PROPOSED CLEAN PROFESSIONAL INFORMATION (PI)

SCHEDULING STATUS

Schedule 4

1 NAME OF THE MEDICINE

SIMPONI® 45 mg/0,45 mL solution for injection in pre-filled pen.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One pre-filled pen contains 45 mg golimumab* in 0,45 mL. 1 mL solution contains 100 mg golimumab.

Each pre-filled pen can deliver 0,1 mL to 0,45 mL (corresponding to 10 mg to 45 mg golimumab) in increments of 0,05 mL.

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

Contains sugar (sorbitol).

Each pre-filled pen contains 18,45 mg sorbitol (E420) per 45 mg dose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection in pre-filled pen (injection), Varioject.

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis (pJIA)

SIMPONI in combination with methotrexate (MTX) is indicated for the treatment of polyarticular juvenile idiopathic arthritis in children 2 years of age and older, who have responded inadequately to previous therapy with MTX.

4.2 Posology and method of administration

Treatment is to be initiated and supervised by qualified medical practitioners experienced in the diagnosis and treatment of conditions for which SIMPONI is indicated.

Posology

The 45 mg/0,45 mL pre-filled pen is for paediatric patients. Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

Paediatric population

Juvenile idiopathic arthritis

Polyarticular juvenile idiopathic arthritis in children with body weight less than 40 kg

The recommended dose of SIMPONI for children with a body weight less than 40 kg with polyarticular juvenile idiopathic arthritis is 30 mg/m^2 body surface area up to maximum single dose of 40 mg administered once a month, on the same date each month. The prescribed volume of injection should be selected according to patient's height and weight as shown in Table 1.

Table 1: SIMPONI dose in millilitres (mL) by height and weight of patients with pJIA

		Total Body Weight (kg)						
		10-12	13-17	18-22	23-27	28-32	33-37	38-39
		Dose (mL)						
Height (cm)	70 to < 75	0,15	0,15	0,2				
	75 to < 85	0,15	0,15	0,2	0,2			
	85 to < 95	0,15	0,2	0,2	0,25	0,25	0,3	
	95 to < 105	0,15	0,2	0,2	0,25	0,25	0,3	0,3
	105 to < 115	0,15	0,2	0,25	0,25	0,3	0,3	0,3
	115 to < 125	0,2	0,2	0,25	0,25	0,3	0,3	0,35
	125 to < 135		0,2	0,25	0,3	0,3	0,35	0,35
	135 to < 145		0,25	0,25	0,3	0,3	0,35	0,35
	145 to < 155			0,25	0,3	0,35	0,35	0,4
	155 to < 165			0,3	0,3	0,35	0,35	0,4
	165 to < 175				0,35	0,35	0,4	0,4
	175 to < 180					0,35	0,4	0,4

Polyarticular juvenile idiopathic arthritis in children with a body weight of at least 40 kg

For children with body weight of at least 40 kg, a 50 mg pre-filled pen or pre-filled syringe is available. For the posology of the 50 mg dosing regimen, see section 4.2 of the SIMPONI 50 mg pre-filled pen or pre-filled syringe professional information.

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 children who show no evidence of therapeutic benefit within this time period.

There is no relevant use of SIMPONI in patients aged less than 2 years for the indication of pJIA.

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

Special populations

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 have not been established in patients with pJIA below the age of 2 years. No data are available.

Method of administration

SIMPONI is for subcutaneous use. After proper training in subcutaneous injection technique, patients may self-inject if their medical practitioner determines that this is appropriate, with medical follow-up as necessary. Patients should be instructed to inject the prescribed amount of SIMPONI according to the comprehensive instructions for use provided in the pack.

4.3 Contraindications

SIMPONI is contraindicated in:

- Patients with a known hypersensitivity to the active substance, golimumab, or to any of the excipients listed in section 6.1
- Active mycobacterium tuberculosis infection (TB) or other severe infections such as sepsis, and opportunistic infections (see section 4.4: Infections and Tuberculosis)
- Moderate or severe heart failure (NYHA class III/IV) (see section 4.4: Congestive heart failure).
- Patients receiving live vaccines (see section 4.4: Live vaccines/Therapeutic infectious medicines and section 4.5).
- Lymphomas.
- Active demyelating pathology of the nervous system (see section 4.4: Demyelinating disorders).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Infections

Infections, some serious and with fatal outcome have been reported in patients receiving TNF blocking medicines including SIMPONI. Infections reported were caused by bacterial (including sepsis and pneumonia), viral, mycobacterial (tuberculosis), invasive fungal and opportunistic pathogens including Legionella and Listeria. Patients have frequently presented with disseminated rather than localised disease. 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.

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 or continuation of SIMPONI therapy. In at-risk patients treated with SIMPONI, an invasive fungal infection should be suspected if they develop serious systemic illness. Antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while diagnostic workup is being performed. The decision to administer empiric antifungal therapy should be made, if feasible, in consultation with a medical practitioner with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy.

SIMPONI should not be given to patients with an active infection, 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.

Tuberculosis

Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent tuberculosis infections prior to treatment with SIMPONI. Treatment of latent tuberculosis infection should be initiated prior to therapy with SIMPONI (see section 4.3).

Anti-tuberculosis therapy should be considered prior to initiation of SIMPONI in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed.

Tests for latent tuberculosis may yield false negative results, especially in patients who are immunocompromised or severely ill. Prior to initiating SIMPONI**,** treatment for latent TB should be considered in patients who have significant risk factors for TB despite a negative test for latent tuberculosis. The decision to initiate anti-tuberculosis therapy in these patients should only be made following consultation with a medical practitioner with expertise in the treatment of tuberculosis and taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy.

In patients receiving SIMPONI, tuberculosis has frequently presented as disseminated or extrapulmonary disease. 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.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hepatitis B virus reactivation

SIMPONI has been associated with reactivation of Hepatitis B virus (HBV) in patients who are chronic carriers of the virus (i.e. surface antigen positive). Patients should be tested for HBV infection before initiating treatment with SIMPONI. For patients who test positive for hepatitis B surface antigen, consultation with a medical practitioner with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of, during treatment with, and for several months following discontinuation of SIMPONI.

Malignancies

The potential role of TNF-blocking therapy in the development of malignancies is not known. Caution should be exercised when considering SIMPONI 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 medicines (initiation of therapy ≤ 18 years of age) in the post marketing setting. Approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. A risk for the development of malignancies in children and adolescents treated with SIMPONI cannot be excluded.

Lymphoma

In the controlled portions of clinical trials more cases of lymphoma have been observed among patients receiving SIMPONI treatment compared with control patients.

Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking medicines, such as SIMPONI (see section 4.8). This type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Nearly all of these cases have occurred in patients with Crohn's disease or ulcerative colitis. The majority were in adolescent and young adult males. Almost all these patients had received treatment with azathioprine (AZA) or 6-mercaptopurine (6–MP) concomitantly with a TNF-blocker at or prior to diagnosis. The potential risk with the combination of AZA or 6-MP and SIMPONI should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Leukaemia

Cases of acute and chronic leukaemia have been reported with TNF-blocker use, including SIMPONI, in rheumatoid arthritis and other indications.

Malignancies other than lymphoma

In the controlled portions of the SIMPONI Phase 2 and Phase 3 clinical trials in Rheumatoid arthritis (RA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), and ulcerative colitis (UC), the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the SIMPONI and the control groups.

In an exploratory trial evaluating the use of SIMPONI in patients with severe persistent asthma, more patients treated with SIMPONI reported malignancies compared with control patients (see section 4.8).

Colon dysplasia/carcinoma

It is not known if SIMPONI treatment influences the risk for developing dysplasia or colon cancer. Therefore, ulcerative colitis patients should be screened at regular intervals before therapy and throughout the disease course.

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF blocking medicines, including SIMPONI (see section 4.8). Periodic skin examination is recommended for all patients, particularly those 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 SIMPONI. Some cases had a fatal outcome. SIMPONI should be used with caution in patients with heart failure. If a decision is made to administer SIMPONI to patients with heart failure, they should be closely monitored during therapy and SIMPONI should be discontinued if new or worsening symptoms of heart failure appear (see section 4.3).

Demyelinating disorders

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 (MS) and peripheral demyelinating disorders,

including Guillan-Barré syndrome. SIMPONI should be discontinued if these disorders develop.

Autoimmune processes

Treatment with TNF blockers, including SIMPONI, may result in the formation of antinuclear antibodies (ANA) and rarely, in the development of a lupus-like syndrome (see section 4.8). If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with SIMPONI, treatment should be discontinued.

Haematologic reactions

There have been reports of pancytopenia, leukopenia, neutropenia, agranulocytosis and/or thrombocytopenia in patients receiving TNF-blockers, including SIMPONI. Caution should be exercised in patients treated with SIMPONI who have a current or past history of significant cytopenias.

Concurrent administration of SIMPONI and anakinra

Serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking medicine, with no added clinical benefit. Similar toxicities may also result from the combination of anakinra and SIMPONI. Therefore, the combination of SIMPONI and anakinra is not recommended.

Concurrent administration of SIMPONI and abatacept

In clinical studies, concurrent administration of TNF-blocking medicines and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking medicines alone, without increased clinical benefit. Because of the nature of the adverse events seen with the combination of TNF-blocking

medicines and abatacept therapy, 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.

Switching between biological therapeutics

When switching from one biologic to another, patients should continue to be monitored, since overlapping biological activity may further increase the risk of infection.

Live vaccines/Therapeutic infectious medicines

Patients treated with SIMPONI may receive concurrent vaccinations, except for live vaccines (see section 4.3). Use of live vaccines could result in clinical infections, including disseminated infections.

Other uses of therapeutic infectious medicines such as live attenuated bacteria (e.g. BCG bladder instillation for the treatment of cancer) could result in clinical infections, including disseminated infections. It is recommended that therapeutic infectious medicines not be given concurrently with SIMPONI.

Non-live vaccines

Psoriatic arthritis patients treated with SIMPONI in one Phase 3 PsA study were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine. Similar numbers of psoriatic arthritis patients receiving SIMPONI and not receiving SIMPONI had at

least a 2-fold increase in antibody titers. The proportions of patients with response to pneumococcal vaccine were lower among SIMPONI and control-treated patients receiving MTX compared with patients not receiving MTX. Overall, the data indicate that SIMPONI does not suppress the humoral immune response to this vaccine.

Allergic reactions

Hypersensitivity 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 occurs, administration of SIMPONI should be discontinued immediately and appropriate therapy instituted.

Latex sensitivity

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

Special populations

Geriatric use

In the Phase 3 SC studies in RA, PsA, AS, and UC, no overall differences in adverse events (AEs), serious adverse events (SAEs), and serious infections in patients age 65 or older who received SIMPONI were observed compared with younger patients. In UC, there were insufficient numbers of patients aged 65 and over to determine whether they respond differently from patients aged 18 to 65. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

There were no patients aged 65 and over in the nr-Axial SpA study.

Paediatrics

Vaccinations

If possible, it is recommended that prior to initiating SIMPONI therapy, paediatric patients be brought up to date with all immunisations in agreement with current immunisation guidelines (see Live vaccines/Therapeutic infectious medicines above).

Excipients

SIMPONI contains sorbitol. Patients with the rare hereditary condition of sorbitol intolerance should not be given SIMPONI.

Potential for medication errors

It is important that the correct dose is administered as indicated in the posology (see section 4.2). Care should be taken to ensure that patients are not underdosed or overdosed.

4.5 Interaction with other medicines 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/therapeutic infectious medicines

Live vaccines should not be given concurrently with SIMPONI (see sections 4.3 and 4.4).

Therapeutic infectious medicines should not be given concurrently with SIMPONI (see section 4.4).

Methotrexate

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

4.6 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 SIMPONI treatment.

Pregnancy

SIMPONI should not be used in pregnant women (see section 4.3).
Women of childbearing potential should be advised not to become pregnant during SIMPONI therapy and should use appropriate contraceptives.

SIMPONI crosses the placenta. Infants exposed during pregnancy to SIMPONI may be at increased risk of infection and administration of live vaccines to infants exposed to SIMPONI *in utero* is not recommended for 6 months following the mother's last injection during pregnancy (see sections 4.4 and 4.5).

Lactation

It is not known whether golimumab is excreted in human breast milk. SIMPONI should not be used in mothers who are breastfeeding their babies (see section 4.3).

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 cause dizziness. Patients should not drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Clinical trial data

Summary of the safety profile

In the controlled period of the pivotal trials in RA, PsA, AS, nr-Axial SpA, and UC, upper respiratory tract infection was the most common adverse reaction (AR) reported in 12,6 % of SIMPONI-treated patients compared with 11,0 % of control patients. The most serious Adverse Reactions (ARs) that have been reported for SIMPONI include serious infections (including sepsis, pneumonia, TB, invasive fungal and opportunistic infections), demyelinating disorders, HBV reactivation, CHF, autoimmune processes (lupus-like syndrome), haematologic reactions, serious systemic hypersensitivity (including anaphylactic reaction), vasculitis, lymphoma and leukaemia (see section 4.4).

Tabulated list of adverse reactions (ARs)

ARs observed in clinical studies of SIMPONI are listed in Table 2. Within the designated system organ classes, the ARs 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Tabulated list of ARs

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (such as pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis
Rare:	Tuberculosis, opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis (pneumocystis jiroveci)], bacterial (including Listeria and Legionella), atypical mycobacterial infection and protozoal), hepatitis B reactivation, bacterial arthritis, infective bursitis
Neoplasms, benign, malignant and unspecified	
Uncommon:	Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus)
Rare:	Lymphoma, leukaemia
Blood and lymphatic system disorders	

Common:	Leukopenia (including neutropenia), anaemia
Uncommon:	Thrombocytopenia, pancytopenia
Rare:	Aplastic anaemia, agranulocytosis
Immune system disorders	
Common:	Allergic reactions (bronchospasm, hypersensitivity, urticaria), autoantibody positive
Rare:	Vasculitis (systemic)
Endocrine disorders	
Uncommon:	Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)
Metabolism and nutrition disorders	
Uncommon:	Increased blood glucose, increased lipids
Psychiatric disorders	
Common:	Depression, insomnia
Nervous system disorders	
Common:	Dizziness, headache, paraesthesia
Uncommon:	Balance disorders
Rare:	Demyelinating disorders (central and peripheral), 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:	Arrhythmia, ischemic coronary artery disorders
Rare:	Congestive heart failure (new onset or worsening)

Vascular disorders	
Common:	Hypertension
Uncommon:	Thrombosis (such as deep venous and aortic), flushing
Rare:	Raynaud's phenomenon
Respiratory, thoracic and mediastinal disorders	
Common:	Asthma and related symptoms (such as wheezing and bronchial hyperactivity)
Uncommon:	Interstitial lung disease
Gastrointestinal disorders	
Common:	Dyspepsia, gastrointestinal and abdominal pain, nausea, gastrointestinal inflammatory disorders (such as gastritis and colitis), stomatitis
Uncommon:	Constipation, gastro-oesophageal reflux disease
Hepatobiliary disorders	
Common:	Increased alanine aminotransferase, increased aspartate aminotransferase
Uncommon:	Cholelithiasis, hepatic disorders
Skin and subcutaneous tissue disorders	
Common:	Pruritus, rash, alopecia, dermatitis
Uncommon:	Psoriasis (new onset or worsening of pre-existing psoriasis, palmar/plantar and pustular), urticaria
Rare:	Vasculitis (cutaneous)
Musculoskeletal and connective tissue disorders	

Rare:	Lupus-like syndrome
Renal and urinary disorders	
Rare:	Bladder disorders, 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), chest discomfort
Rare:	Impaired healing
Injury, poisoning and procedural complications	
Common:	Bone fractures

Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all SIMPONI use. Where SIMPONI use is described by dose, the median duration of follow-up varies (approximately 2 years for 50 mg dose, approximately 3 years for 100 mg dose) as patients may have switched between doses.

Description of selected adverse reactions

Infections

In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12,6 % of SIMPONI-treated patients (incidence per 100 subject-years: 60.8; 95 % CI: 55.0, 67.1) compared with 11,0 % of control patients (incidence per 100 subject-years: 54.5; 95% CI: 46.1, 64.0). In controlled and

uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per 100 subject-years of upper respiratory tract infections was 34,9 events; 95% CI: 33.8, 36.0 for SIMPONI treated patients.

In the controlled period of pivotal trials, infections were observed in 23,0 % of SIMPONI-treated patients (incidence per 100 subject-years: 132.0; 95% CI: 123.3, 141.1) compared with 20,2 % of control patients (incidence per 100 subject-years: 122.3; 95% CI: 109.5, 136.2). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per 100 subject-years of infections was 81,1 events; 95% CI: 79.5, 82.8 for SIMPONI treated patients.

Serious infections observed in SIMPONI-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections and tuberculosis.

In the controlled period of RA, PsA, AS, UC and nr-Axial SpA trials, serious infections were observed in 1,2 % of SIMPONI-treated patients and 1,2 % of control-treated patients. The incidence of serious infections per 100 subject-years of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 7.3; 95% CI: 4.6, 11.1 for the golimumab 100 mg group, 2.9; 95% CI: 1.2, 6.0 for the golimumab 50 mg group and 3.6; 95% CI: 1.5, 7.0 for the placebo group.
In the controlled period of UC trials of SIMPONI induction, serious infections were observed in 0,8 % of SIMPONI-treated patients compared with 1,5% of control-treated patients.

In the controlled and uncontrolled portions of the pivotal trials with a median follow up of up to 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB, in patients receiving golimumab 100 mg compared with patients

receiving golimumab 50 mg. The incidence per 100 subject-years of all serious infections was 4.1; 95% CI: 3.6, 4.5, in patients receiving golimumab 100 mg and 2.5; 95% CI: 2.0, 3.1, in patients receiving golimumab 50 mg

These results may be confounded by the designs of the pivotal trials and different durations of follow up across treatment groups.

Malignancies

Lymphoma

The incidence of lymphoma in SIMPONI-treated patients during the pivotal trials was higher than expected in the general population.

In the controlled and uncontrolled portions of these trials with a median follow up of to 3 years, a greater incidence of lymphoma was observed in patients receiving golimumab 100 mg compared with patients receiving golimumab 50 mg. These results may be confounded by the small number of events, designs of the Phase 3 studies, and different durations of follow-up across treatment groups. The majority of lymphomas occurred in the RA, Study 2, which enrolled patients previously exposed to anti-TNF medicines who had longer disease duration and more refractory disease.

Malignancies other than lymphoma

In the controlled periods of pivotal trials, the incidence of non-lymphoma malignancies (excluding nonmelanoma skin cancer) was similar between the golimumab and the control groups. Through approximately 4 years of follow-up, the incidence of non-lymphoma malignancies (excluding nonmelanoma skin cancer) was similar to the general population.

In an exploratory clinical trial involving patients with severe persistent asthma, more patients treated with golimumab had malignancies compared with control patients. The potential role of TNF-blocking therapy in the development of malignancies is unknown.

Neurological events

In the controlled and uncontrolled periods of the pivotal trials with a median follow-up of up to 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). These results may be confounded by the small number of events, designs of the pivotal trials, and different durations of follow-up across treatment groups.

Liver enzyme elevations

In the controlled period of RA and PsA pivotal trials, mild ALT elevations (> 1 and < 3 x upper limit of normal (ULN)) occurred in similar proportions of SIMPONI and control patients (22,1 % to 27,4 % of patients); in the AS and nr-Axial SpA studies, more SIMPONI-treated patients (26,9 %) than control patients (10,6 %) had mild ALT elevations. In the controlled and uncontrolled periods of the RA and PsA pivotal trials, with a median follow-up of approximately 5 years, the incidence of mild ALT elevations was similar in the SIMPONI-treated and control patients. In the AS pivotal trial, the incidence of mild ALT elevations was higher in the SIMPONI-treated patients than in control patients.

In the controlled period of the UC pivotal trials of SIMPONI induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of SIMPONI-treated and control patients (8,0 % to 6,9 %, respectively). In controlled and uncontrolled periods of the UC pivotal trials with a median follow-up of approximately 2 years, the proportion of patients

with mild ALT elevations was 24,7 % in patients receiving SIMPONI during the maintenance portion of the UC study.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more SIMPONI-treated patients (0,4 % to 0,9 %) than control patients (0,0%). This trend was not observed in the PsA population. In the controlled and uncontrolled periods of RA, PsA and AS pivotal trials, with a median follow-up of 5 years, the incidence of ALT elevations ≥ 5 x ULN was similar in both SIMPONI-treated and control patients. The majority of these elevations were asymptomatic.

No cases were reported in the controlled and uncontrolled periods of the nr-Axial SpA study (up to 1 year).

In the controlled periods of the pivotal UC trials, of SIMPONI induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of SIMPONI-treated patients compared to placebo-treated patients (0,3 % to 1,0 %, respectively). In the controlled and uncontrolled periods of the pivotal UC trials with a median follow-up of approximately 2 years, the proportion of patients with ALT elevations ≥ 5 x ULN was 0,8% in patients receiving SIMPONI during the maintenance portion of the UC study.

Administration reactions

In the controlled periods of pivotal trials, 5,4 % of SIMPONI-treated patients had injection site reactions compared with 2,0 % in control patients. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema.

Antinuclear antibodies (ANA)/anti-double-stranded DNA (dsDNA) antibodies

Use of TNF blocking medicines has been associated with the formation of auto-antibodies and in the development of a lupus-like syndrome.

In the controlled and uncontrolled periods of pivotal trials through 1 year of follow-up, 3,5 % of SIMPONI-treated patients and 2,3 % 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 1,1 %.

Paediatric population

Polyarticular juvenile idiopathic arthritis

The safety of SIMPONI has been studied in a phase 3 study of 173 pJIA patients from 2 to 17 years of age. The average follow-up was approximately two years. In this study, the type and frequency of adverse events reported were generally similar to those seen in adult RA studies.

Post marketing experience

Immune system disorders

Serious systemic hypersensitivity reactions (including anaphylactic reaction), sarcoidosis

Skin and subcutaneous tissue disorders

Skin exfoliation, bullous skin reaction, Lichenoid reactions

Neoplasm benign and malignant

Melanoma, Merkel cell carcinoma, hepatosplenic T-cell Lymphoma*

* Observed with other TNF-blocking medicines

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 tumour necrosis factor (TNF), which prevents the binding of TNF to its receptors.

Pharmacodynamic effects

The binding of human TNF by golimumab was shown to neutralise TNF-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. 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.

Clinical studies

In clinical studies golimumab was effective in modulating select markers of inflammation and bone metabolism. Improvement in C-reactive protein (CRP) levels were observed and treatment with golimumab resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix metalloproteinase-3 (MMP-3) and vascular endothelial growth factor (VEGF). In addition, levels of TNFα were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients.

5.2 Pharmacokinetic studies

Absorption

Following a single subcutaneous (SC) administration of golimumab to healthy subjects or patients with Rheumatoid arthritis (RA), the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A SC injection of 50 mg golimumab to healthy subjects produced a mean $\pm$ standard deviation maximum serum concentration (C_{max}) of 3,1 $\pm$ 1,4 μg/mL. Both C_{max} and area under the concentration-time curve (AUC) increased proportionally with doses over the range of 50 to 400 mg following a single SC administration.

Following a single SC injection of 100 mg in healthy subjects, 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 SC administration, the absolute bioavailability of a golimumab 50 mg or 200 mg dose is expected to be similar to the 100 mg dose.

Distribution

Following a single IV administration over the dose range of 0,1 to 10,0 mg/kg in patients with active RA, mean volume of distribution ranged from 58 to 126 mL/kg. The volume of distribution for golimumab indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Metabolism

The exact metabolic pathway of golimumab is unknown.

Elimination

Following a single IV administration, the mean systemic clearance of golimumab was estimated to be 6,9 ± 2,0 mL/day/kg in healthy subjects and 7,6 ± 2,0 mL/day/kg in patients with RA. Terminal half life was consistent between IV and SC administration of golimumab. The terminal half-life was estimated to be 12 ± 3 days in healthy subjects and similar half-life was observed in patients with RA, Psoriatic arthritis (PsA), Ankylosing spondylitis (AS) or Ulcerative colitis (UC).

Population pharmacokinetic analysis in patients with RA also indicated that concomitant use of MTX could reduce the apparent clearance of golimumab by 17,1 %. However, concomitant use of non-steroidal anti-inflammatory medicines, oral corticosteroids or sulfasalazine, were not found to influence the apparent clearance of golimumab.

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

Dose linearity

Following a single IV dose in patients with RA, golimumab exhibited dose-proportional pharmacokinetics over a dose range of 0,1 to 10,0 mg/kg. Following a single SC dose in healthy subjects, dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Single dose versus multiple doses

When 50 mg golimumab was administered SC 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 SC every 4 weeks resulted in a mean steady-state trough serum concentration of approximately 0,6 μg/mL in RA patients with active RA despite MTX therapy, and approximately 0,5 μg/mL in patients with active PsA and approximately 0,6 μg/mL in patients with AS. Patients with RA, PsA or AS who did not receive concomitant use of MTX had approximately 30 % lower steady-state trough concentrations of golimumab than those who received golimumab with MTX.

Following induction doses of 200 mg and 100 mg golimumab SC at week 0 and 2 respectively, and maintenance doses of 100 mg golimumab SC every 4 weeks thereafter in patients with UC, serum golimumab concentrations reached steady-state approximately 14 weeks after the start of therapy. Treatment with 100 mg golimumab SC every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 1,8 ± 1,1 μg/mL. Concomitant use of immunomodulators did not have any

apparent effect on steady state trough levels of golimumab when 100 mg golimumab was administered SC every 4 weeks to UC patients

Effect of weight on pharmacokinetics

Population pharmacokinetic analyses showed there was a trend toward higher apparent clearance of golimumab with increasing weight. However, subgroup analyses by weight quartiles did not demonstrate a meaningful difference in clinical efficacy between the different dose groups. Treatment with the recommended dose regimen of golimumab in UC patients did not result in meaningful differences in clinical efficacy among the different weight subgroups. Therefore, there is no need to adjust the dosage of golimumab based on the patient's weight.

Paediatric population

The pharmacokinetics of golimumab were determined in 173 children with pJIA with an age range from 2 to 17 years of age. In the pJIA study, children who received golimumab 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks, had median steady-state trough golimumab concentrations which were similar across different age groups, and which were also similar to or slightly higher than those seen in adult RA patients who received 50 mg golimumab every 4 weeks.

Population pharmacokinetic/pharmacodynamic modelling and simulation in children with pJIA confirmed the relationship between golimumab serum exposures and clinical efficacy and supports the dosing regimen of golimumab 30 mg/m^2 every 4 weeks in children with pJIA.

Immunogenicity:

Following SC administration in patients with RA, PsA or AS, antibodies to golimumab, nearly all neutralising *in vitro*, were detected in 5 % of golimumab treated patients through week 52. 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 % versus 8 %, respectively).

Following SC administration in patients with nr-Axial SpA, antibodies to golimumab, all neutralising *in vitro,* were detected in 4 % of golimumab treated patients through week 16.

Following SC administration in UC patients, antibodies to golimumab were detected in 2,7 % of golimumab-treated patients through week 54. Sixty-eight percent of antibody-positive patients had neutralising antibodies *in vitro.* Treatment with concomitant immunomodulators (azathioprine, 6-mercaptopurine and MTX) resulted in a lower portion of patients with antibodies to golimumab than patients receiving golimumab without immunomodulators (1,3 % versus 3,4 % respectively).

In the Phase 3 pJIA study through Week 48, antibodies to golimumab were detected by the drug-tolerant EIA method in 40% of golimumab-treated children following SC administration, of which a majority had a titer lower than 1:1000. An effect on serum golimumab concentrations was seen at titers of > 1:100 while an effect on efficacy was not seen until titers of > 1:1000, though the numbers of children with titers of > 1:1000 were low (N=8). Among the children who tested positive for antibodies to golimumab, 39 % had neutralising antibodies. The higher incidence of antibodies with the drug-tolerant EIA method, because

they were mainly low titer antibodies, did not have an apparent impact on drug levels, efficacy and safety and therefore does not represent any new safety signal

The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

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

5.3 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 SIMPONI.

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)

Histidine

Histidine hydrochloride monohydrate

Polysorbate 80

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

Do not freeze.

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

SIMPONI may be stored at temperatures up to a maximum of 25 °C for a single period of up to 30 days, but not exceeding the original expiry date printed on the carton. The new expiry date must be written on the carton (up to 30 days from the date removed from the refrigerator).

Once SIMPONI has been stored at room temperature, it should not be returned to refrigerated storage. SIMPONI must be discarded if not used within the 30 days of room temperature storage.

6.5 Nature and contents of container

SIMPONI 45 mg/0,45 mL solution for injection

0,45 mL solution in a pre-filled syringe (Type 1 glass) with a fixed needle (stainless steel) and a needle cover (rubber containing latex) in a pre-filled pen. Each pre-filled pen can deliver 0,1 mL to 0,45 mL in increments of 0,05 mL.

Pack size of 1 pre-filled pen.

6.6 Special precautions for disposal and other handling

SIMPONI is supplied in a single use pre-filled pen called VarioJect. Each pack is provided with instructions for use that fully describe the use of the pen. After removing the pre-filled pen from the refrigerator it 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 included in the pack.

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

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (Pty) Ltd

(Reg. No. 1980/011122/07)

2 Medical Road, Halfway House,

Midrand, 1685

Tel: +27 (11) 518 7000

medinfoza@its.jnj.com

8 REGISTRATION NUMBER

54/30.1/0804

9 DATE OF FIRST AUTHORISATION

Date of registration: 3 November 2020

10 DATE OF REVISION OF TEXT

3 November 2020