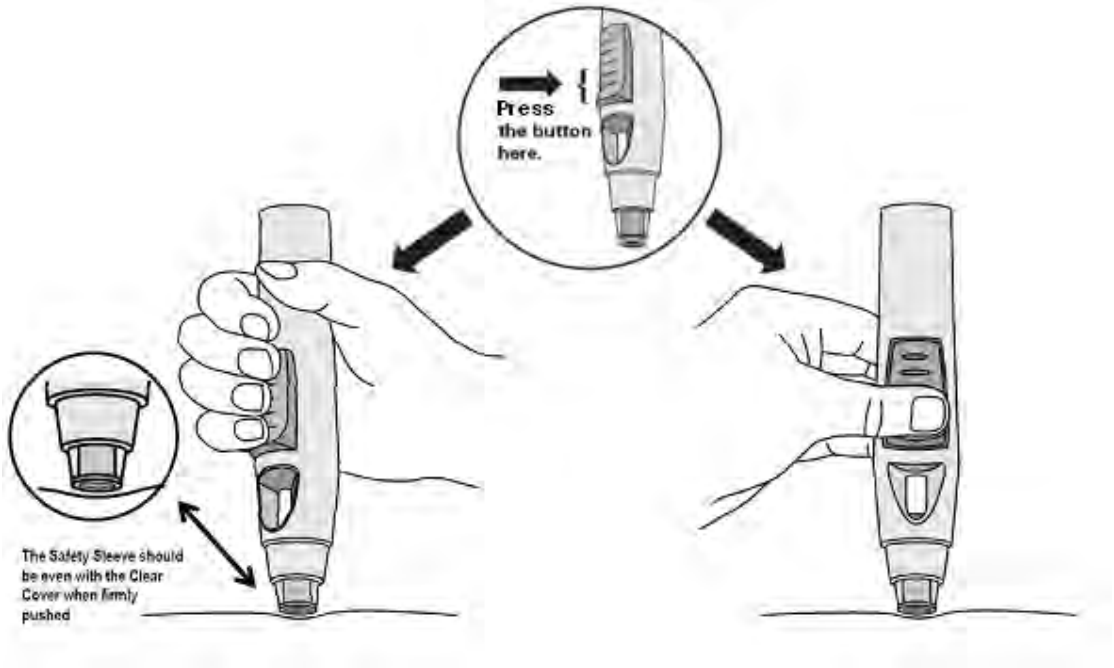


Figure 7

- **You will hear a loud 'click' sound – don't be alarmed.** The first "click" means that the needle has been inserted and the injection has started. You may or may not feel a needle prick at this time.

Do not lift the pen away from your skin. If you pull the pen away from your skin, you may not get your full dose of medicine.

Continue to hold until the second "click" (see figure 8)

- **Continue to hold the pen down firmly against your skin until you hear a second "click'. This usually takes about 3-6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound.**
- The second "click" means that the injection is finished and the needle has gone back into the pen.
- Lift the pen from the injection site.

If you have hearing problem, count 15 seconds from the time you first press the button and then lift the pen from the injection site.

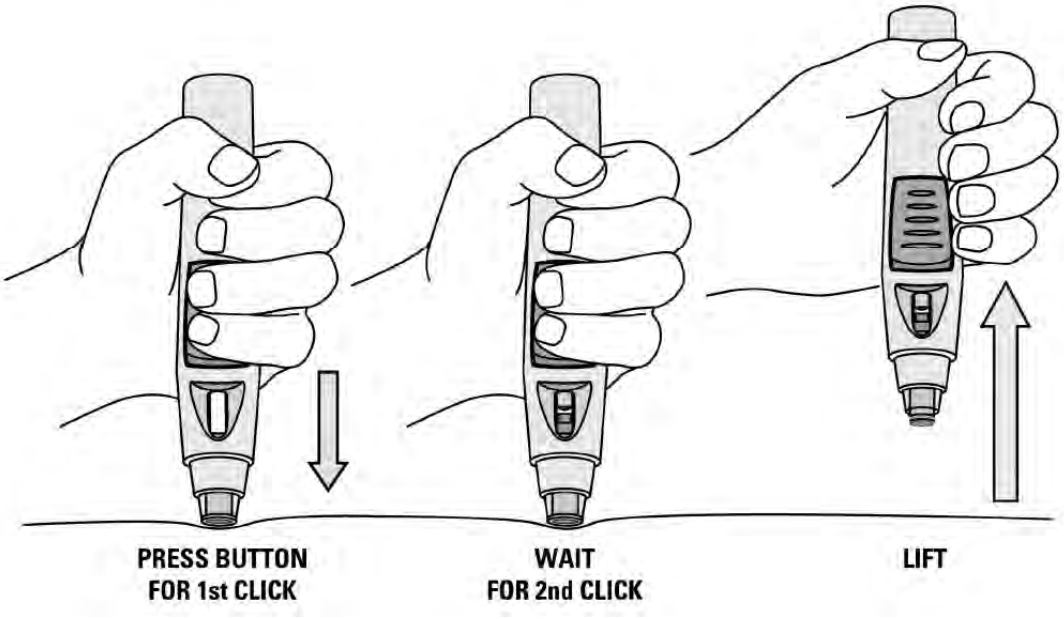


Figure 8

4. After the injection

Use cotton ball or gauze

- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site for 10 seconds.
- You may cover the injection site with a small adhesive bandage, if necessary.

Do not rub your skin.

Check the window – a yellow indicator confirms proper administration (see figure 9)

Talk to your doctor or pharmacist if the yellow indicator is not visible in the window or if you suspect that you may not have received a complete dose. Do not administer a second dose without speaking to your doctor.

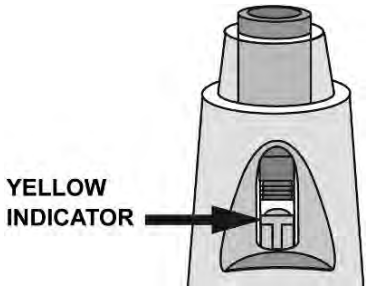


Figure 9

Throw the pen away (see figure 10)

- Place your pen in a sharps container straight away. Make sure you dispose of the bin as instructed by your doctor or nurse.

If you feel that something has gone wrong with the injection or if you are not sure, talk to your doctor or pharmacist.

Figure 10

Package Leaflet: Information for the user

Simponi 100 mg solution for injection in a pre-filled syringe
golimumab

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

Your doctor will also give you a Patient Alert Card, which contains important safety information you need to be aware of before and during your treatment with Simponi.

What is in this leaflet

1. What Simponi is and what it is used for

Simponi contains the active substance called golimumab.

Simponi belongs to a group of medicines called 'TNF blockers'. It is used in adults for the treatment of the following inflammatory diseases:
- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis.

Simponi works by blocking the action of a protein called 'tumour necrosis factor alpha' (TNF-α). This protein is involved in inflammatory processes of the body, and blocking it can reduce the inflammation in your body.

Rheumatoid arthritis
Rheumatoid arthritis is an inflammatory disease of the joints. If you have active rheumatoid arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi which you will take in combination with another medicine called methotrexate to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Psoriatic arthritis
Psoriatic arthritis is an inflammatory disease of the joints, usually accompanied by psoriasis, an inflammatory disease of the skin. If you have active psoriatic arthritis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Slow down the damage to your bones and joints.
- Improve your physical function.

Ankylosing spondylitis
Ankylosing spondylitis is an inflammatory disease of the spine. If you have ankylosing spondylitis you will first be given other medicines. If you do not respond well enough to these medicines, you may be given Simponi to:
- Reduce the signs and symptoms of your disease.
- Improve your physical function.

2. What you need to know before you use Simponi

Do not use Simponi:
- if you are allergic (hypersensitive) to golimumab or any of the other ingredients of this medicine (listed in Section 6).
- if you have tuberculosis (TB) or any other severe infection.
- if you have moderate or severe heart failure.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Simponi.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Simponi.

Infections
Tell your doctor straight away if you already have or get any symptoms of infection, during or after your treatment with Simponi. Symptoms of infection include fever, cough, shortness of breath, flu-like symptoms, diarrhoea, wounds, dental problems or a burning feeling when urinating.
- You may get infections more easily while using Simponi.
- Infections may progress more rapidly and may be more severe. In addition, some previous infections may reappear.

Tuberculosis (TB)
Tell your doctor straight away if symptoms of TB appear during or after your treatment. Symptoms of TB include persistent cough, weight loss, tiredness, fever or night sweats.
- Cases of TB have been reported in patients treated with Simponi, in rare occasions even in patients who have been treated with medications for TB. Your doctor will test you to see if you have TB. Your doctor will record these tests on your Patient Alert Card.
- It is very important that you tell your doctor if you have ever had TB, or if you have been in close contact with someone who has had or has TB.
- If your doctor feels that you are at risk of TB, you may be treated with medicines for TB before you begin using Simponi.

Hepatitis B virus (HBV)
- Tell your doctor if you are a carrier or if you have or have had HBV before you are given Simponi.
- Tell your doctor if you think you might be at risk of contracting HBV
- Your doctor should test you for HBV
- Treatment with TNF blockers such as Simponi may result in reactivation of HBV in patients who carry this virus, which can be life-threatening in some cases.

Invasive fungal infections
If you have lived in or travelled to an area where infections caused by specific type of fungi that can affect the lungs or other parts of the body (called histoplasmosis, coccidioidomycosis, or blastomycosis), are common, tell your doctor straight away. Ask your doctor if you don't know if these fungal infections are common in the area in which you have lived or travelled.

Cancer and lymphoma

Tell your doctor if you have ever been diagnosed with lymphoma (a type of blood cancer) or any other cancer before you use Simponi.

- If you use Simponi or other TNF blockers, your risk for developing lymphoma or another cancer may increase.
- Patients with severe rheumatoid arthritis and other inflammatory diseases, who have had the disease for a long time, may be at higher than average risk of developing lymphoma.
- There have been cases of cancers, including unusual types, in children and teenage patients taking TNF-blocking agents, which sometimes resulted in death.
- Patients with severe persistent asthma, chronic obstructive pulmonary disease (COPD), or are heavy smokers may be at increased risk for cancer with Simponi treatment. If you have severe persistent asthma, COPD or are a heavy smoker, you should discuss with your doctor whether treatment with a TNF blocker is appropriate for you.
- Some patients treated with golimumab have developed certain kinds of skin cancer. If any changes in the appearance of the skin or growths on the skin occur during or after therapy, tell your doctor.

Heart failure

Tell your doctor straight away if you get new or worsening symptoms of heart failure. Symptoms of heart failure include shortness of breath or swelling of your feet.

- New and worsening congestive heart failure has been reported with TNF blockers.
- If you have mild heart failure and you are being treated with Simponi, you must be closely monitored by your doctor.

Nervous system disease

Tell your doctor straight away if you have ever been diagnosed with or develop symptoms of a demyelinating disease such as multiple sclerosis. Symptoms may include changes in your vision, weakness in your arms or legs or numbness or tingling in any part of your body. Your doctor will decide if you should receive Simponi.

Operations or dental procedures

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

Autoimmune disease

Tell your doctor if you develop symptoms of a disease called lupus. Symptoms include persistent rash, fever, joint pain and tiredness.

- On rare occasions, people treated with TNF blockers have developed lupus.

Blood disease

In some patients the body may fail to produce enough of the blood cells that help your body fight infections or help you to stop bleeding. If you develop a fever that does not go away, bruise or bleed very easily or look very pale, call your doctor right away. Your doctor may decide to stop treatment.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Vaccinations

Talk to your doctor if you have had, or are due to have a vaccine.

- You should not receive certain (live) vaccines while using Simponi.
- Certain vaccinations may cause infections. If you received Simponi while you were pregnant, your baby may be at higher risk for getting such an infection for up to approximately six months after the last dose you received during pregnancy. It is important that you tell your baby's doctors and other health care professionals about your Simponi use so they can decide when your baby should receive any vaccine.

Allergic reactions
Tell your doctor straight away if you develop symptoms of an allergic reaction after your treatment with Simponi. Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles.

- Some of these reactions may be serious or, rarely, life-threatening.
- Some of these reactions occurred after the first administration of Simponi.

Children and adolescents
Simponi is not recommended for children and adolescents (younger than 18 years) because it has not been studied in this age group.

Other medicines and Simponi

- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including any other medicines to treat rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis.
- You should not take Simponi with medicines containing the active substance anakinra or abatacept. These medicines are used for the treatment of rheumatic diseases.
- Tell your doctor or pharmacist if you are taking any other medicines that affect your immune system.
- You should not receive certain (live) vaccines while using Simponi.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using Simponi.

Pregnancy and breast-feeding
Talk to your doctor before using Simponi if:

- You are pregnant or are planning to become pregnant while using Simponi. The effects of this medicine in pregnant women are not known. The use of Simponi in pregnant women is not recommended. If you are being treated with Simponi, you must avoid becoming pregnant by using adequate contraception during your treatment and for at least 6 months after the last Simponi injection.
- You are a (potential) nursing mother. Before starting breast-feeding, your last treatment with Simponi must be at least 6 months ago. You must stop breast-feeding if you are to be given Simponi.
- If you received Simponi during your pregnancy, your baby may have a higher risk for getting an infection. It is important that you tell your baby's doctors and other health care professionals about your Simponi use before the baby receives any vaccine (for more information see section on vaccination).

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

Driving and using machines
Simponi may have a minor influence on your ability to drive and use tools or machines. Dizziness may occur after you take Simponi. If this happens, do not drive or use any tools or machines.

Simponi contains latex and sorbitol
Latex sensitivity
A part of the pre-filled syringe, the needle cover, contains latex. Because latex may cause severe allergic reactions, talk to your doctor before using Simponi if you or your carer are allergic to latex.

Sorbitol intolerance
Simponi contains sorbitol (E420). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to use Simponi

Always use this medicine exactly as your doctor or pharmacist has told you. You should check with your doctor or pharmacist if you are not sure.

How much Simponi is given
- The recommended dose is 50 mg given once a month, on the same date each month.
- Talk to your doctor before taking your fourth dose. Your doctor will determine if you should continue Simponi treatment.
    - If you weigh more than 100 kg, the dose might be increased to 100 mg (the content of 1 pre-filled syringe) given once a month, on the same date each month.

How Simponi is given
- Simponi is given by injection under the skin (subcutaneously).
- At the start, your doctor or nurse may inject Simponi. However, you and your doctor may decide that you may inject Simponi yourself. In this case you will get training on how to inject Simponi yourself.

Talk to your doctor if you have any questions about giving yourself an injection. You will find detailed "Instructions for administration" at the end of this leaflet.

If you use more Simponi than you should
If you have used or been given too much Simponi (either by injecting too much on a single occasion, or by using it too often), talk to your doctor or pharmacist straight away. Always take the outer carton with you, even if it is empty.

If you forget to use Simponi
If you forget to use Simponi on your planned date, inject the forgotten dose as soon as you remember.

Do not use a double dose to make up for a forgotten dose.

When to inject your next dose:
- If you were less than 2 weeks late, inject the forgotten dose as soon as you remember and stay on your original schedule.
- If you were more than 2 weeks late, inject the forgotten dose as soon as you remember and talk to your doctor or pharmacist to ask when you need to take the next dose.

If you are not sure what to do, talk to your doctor or pharmacist.

If you stop using Simponi
If you are considering stopping Simponi, talk to your doctor or pharmacist first.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some patients may experience serious side effects and may require treatment. The risk of certain side effects is greater with the 100 mg dose compared with the 50 mg dose. Side effects may appear up to several months after the last injection.

Tell your doctor straight away if you notice any of the following serious side effects of Simponi which include:
- **allergic reactions which may be serious, or rarely, life-threatening (rare).** Symptoms of an allergic reaction may include swelling of the face, lips, mouth or throat which may cause difficulty in swallowing or breathing, skin rash, hives, swelling of the hands, feet or ankles. Some of these reactions occurred after the first administration of Simponi.

- **serious infections (including TB, bacterial infections including serious blood infections and pneumonia, severe fungal infections and other opportunistic infections) (uncommon).** Symptoms of an infection can include fever, tiredness, (persistent) cough, shortness of breath, flu-like symptoms, weight loss, night sweats, diarrhoea, wounds, dental problems and a burning feeling when urinating.
- **reactivation of hepatitis B virus if you are a carrier or have had hepatitis B before (rare).** Symptoms can include yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever, feeling sick, being sick, and feeling very tired.
- **nervous system disease such as multiple sclerosis (uncommon).** Symptoms of nervous system disease can include changes in your vision, weakness in your arms or legs, numbness or tingling in any part of your body.
- **cancer of the lymph nodes (lymphoma) (rare).** Symptoms of lymphoma can include swelling of the lymph nodes, weight loss, or fever.
- **heart failure (uncommon).** Symptoms of heart failure can include shortness of breath or swelling of your feet.
- **signs of an immune system disorder called lupus (rare).** Symptoms can include joint pain or a rash on cheeks or arms that is sensitive to the sun.
- **blood disease.** Symptoms of blood disease can include a fever that does not go away, bruising or bleeding very easily or looking very pale.

Tell your doctor straight away if you notice any of the above symptoms.

The following additional side effects have been observed with Simponi:

Very common side effects (may affect more than 1 in 10 people):

- Upper respiratory tract infections, sore throat or hoarseness, runny nose

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

- Abnormal liver tests (increased liver enzymes) found during blood tests done by your doctor
- Feeling dizzy
- Headache
- Superficial fungal infections
- Bacterial infections (such as cellulitis)
- Low red blood cell counts
- Positive blood lupus test
- Difficulty sleeping
- Depression
- Constipation
- Hair loss
- Allergic reactions
- Rash and itching of the skin
- Indigestion
- Stomach pain
- Feeling sick (nausea)
- Feeling numb or having a tingling feeling
- Flu
- Bronchitis
- Sinus infection
- Cold sores
- High blood pressure
- Fever
- Injection site reactions (including redness, hardness, pain, bruising, itching, tingling and irritation)
- Feeling weak
- Impaired healing
- Chest discomfort

Uncommon side effects (may affect up to 1 in 100 people):
- Infection of the joints or the tissue around them
- Kidney infection
- Abscess
- cancers, including skin cancer and non-cancerous growths or lumps, including skin moles
- Psoriasis (including on the palms of your hand and/or the soles of your feet and/or in the form of skin blisters)
- Low platelet count
- Low white blood cell counts
- Combined low platelet, red, and white blood cell count
- Thyroid disorders
- Increase in blood sugar levels
- Increase in blood cholesterol levels
- Balance disorders
- Taste disturbances
- Vision disturbances
- Sensation of heart beating irregularly
- Narrowing of the blood vessels in the heart
- Blood clots
- Pain and discoloration in the fingers or toes
- Flushing
- Asthma, shortness of breath, wheezing
- Stomach and bowel disorders which include inflammation of the stomach lining and colon which may cause fever
- Acid reflux
- Pain and ulcers in the mouth
- Gall stones
- Liver disorders
- Bladder disorders
- Breast disorders
- Menstrual disorders
- Bone fractures
- Inflammation of the blood vessels in your skin which results in rash

Rare side effects (may affect up to 1 in 1,000 people):
- Chronic inflammatory condition of the lungs
- Kidney disorders
- Inflammation of blood vessels in internal organs
- Leukaemia
- Melanoma (a type of skin cancer)
- Scaly, peeling skin
- Immune disorders that could affect the lungs, skin and lymph nodes (most commonly presenting as sarcoidosis)

Side effects of which the frequency is not known:
- Failure of the bone marrow to produce blood cells
- Merkel cell carcinoma (a type of skin cancer)

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

5. How to store Simponi

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C-8°C). Do not freeze.
- Keep the pre-filled syringe in the outer carton in order to protect it from light.
- Do not use this medicine if you notice that the liquid is not a clear to light yellow colour, cloudy, or contains foreign particles.
- Do not throw away any medicines via wastewater or household waste. Ask your doctor or pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Simponi contains
The active substance is golimumab. One 1 ml pre-filled syringe contains 100 mg of golimumab.
The other ingredients are sorbitol (E420), L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80 and water for injections.

What Simponi looks like and contents of the pack
Simponi is supplied as solution for injection in a single-use pre-filled syringe Simponi is available in packs containing 1 pre-filled syringe and multipacks containing 3 (3 packs of 1) pre-filled syringes. Not all pack sizes may be marketed.

The solution is clear to slightly opalescent (having a pearl-like shine), colourless to light yellow and may contain a few small translucent or white particles of protein. Do not use Simponi if the solution is discoloured, cloudy or you can see foreign particles in it.

Marketing Authorisation Holder and Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
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The Netherlands

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

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

INSTRUCTIONS FOR ADMINISTRATION

If you would like to self inject Simponi, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your doctor, nurse or pharmacist to schedule a training session.

In these instructions:
1. Preparing for use of the syringe
2. Choosing and preparing the injection site
3. Injecting the medicine
4. After the injection

The diagram below (see figure 1) shows what the pre-filled syringe looks like. In this leaflet "pre-filled syringe" may sometimes be shortened to "syringe".

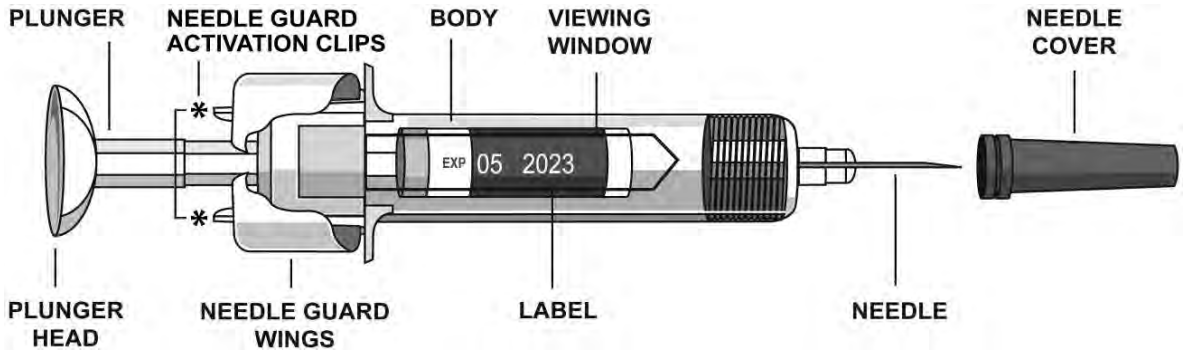

Figure 1

1. Preparing for use of the syringe
Hold the pre-filled syringe by the body of the syringe

- Do not hold by the plunger head, plunger, needle guard wings, or needle cover.
- Do not pull back on the plunger at any time.
- Do not shake the pre-filled syringe at any time.
- Do not remove the needle cover from the pre-filled syringe until instructed to do so.
- Do not touch the needle guard activation clips (as indicated by asterisks * in figure 1) to prevent prematurely covering the needle with the needle guard.

Check the number of pre-filled syringes
Check the pre-filled syringes to make sure
- the number of pre-filled syringes and strength is correct
  - If your dose is 100 mg, you will get one 100 mg pre-filled syringe

Check expiry date (see figure 2)
- Check the expiration date (as indicated by "EXP") on the label by looking through the viewing window located within the body of the pre-filled syringe.
- If you cannot see the expiration date through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the expiration date to the viewing window.
- You can also check the expiration date printed on the carton.

Do not use the pre-filled syringe if the expiration date has passed. The expiration date refers to the last day of the month. Please contact your doctor or pharmacist for assistance.

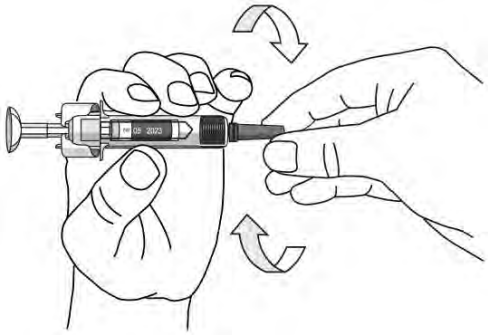

Figure 2

Wait 30 minutes to allow syringe to reach room temperature

- To ensure proper injection, allow the syringe to sit at room temperature outside the box for 30 minutes, out of the reach of children.

Do not warm the syringe in any other way (for example, do not warm it in a microwave or in hot water).
Do not remove the syringe's needle cover while allowing it to reach room temperature.

Get the rest of your equipment ready

While you are waiting you can get the rest of your equipment ready, including an alcohol swab, a cotton ball or gauze and a sharps container.

Check the liquid in the syringe

- Hold the pre-filled syringe by its body with the covered needle pointing downward.
- Look at the liquid through the viewing window of the syringe and make sure that it is clear to slightly opalescent (having a pearl-like shine) and colourless to light yellow. The solution can be used if it contains a few small translucent or white particles of protein.
- If you cannot see the liquid through the viewing window, hold the pre-filled syringe by its body and rotate the needle cover to line up the liquid to the viewing window (see figure 2).

Do not use the syringe if the liquid is the wrong colour, cloudy, or contains larger particles. If this happens, talk to your doctor or pharmacist.

2. Choosing and preparing the injection site (see figure 3)

- You usually inject the medicine into the front of the middle thighs.
- You can also use the lower stomach (abdomen) below the belly button, except for approximately the 5 cm area directly underneath the belly button.
- Do not inject into areas where the skin is tender, bruised, red, scaly, hard or has scars or stretch marks.
- If multiple injections are required, the injections should be administered at different sites on the body.

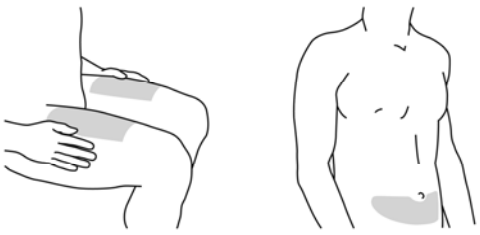

Figure 3

Injection site selection for caregivers (see figure 4)

- If a caregiver is giving you the injection, they can also use the outer area of the upper arms.
- Again, all sites mentioned can be used regardless of your body type or size.

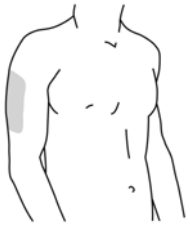

Figure 4

Preparing injection site

- Wash your hands thoroughly with soap and warm water.
- Wipe the injection site with an alcohol swab.
- Allow the skin to dry before injecting. Do not fan or blow on the clean area.

Do not touch this area again before giving the injection.

3. Injecting the medicine

The needle cover should not be removed until you are ready to inject the medication. The medication should be injected within 5 minutes after the needle cover has been removed.

Do not touch the plunger during needle cover removal.

Remove the needle cover (see figure 5)

- When you are ready to inject, hold the body of the syringe with one hand.
- Pull the needle cover straight off and throw it away after your injection. Do not touch the plunger while you do this.
- You may notice an air bubble in the pre-filled syringe or a drop of liquid at the end of the needle. These are both normal and do not need to be removed.
- Inject the dose promptly after removing the needle cover.

Do not touch the needle or allow it to touch any surface.
Do not use the syringe if it is dropped without the needle cover in place. If this happens, please contact your doctor or pharmacist.

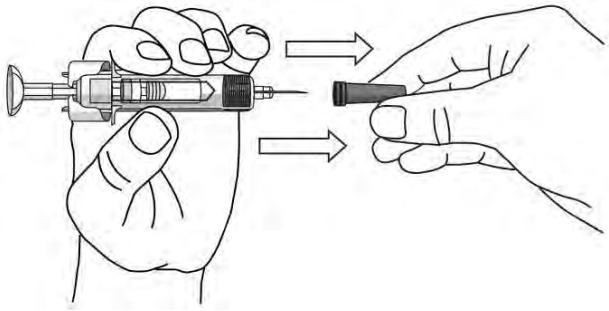

Figure 5

Position the syringe to inject

- Hold the body of the syringe with one hand between the middle and index fingers and place the thumb on top of the plunger head and use the other hand to gently pinch the area of skin that you previously cleaned. Hold firmly.

Do not pull back on the plunger at any time.

Inject the medicine

- Place the needle at approximately a 45-degree angle to the pinched skin. In a single and swift motion, insert the needle through the skin as far as it will go (see figure 6).

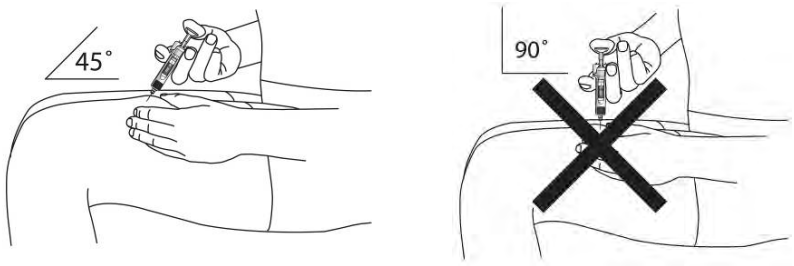

Figure 6

- Inject all of the medication by pushing in the plunger until the plunger head is completely between the needle guard wings (see figure 7).

Figure 7

- When the plunger is pushed as far as it will go, continue to keep the pressure on the plunger head, take out the needle and let go of the skin (see figure 8).

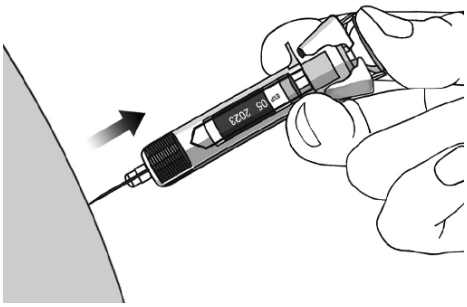

Figure 8

- Slowly take your thumb off the plunger head to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the figure 9:

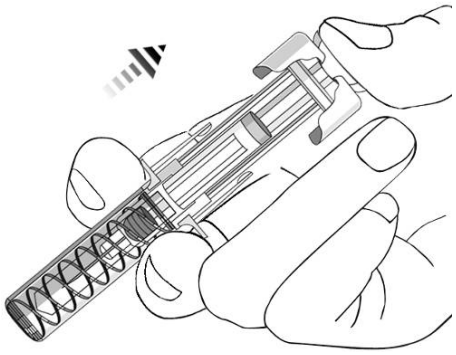

Figure 9

4. After the injection

Use cotton ball or gauze

- There may be a small amount of blood or liquid at the injection site. This is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.
- You may cover the injection site with a small adhesive bandage, if necessary.

Do not rub your skin.

Throw the syringe away (see figure 10)

- Place your syringe in a sharps container straight away. Make sure you dispose of the bin as instructed by your doctor or nurse.

Do not attempt to recap the needle.
Do not ever re-use a syringe, for your safety and health and for the safety of others.

If you feel that something has gone wrong with the injection or if you are not sure, talk to your doctor or pharmacist.

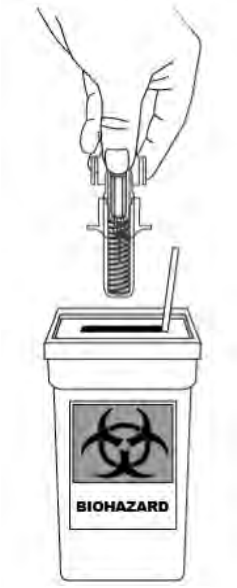

Figure 10