Attachment 1: Product information for AusPAR Simponi and Simponi Smartject injector; golimumab (rmc); Janssen-Cilag Pty Ltd PM-2012-01202-3-3 Date of Finalisation 16 August 2013. This Product Information was approved at the time this AusPAR was published.

SIMPONI®

Solution for Injection in a pre-filled syringe
Solution for Injection in a pre-filled pen, SmartJect®

Golimumab

PRODUCT INFORMATION

NAME OF THE MEDICINE

Golimumab (rmc)

DESCRIPTION

Each 0.5 mL single-use pre-filled syringe or pre-filled pen contains 50 mg of golimumab. The solution is clear to slightly opalescent, colourless to light yellow. Inactive Ingredients: Sorbitol, histidine, histidine hydrochloride monohydrate, polysorbate 80 and water for injections.

PHARMACOLOGY

Golimumab is a human IgG1κ monoclonal antibody produced by a murine hybridoma cell line with recombinant DNA technology. It 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. Elevated expression of TNF has been linked to chronic inflammatory diseases such as rheumatoid arthritis (RA), as well as spondyloarthropathies such as psoriatic arthritis (PsA) and ankylosing spondylitis (AS), and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.

Pharmacodynamics

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.

SIMPONI was effective in modulating select markers of inflammation and bone metabolism across indications. 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-3 (MMP-3) and vascular endothelial growth factor (VEGF) compared to control treatment.

In addition, levels of TNFa 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 sustained through weeks 14 and/or 24. SIMPONI with or without methotrexate (MTX) resulted in significant changes in serum levels of select markers of bone metabolism [increases in osteocalcin and procollagen type I N-terminal propeptide (PINP) and decreases in deoxy-pyridinolin (DPD) levels] at week 4.

Pharmacokinetics

Following subcutaneous (SC) administration of SIMPONI to healthy subjects or patients with 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 ± standard deviation maximum serum concentration (C_{max}) of 3.1 ± 1.4 mg/mL. Golimumab exhibited dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous (IV) dose. Following a single IV administration over the same dose range in patients with RA, mean systemic clearance of golimumab was estimated to be 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg, which indicates that golimumab is distributed primarily in the circulatory system with limited extravascular distribution. Median terminal half-life values were estimated to be 12 ± 3 days in healthy subjects and patients with RA, PsA or AS. Following a single SC injection of 100 mg, the absorption of SIMPONI was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since SIMPONI exhibited approximately dose proportional pharmacokinetics following a SC administration, the absolute bioavailability of the SIMPONI 50 mg dose is expected to be similar to the 100 mg dose.

When 50 mg SIMPONI 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 SIMPONI SC every 4 weeks resulted in a median steady-state trough serum concentration of approximately 0.6 mg/mL in RA patients with active RA despite MTX therapy, and approximately 0.5 mg/mL in patients with active PsA and approximately 0.6 mg/mL in patients with AS. Patients with RA, PsA and AS treated with SIMPONI 50 mg and MTX had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of golimumab, respectively, compared with those treated with SIMPONI 50 mg without MTX. The presence of MTX also decreased anti-golimumab antibody incidence from 7% to 2% (see CLINICAL TRIALS, “Immunogenicity”). 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 drugs, oral corticosteroids or sulfasalazine (SSZ) were not found to influence the apparent clearance of golimumab.

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. Therefore, there is no need to adjust the dosage of SIMPONI based on the patient’s weight.

Patients who developed anti-golimumab antibodies generally had increased clearance and low trough steady-state serum concentrations of golimumab (see CLINICAL TRIALS, “Immunogenicity”).

Phase 3 studies evaluated the safety and efficacy of SIMPONI at a dosage regimen of every 4 weeks with a prospectively allowed window of 3 to 7 days. Patients would receive a total of 13 doses over 1 year when SIMPONI is given every 4 weeks instead of 12 doses when given monthly. This results in a calculated difference in golimumab exposure of approximately 8% when administered monthly as recommended.

No formal study of the effect of renal or hepatic impairment on the pharmacokinetics of golimumab was conducted.

CLINICAL TRIALS

Rheumatoid arthritis

The efficacy and safety of SIMPONI were evaluated in three multi-centre, randomised, double-blind, placebo-controlled studies in over 1,500 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 was administered subcutaneously at doses of 50 mg or 100 mg, with or without MTX, every 4 weeks. Placebo-controlled efficacy data were collected and analysed through week 24.

GO-FORWARD evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX. This study excluded patients who previously received TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure (CHF), demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancers. Patients were randomised to receive placebo + MTX (n=133), SIMPONI 50 mg + MTX (n=89), SIMPONI 100 mg + MTX (n=89) or SIMPONI 100 mg monotherapy + placebo (n=133). The use of disease-modifying anti-rheumatic drugs (DMARDs) including sulfasalazine (SSZ), hydroxychloroquine (HCQ), cytotoxic agents, or other biologicals was prohibited.

GO-AFTER evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. This study excluded patients with serious or chronic infections, history of CHF, demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancers. Patients were randomised to receive placebo (n=150), SIMPONI 50 mg (n=147), or SIMPONI 100 mg (n=148). Patients were allowed to continue concomitant DMARD therapy with MTX, SSZ, and/or HCQ during the study. Discontinuation of prior anti-TNF therapies could have been for reasons including lack of efficacy (58%), intolerance (17%), and/or reasons other than safety or efficacy (40%). Other than MTX, SSZ, and HCQ, the use of other DMARDs including cytotoxic agents or other biologics was prohibited.

GO-BEFORE evaluated 637 patients with active RA who were MTX-naïve. This study excluded patients who previously received TNF blocking agents, and patients with serious or chronic infections, history of CHF, demyelinating disorders or history of malignancy with exception of treated non-melanoma skin cancers. Patients were randomised to receive placebo + MTX (n = 160), SIMPONI 50 mg + MTX (n = 159), SIMPONI 100 mg + MTX (n = 159) or SIMPONI 100 mg monotherapy + placebo (n = 159). For patients receiving active MTX, MTX was administered at a dose of 10 mg/week beginning at week 0 and increased to 20 mg/week by week 8. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

In GO-AFTER, GO-FORWARD, and GO-BEFORE, the median duration of RA disease was 9.4, 5.7, and 1.2 years, respectively.

The co-primary endpoint in GO-FORWARD and the primary endpoint in GO-AFTER was the percentage of patients achieving an ACR 20 response at week 14. The other co-primary endpoint in GO-FORWARD was the improvement from baseline in the Health Assessment Questionnaire (HAQ) score at week 24. The primary endpoint for GO-BEFORE was the percentage of patients achieving ACR 50 response at week 24. In addition to the primary endpoint(s), additional assessments of the impact of SIMPONI treatment on the signs and symptoms of arthritis, physical function and health-related quality of life were performed.

Key results for the 50 mg dose are shown in Tables 1 and 2 below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI 50 mg and 100 mg dosing regimens. In GO-FORWARD and GO-BEFORE, the SIMPONI 100 mg monotherapy groups were not statistically different from the MTX monotherapy groups in ACR response.

Signs and symptoms: In all phase 3 RA studies, a greater percentage of SIMPONI-treated patients achieved ACR and Disease Activity Score 28 (DAS28) responses at weeks 14 and 24 versus the control groups. Responses were observed at the first assessment (week 4) after the initial SIMPONI administration and were maintained through week 24.

Table 1: Key efficacy outcomes from 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% p=0.028
ACR 50						
Week 14	10%	35%*	7%	15% p=0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40% p=0.042[b]**
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% p=0.064

a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
*: p £ 0.001
b: This p-value (50 mg vs. placebo) should not be interpreted as implying statistical significance, because the p-value for the primary analysis (combined SIMPONI 50 mg and 100 mg groups vs. placebo) was not statistically significant (p=0.053) and a hierarchical approach was used for the statistical analyses.
NA: Not applicable, as data was not collected at week 14 in this study.

In GO-FORWARD and GO-AFTER all individual components of the ACR response criteria [number of tender and swollen joints, patient's assessment of pain, patient's and physician's global assessment of disease activity, disability index (as measured by HAQ) and CRP] were significantly improved in the SIMPONI-treated patients versus control patients ($p < 0.001$). The results of the components of the ACR response criteria are shown in Table 2.

Table 2: Percent improvement in components of ACR Response in RA trials 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
Number of swollen joints						
Baseline	12.0	13.0	14	15	11	13
Week 14	38 %	62 %	20 %	44 %	NA	NA
Week 24	32 %	72 %	1 %	33 %	67 %	76 % (p=0.127)
Number of tender joints						
Baseline	21.0	26.0	26	28	26	26
Week 14	30 %	60 %	6 %	34 %	NA	NA
Week 24	21 %	62 %	-7 %	29 %	57 %	67 % (p=0.023)
Patient's assessment of pain						
Baseline	5.7	6.1	7.1	7.0	7	7
Week 14	18 %	55 %	12 %	25 %	NA	NA
Week 24	15 %	50 %	4 %	25 %	44 %	52 % (p=0.028)
Patient's global assessment of disease activity						
Baseline	5.3	6.0	6.7	6.8	6	6
Week 14	15 %	45 %	8 %	29 %	NA	NA
Week 24	17 %	48 %	2 %	22 %	37 %	50 % (p=0.042)
Physician's global assessment of disease activity						
Baseline	5.7	6.1	6.3	6.5	6	6
Week 14	35 %	55 %	12 %	38 %	NA	NA
Week 24	39 %	62 %	10 %	35 %	63 %	67 % (p=0.206)
HAQ score						
Baseline	1.25	1.38	1.75	1.63	1.50	1.50
Week 14	10 %	29 %	0 %	13 %	NA	NA
Week 24	7 %	31 %	0 %	11 %	37 %	44 % (p=0.141)
CRP (mg/L)						
Baseline	8.0	10.0	10.0	9.0	14.0	13.0
Week 14	2 %	44 %	0 %	37 %	NA	NA
Week 24	0 %	39 %	0 %	15 %	43 %	57 % (p=0.002)

*: p £ 0.001 for all comparisons.
a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint.
NA: Not applicable, as data was not collected at week 14 in this study.

In GO-AFTER, the percentage of patients achieving an ACR 20 response was greater for patients receiving SIMPONI 50 mg than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Physical function and health-related quality of life: In GO-AFTER and GO-FORWARD, the SIMPONI 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to week 24: 0.23 vs. 0.03 in GO-AFTER, 0.47 vs. 0.13 in GO-FORWARD, respectively. Also in GO-AFTER and GO-FORWARD, the SIMPONI 50 mg groups compared to the control groups had a greater proportion of HAQ responders (change from baseline > 0.22) at week 24: 44% vs. 28%, 65% vs. 35%, respectively.

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.

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 3 swollen joints and ³ 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 with a qualifying psoriatic skin lesion of at least 2 cm in diameter. 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%). The median duration of PsA disease was 5.1 years. This study excluded patients previously treated with TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure, demyelinating disorders or a history of malignancy with the exception of treated basal skin cancer. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg, with or without MTX, every 4 weeks. Patients were randomly assigned to placebo (n=113), SIMPONI 50 mg (n=146), and SIMPONI 100 mg (n=146). The primary endpoint was the percentage of patients achieving ACR 20 response at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

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

Table 3: Key efficacy outcomes from GO-REVEAL

	Placebo	SIMPONI 50 mg*
N[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	**9 %**	**51 %**
Week 24	12 %	52 %
ACR 50		
Week 14	2 %	30 %
Week 24	4 %	32 %
ACR 70		
Week 14	1 %	12 %
Week 24	1 %	19 %
PASI 75[b]		
Week 14	3 %	40 %
Week 24	1 %	56 %
HAQ Baseline score		
Median	1.00	1.00
Improvement in HAQ		
Week 14 and 24 Median	0.00	0.25

*: $p < 0.05$ for all comparisons; p-value calculations are based on comparisons of median values for continuous variables

a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

b: Based on the subset of patients with ³ 3% body surface area (BSA) involvement at baseline

Improvements in key measures of disease activity were observed at the first assessment (week 4) after the initial SIMPONI administration and were maintained through week 24. Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes including polyarticular arthritis with no rheumatoid nodules, asymmetric peripheral arthritis, DIP arthritis, and spondylitis with peripheral arthritis. The number of patients with arthritis mutilans was too small to allow meaningful assessment. Responses observed in the SIMPONI-treated groups were similar in patients receiving and not receiving concomitant MTX.

Improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the SIMPONI-treated patients.

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

Ankylosing spondylitis

The safety and efficacy of SIMPONI were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a visual analog score (VAS) for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had symptoms of active disease despite current or previous NSAID or DMARD therapy. The median duration of AS disease was 5.6 years. Patients with complete ankylosis of the spine were excluded from study participation. This study also excluded patients previously treated with TNF blocking agents, and patients with serious or chronic infections, history of congestive heart failure, demyelinating disorders or a history of malignancy with the exception of treated non-melanoma skin cancer. SIMPONI was administered subcutaneously at doses of 50 mg or 100 mg every 4 weeks. Patients were randomly assigned to placebo (n=78), SIMPONI 50 mg (n=138) and SIMPONI 100 mg (n=140). The primary endpoint was the percentage of patients achieving a 20% improvement in the Assessment in Ankylosing Spondylitis (ASAS 20) response criteria at week 14. Placebo-controlled efficacy data were collected and analysed through week 24.

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

Table 4: Key efficacy outcomes from GO-RAISE

	Placebo	SIMPONI 50 mg*
N[a]	78	138
Responders, % of patients		
ASAS 20		
Week 14	**22 %**	**59 %**
Week 24	23 %	56 %
ASAS 40		
Week 14	15 %	45 %
Week 24	15 %	44 %
ASAS 5/6		
Week 14	8 %	50 %
Week 24	13 %	49 %
BASFI (0-10): median change from baseline		
Baseline (median)	4.9	5.0
Week 14	0.1	-1.4
Week 24	0.4	-1.6

*: p £ 0.001 for all comparisons
a: N reflects randomised patients; actual number of patients evaluable for each endpoint may vary by timepoint

Compared with placebo, SIMPONI treatment resulted in a significant improvement in signs and symptoms as demonstrated by the ASAS and BASDAI scores at weeks 14 and 24. Patients treated with SIMPONI achieved significantly greater improvement in all ASAS 20 components compared with placebo. 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 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 the Bath Ankylosing Spondylitis Functional Index (BASFI) at weeks 14 and 24. Median improvement in BASFI at week 14 was 1.4 in the SIMPONI 50 mg group, compared with worsening by 0.1 in the placebo group ($p < 0.001$). The improvement in physical function was maintained through week 24 in SIMPONI-treated patients. 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: Antibodies to golimumab, nearly all neutralising *in vitro*, were detected in 4.3% (57/1322) of SIMPONI-treated patients across the Phase 3 RA, PsA and AS studies through week 24, and 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 SIMPONI without MTX (approximately 2% [14/719] versus 7% [43/603], respectively).

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.

INDICATIONS

Rheumatoid arthritis (RA)
SIMPONI, in combination with methotrexate, is indicated for:

The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate.

Psoriatic arthritis (PsA)
SIMPONI, alone or in combination with methotrexate, is indicated for:

The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. SIMPONI has also been shown to improve physical function.

Ankylosing spondylitis (AS)
SIMPONI is indicated for:

The treatment of active ankylosing spondylitis in adult patients.

CONTRAINDICATIONS

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

Concurrent administration of SIMPONI with anakinra or abatacept (see PRECAUTIONS).

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

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

PRECAUTIONS

Infections

Serious and sometimes fatal infections due to bacterial (including sepsis and pneumonia), mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving TNF-blockers including SIMPONI. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis, candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly reported with TNF-blockers. Patients have frequently presented with disseminated rather than localised disease, and were often taking concomitant immunosuppressants such as methotrexate (MTX) or corticosteroids. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these biologic products is not recommended (see CONTRAINDICATIONS and PRECAUTIONS, “Interactions with other medicines”).

Treatment with SIMPONI should not be initiated in patients with an active infection, including clinically important localised infections. The risks and benefits of treatment should be considered prior to initiating SIMPONI in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;

- who have resided or travelled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with SIMPONI. Because the elimination of golimumab may take up to 5 months, monitoring should be continued throughout this period. SIMPONI should be discontinued if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with SIMPONI should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

Invasive Fungal Infections

For SIMPONI-treated patients who reside or travel in regions where mycoses are endemic, invasive fungal infection should be suspected if they develop a serious systemic illness. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician 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.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including SIMPONI. In addition, patients who have previously received treatment for latent or active tuberculosis have developed tuberculosis while receiving TNF-blockers. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be evaluated for tuberculosis risk factors (including close contact with a person with active tuberculosis) and tested for latent infection prior to initiating SIMPONI and periodically during therapy. Treatment of latent tuberculosis infection should be initiated prior to therapy with SIMPONI.

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 tuberculosis should be considered in patients who have significant risk factors for tuberculosis 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 physician 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.

Patients receiving SIMPONI should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis infections. Tuberculosis should be strongly considered in patients who develop a new infection during SIMPONI treatment, especially in patients who have previously or recently travelled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

In the controlled and uncontrolled portions of the Phase 2 RA and Phase 3 RA, PsA, and AS trials, the incidence of active tuberculosis was 0.23 and 0 per 100 patient-years in 2347 SIMPONI-treated patients and 674 placebo-treated patients, respectively. Cases of tuberculosis included pulmonary and extra pulmonary tuberculosis. The overwhelming majority of the tuberculosis cases occurred in countries with a high incidence rate of tuberculosis.

Hepatitis B virus reactivation

The use of TNF-blockers including SIMPONI has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e. surface antigen positive). Patients should be tested for Hepatitis B virus (HBV) infection before initiating treatment with immunosuppressants, including SIMPONI. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

In patients who develop HBV reactivation, TNF-blockers should be stopped and antiviral therapy with appropriate supportive treatment should be initiated. The safety of resuming TNF-blockers after HBV reactivation has been controlled is not known. Therefore, physicians should exercise caution when considering resumption of TNF-blockers in this situation and monitor patients closely.

Malignancies

The potential role of TNF-blocking therapy in the development of malignancies is not known. 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

Post-marketing cases of malignancies, some fatal, have been reported among children, adolescents and young adults (up to 22 years of age) who received TNF-blocking agents (initiation of therapy ≤ 18 years of age) to treat Juvenile Idiopathic Arthritis (JIA), Crohn's disease or other conditions. Approximately half the reports were lymphomas (Hodgkin's and non-Hodgkin's lymphoma). The other cases represented a variety of different malignancies and included malignancies that are not usually observed in children and adolescents. Most of the patients were receiving concomitant immunosuppressants, such as methotrexate, azathioprine or 6-mercaptopurine. The role of TNF blockers in the development of malignancies in children and adolescents remains unclear.

Lymphoma

In the controlled portions of clinical trials of all the TNF-blocking agents including SIMPONI, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the SIMPONI Phase 2 and Phase

3 clinical trials, the incidence of lymphoma in SIMPONI-treated patients was higher than expected in the general population. Patients with rheumatoid arthritis and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

Leukaemia
Cases of acute and chronic leukaemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukaemia.

Malignancies other than lymphoma
In the controlled portions of the SIMPONI Phase 2 and Phase 3 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 ADVERSE EFFECTS). The significance of this finding is unknown.

In an exploratory clinical trial evaluating the use of another anti-TNF agent, infliximab, in patients with moderate to severe chronic obstructive pulmonary disease (COPD), more malignancies, mostly in the lung or head and neck, were reported in infliximab-treated patients compared with control patients. All patients had a history of heavy smoking. Therefore, caution should be exercised when using any TNF-antagonist in COPD patients, as well as in patients with increased risk for malignancy due to heavy smoking.

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 ADVERSE EFFECTS). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Congestive Heart Failure
Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF-blockers including SIMPONI. Cases of CHF in patients with known cardiovascular risk factors have been observed with SIMPONI. In several exploratory trials of other TNF-blockers in the treatment of CHF, there were greater proportions of TNF-blocker treated patients who had CHF exacerbations requiring hospitalisation or increased mortality. SIMPONI has not been studied in patients with a history of CHF and SIMPONI should be used with caution in patients with CHF. If a decision is made to administer SIMPONI to patients with CHF, these patients should be closely monitored during therapy, and SIMPONI should be discontinued if new or worsening symptoms of CHF appear.

Neurological events

Use of TNF-blocking agents 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 Guillain-Barré syndrome. Prescribers should exercise caution in considering the use of TNF-blockers, including SIMPONI, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI should be considered if these disorders develop.

Haematological cytopaenias

There have been post-marketing reports of pancytopaenia, leukopaenia, 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 haematological abnormalities.

Concurrent administration of SIMPONI with anakinra

Serious infections and neutropaenia were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, 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. Therefore, the combination of SIMPONI and anakinra is not recommended (see CONTRAINDICATIONS and PRECAUTIONS, "Interactions with other medicines").

Concurrent administration of SIMPONI with abatacept

In controlled trials, the concurrent administration of another TNF-blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI and abatacept is not recommended (see CONTRAINDICATIONS and PRECAUTIONS, "Interactions with other medicines").

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.

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. In Phase I RA studies, in 81 patients evaluated, there were no substantial differences between subjects receiving golimumab and placebo with respect to responses to delayed-type hypersensitivity antigens. The impact of treatment with golimumab on the development and course of malignancies, as well as active and/or chronic infections, is not fully understood.

Vaccinations

Patients treated with SIMPONI may receive concurrent vaccinations, except for live vaccines. 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. 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 titres. 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

Allergic reactions (e.g., rash, urticaria, and rarely anaphylaxis and serum sickness-like reactions) have been observed in patients treated with TNF-blocking agents. Serious allergic adverse reactions have not been reported with subcutaneous administration of SIMPONI during clinical trials. Non-serious allergic reactions associated with SIMPONI occurred in clinical trials, and included urticaria, bronchospasm and hypersensitivity. If an anaphylactic reaction or other serious allergic reactions occurs, administration of SIMPONI should be discontinued immediately and appropriate therapy initiated.

Latex sensitivity

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

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 or other serious allergic reaction occurs, administration of SIMPONI should be discontinued immediately and appropriate therapy instituted.

Autoimmunity

Treatment with SIMPONI may result in the formation of autoantibodies and, rarely, in the development of a lupus-like syndrome. If a patient develops symptoms of a lupus-like syndrome following treatment with golimumab, treatment should be discontinued (see ADVERSE EFFECTS, “Antinuclear antibodies (ANA)/anti-double-stranded DNA (dsDNA) antibodies”).

Use in children and adolescents

Specific studies of SIMPONI in paediatric patients have not been conducted.

Use in the elderly

In the Phase 3 studies in RA, PsA, and AS, no overall differences in adverse effects (AEs), serious adverse effects (SAEs), and serious infections in patients age 65 or older (N=155) who received SIMPONI were observed compared with younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Renal and hepatic insufficiency

Specific studies of SIMPONI have not been conducted in patients with renal or hepatic impairment.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Use in Pregnancy (Category C)

The use of SIMPONI in pregnant women is not recommended. Women of childbearing potential should be advised to use adequate contraception and continue its use for at least 6 months after the last SIMPONI treatment. Studies in cynomolgus monkeys have shown no untoward effects on the course of pregnancy, embryofoetal development, parturition or neonatal development, at doses achieving serum concentrations in excess of those expected with the recommended dose.

Golimumab crosses the placenta. Following treatment with another TNF-blocking monoclonal antibody during pregnancy, the antibody has been detected for up to 6 months in the serum of the infants born by the treated women. Consequently, these infants may be at an 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 PRECAUTIONS, Vaccinations and PRECAUTIONS, Interactions with other medicines).

Use in lactation

It is unknown whether golimumab is excreted in human breast milk or absorbed systemically by infants after ingestion. Golimumab was detected in monkey breast milk at low concentrations. The mean breast milk to plasma concentration ratio was 0.002:1. Because immunoglobulins are excreted in human milk, and because of the potential effects in infants, the use of SIMPONI while breastfeeding is not recommended. Breastfeeding should be discontinued for at least 6 months after the last SIMPONI treatment.

Genotoxicity

No genotoxicity tests have been conducted with golimumab.

Carcinogenicity

Long-term animal carcinogenicity studies with golimumab have not been conducted.

Effects on fertility

The potential effects of golimumab on fertility have not been investigated in animal studies.

Interactions with other medicines

No interaction studies have been performed.

Concurrent use of SIMPONI with other Biological Therapeutics

An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI with abatacept or anakinra is not recommended (see CONTRAINDICATIONS and PRECAUTIONS). A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker.

The combination of SIMPONI with other biological therapeutics used to treat the same conditions as SIMPONI is not recommended.

Live vaccines

Live vaccines should not be given concurrently with SIMPONI (see PRECAUTIONS).

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 PHARMACOLOGY, "Pharmacokinetics").

ADVERSE EFFECTS

Safety data from Phase 2 and 3 clinical trials are available from 2578 SIMPONI-treated patients including 1600 with RA, 394 with PsA, 353 with AS, and 231 with severe persistent asthma.

Table 5 summarises the adverse drug reactions that occurred at a rate equal to or higher than 1% in SIMPONI groups and at a frequency higher than the placebo group during the placebo-controlled period of the Phase 3 studies in RA, AS and PsA, respectively (in 639 placebo and 1659 golimumab exposed patients).

The proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase 3 trials through Week 16 in RA, PsA, and AS was 2% for SIMPONI-treated patients and 3% for placebo-treated patients. The most common adverse reactions leading to discontinuation of SIMPONI in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%).

Table 5: Adverse Drug Reactions Reported by ≥ 1% of Patients in the Phase 3 Trials of RA, PsA and AS through week 16[a]

	Placebo ± DMARDs N=639	SIMPONI ± DMARDs N=1659
Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis and rhinitis)	92 (14%)	279 (17%)
Bacterial infections (such as cellulitis)	6 (1%)	24 (1%)
Viral infections (such as influenza and herpes)	20 (3%)	75 (5%)
Bronchitis	9 (1%)	31 (2%)
Sinusitis	8 (1%)	27 (2%)
Superficial fungal infections	8 (1%)	31 (2%)
Anaemia	6 (1%)	20 (1%)
Allergic reactions (bronchospasm, hypersensitivity, urticaria)	7 (1%)	24 (1%)
Depression	6 (1%)	18 (1%)
Insomnia	7 (1%)	22 (1%)
Dizziness	8 (1%)	33 (2%)
Paraesthesia	3 (1%)	27 (2%)
Headache	36 (6%)	75 (5%)
Hypertension	10 (2%)	51 (3%)
Constipation	2 (0%)	18 (1%)
Dyspepsia	10 (2%)	38 (2%)
Gastrointestinal and abdominal pain	17 (3%)	56 (3%)

	Placebo ± DMARDs N=639	SIMPONI ± DMARDs N=1659
Alanine aminotransferase increased	18 (3%)	58 (4%)
Aspartate aminotransferase increased	10 (2%)	44 (3%)
Alopecia	4 (1%)	18 (1%)
Dermatitis	7 (1%)	17 (1%)
Pruritus	10 (2%)	33 (2%)
Rash	15 (2%)	48 (3%)
Pyrexia	4 (1%)	20 (1%)
Asthenia	22 (3%)	70 (4%)
Injection site reaction (such as injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation and paraesthesia)	14 (2%)	97 (6%)
Chest discomfort	7 (1%)	17 (1%)
a: Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids (≤ 10 mg of prednisone/day or equivalent), and/or NSAIDs during the trials).		

Less common clinical trial adverse drug reactions (<1%)

Adverse drug reactions that occurred at rates less than 1% during the SIMPONI clinical trials included the following events listed by system organ class:

Infections and infestations: Septic shock, sepsis, tuberculosis, lower respiratory tract infection (such as pneumonia), opportunistic infections (such as invasive fungal infections [histoplasmosis, coccidioidomycosis, pneumocytosis], bacterial, atypical mycobacterial infection and protozoal), pyelonephritis, abscess, arthritis bacterial, bursitis infective, Hepatitis B reactivation

Neoplasms benign, malignant and unspecified: Neoplasms (such as skin cancer, squamous cell carcinoma and melanocytic naevus), lymphoma, leukaemia, paediatric malignancy*,

Investigations: Neutrophil count decreased

Blood and lymphatic system disorders: Leukopaenia, thrombocytopaenia, pancytopaenia, aplastic anaemia*

Endocrine disorders: Thyroid disorder (such as hypothyroidism, hyperthyroidism and goitre)

Metabolism and nutrition disorders: Blood glucose increased, lipids increased

Nervous system disorders: Demyelinating disorders (central and peripheral), balance disorders, dysguesia

Eye disorders: Visual disorders (such as blurred vision and decreased vision acuity), conjunctivitis, eye allergy (such as pruritus and irritation)

Cardiac disorders: Congestive heart failure (new onset or worsening), arrhythmia, ischaemic coronary artery disorders

Vascular disorders: Thrombosis (such as deep venous and aortic), Raynaud's phenomenon, flushing, vasculitis (systemic)

Respiratory, thoracic and mediastinal disorders: Asthma and related symptoms (such as wheezing and bronchial hyperactivity), interstitial lung disease

Gastrointestinal disorders: Gastrointestinal inflammatory disorders (such as gastritis and colitis), gastroesophageal reflux disease, stomatitis

Hepatobiliary disorders: Cholelithiasis, hepatic disorders

Skin and subcutaneous tissue disorders: Psoriasis (new onset, palmar/plantar, and pustular), urticaria, vasculitis (cutaneous)

Musculoskeletal and connective tissue disorders: Lupus-like syndrome

Renal and urinary disorders: Bladder disorders, renal disorders

Reproductive system and breast disorders: Breast disorders, menstrual disorders

General disorders and administration site conditions: Impaired healing

Injury, poisoning and procedural complications: Bone fractures

[*Observed with other TNF-blockers, but not observed in clinical studies with golimumab].

Post-marketing Experience

The frequencies provided below reflect reporting rates of adverse drug reactions from the worldwide post-marketing experience with SIMPONI and precise estimates of incidence cannot be made due to voluntary reporting from a population of uncertain size. These adverse drug reactions are ranked by frequency, using the following convention: Very common (≥1/10), common (≥1/100 and < 1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and < 1/1000), very rare (<1/10,000, including isolated reports).

System Organ Class	Adverse Drug Reaction	Frequency
Neoplasm Benign and Malignant	Melanoma Merkel cell carcinoma	Rare Unknown*
Immune System Disorders	Serious systemic hypersensitivity reactions (including anaphylactic reaction) Sarcoidosis	Rare Very rare
Skin and Subcutaneous Tissue Disorders	Skin exfoliation	Rare

*observed with other TNF-blocking agents

Infections (see PRECAUTIONS)

Upper respiratory tract infection was the most common adverse reaction reported in the combined Phase 3 RA, PsA and AS studies through week 16, occurring in 7.2% of SIMPONI-treated patients (incidence per patient-year: 0.26; 95% CI: 0.22, 0.31) as compared with 5.8% of control patients (incidence per patient-year: 0.23; 95% CI: 0.17, 0.31). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per patient year of upper respiratory tract infections was 0.17 events; 95% CI: 0.16, 0.19, for SIMPONI-treated patients.

In controlled Phase 3 trials through week 16 in RA, PsA, and AS, infections were observed in 28.3% of SIMPONI-treated patients (incidence per patient-year: 1.28; 95% CI: 1.18, 1.38) compared with 24.7% of control patients (incidence per patient-year: 1.17; 95% CI: 1.02, 1.33). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per patient year of infections was 0.96 events; 95% CI: 0.93, 0.99, for SIMPONI treated patients.

In controlled Phase 3 trials through week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI-treated patients and 1.3% of control-treated patients. Through Week 16, the incidence of serious infections per patient-year of follow-up was 0.07; 95% CI: 0.05, 0.11 for the SIMPONI 100 mg group, 0.03; 95% CI: 0.01, 0.07 for the SIMPONI 50 mg group and 0.04; 95% CI: 0.02, 0.08 for the placebo group. Serious infections observed in SIMPONI-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections and tuberculosis. In the controlled and uncontrolled portions of the Phase 2 and Phase 3 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 SIMPONI 100 mg compared with patients receiving SIMPONI 50 mg. The incidence per patient-year of all serious infections was 0.05; 95% CI: 0.04, 0.06, in patients receiving SIMPONI 100 mg and 0.03; 95% CI: 0.02, 0.04, in patients receiving SIMPONI 50 mg. These results may be confounded by the designs of the Phase 3 studies and different durations of follow-up across treatment groups.

Malignancies (see PRECAUTIONS)

Lymphoma

The incidence of lymphoma in SIMPONI-treated patients with RA, PsA and AS during the controlled portions of Phase 2b and Phase 3 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 SIMPONI 100 mg compared with patients receiving SIMPONI 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. 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 SIMPONI 50 mg and 100 mg respectively. The majority of lymphomas occurred in GO-AFTER, which enrolled patients previously exposed to anti-TNF agents who had longer disease duration and more refractory disease.

Malignancies other than lymphoma

In the controlled portions of the SIMPONI Phase 2 and Phase 3 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. Through

approximately 3 years of follow-up, the incidence of non-lymphoma malignancies was similar to the general population.

Through approximately 3 years of follow-up of the Phase 2b and Phase 3 studies in RA, PsA and AS, among patients receiving SIMPONI, non-melanoma skin cancer was diagnosed in 28 subjects (10 in SIMPONI 50 mg and 18 in SIMPONI 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.49 (0.33, 0.71) events for SIMPONI.

Through approximately 3 years of follow-up, of the Phase 2b and Phase 3 studies in rheumatologic indications, among patients receiving SIMPONI, malignancies besides non-melanoma skin cancer and lymphoma were diagnosed in 32 subjects (18 in SIMPONI 50 mg and 14 in SIMPONI 100 mg treatment groups) with an incidence (95% CI) per 100 subject-years of follow-up of 0.56 (0.38, 0.79) events for SIMPONI.

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 were reported 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.

The potential role of TNF-blocking therapy in the development of malignancies is unknown.

<u>Demyelinating Disorders (see PRECAUTIONS)</u>

In the controlled and uncontrolled portions of the Phase 2 RA and the phase 3 RA, PsA, and AS trials with a median follow-up of approximately 3 years, a greater incidence of demyelination was observed in patients receiving SIMPONI 100 mg compared with patients receiving SIMPONI 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.

<u>Liver enzyme elevations</u>

In the Phase 3 trials through week 16, ALT elevations were seen more commonly than AST elevations. Among those subjects with normal ALT levels at baseline, proportions of ALT elevations were in general greater for treatment regimens that included MTX compared with treatment regimens that did not.

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers. In controlled Phase 3 trials through week 16, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of SIMPONI and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS study, more SIMPONI-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 the SIMPONI-treated and control patients in the RA and PsA studies. In the AS study, the incidence of mild ALT elevations was higher in SIMPONI-treated patients than in control patients.

In the RA and AS studies through week 16, ALT elevations ³ 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. Through approximately 3 years of follow-up, the incidence of ALT elevations ≥ 5 x ULN was similar in both SIMPONI-treated and control patients in the Phase 3 RA, PsA and AS studies. The majority of these elevations were asymptomatic.

Hepatobiliary adverse events

In controlled Phase 3 trials in RA, PsA and AS through Week 16, the proportions of patients with hepatobiliary adverse events were 0.8% in the SIMPONI-treated patients and 0.6% in control patients.

Psoriasis: New-Onset and Exacerbations

Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, have been reported with the use of TNF-blockers, including SIMPONI. Cases of exacerbation of pre-existing psoriasis have also been reported with the use of TNF-blockers. Many of these patients were taking concomitant immunosuppressants (e.g., MTX, corticosteroids). Some of these patients required hospitalisation. Most patients had improvement of their psoriasis following discontinuation of their TNF-blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF-blocker. Discontinuation of SIMPONI should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Injection site reactions

In controlled Phase 3 trials through week 16 in RA, PsA and AS, 5.8% of SIMPONI-treated patients had injection site reactions compared with 2.2% in control patients. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema.

In controlled phase 2 and 3 trials in RA, PsA, AS and severe persistent asthma, no patients treated with SIMPONI developed anaphylactic reactions.

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

Use of TNF-blocking agents has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome.

In Phase 3 trials in RA, PsA, and AS at 1 year of follow-up, 4.0% of SIMPONI-treated patients and 2.6% of control patients were newly ANA-positive (at titres of 1:160 or greater) compared with baseline. The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients with anti-dsDNA negative at baseline was uncommon.

DOSAGE AND ADMINISTRATION

Rheumatoid arthritis

SIMPONI 50 mg given as a subcutaneous injection once a month, on the same date each month.

Psoriatic arthritis

SIMPONI 50 mg given as a subcutaneous injection once a month, on the same date each month.

Ankylosing spondylitis

SIMPONI 50 mg given as a subcutaneous injection once a month, on the same date each month

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.

After proper training in SC injection technique, patients may self-inject with SIMPONI if their physician determines that this is appropriate, with medical follow-up as necessary.

Elderly patients (≥ 65 years)

No dosage adjustment is required in the elderly.

Paediatric patients (< 18 years)

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

Patients with impaired renal and/or hepatic function

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

Instructions for administration and disposal

Prior to administration, visually inspect the solution for particles and discolouration through the viewing window. SIMPONI should be clear to slightly opalescent and colourless to light yellow. The solution should not be used if discoloured, or cloudy, or if foreign particles are present.

The needle cover on the pre-filled syringe as well as the pre-filled syringe in the pre-filled pen, contains dry natural rubber (a derivative of latex), which should not be handled by persons sensitive to latex (see PRECAUTIONS).

Injection sites should be rotated and injections should never be given into areas where the skin is tender, bruised, red, or hard.

Comprehensive instructions for the administration of SIMPONI are given in the Patient Instruction Leaflet. This product is for single use in one patient only. Patients should be instructed to inject the full amount of SIMPONI according to the directions provided in the Patient Instruction Leaflet. Discard any residue; any unused product or waste material should be disposed of in accordance with local requirements.

In the absence of compatibility studies, SIMPONI must not be mixed with other medicinal products. SIMPONI contains no antimicrobial agent.

OVERDOSAGE

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.

Contact the Poisons Information Centre on 131126 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

SIMPONI pre-filled syringe

SIMPONI is supplied as a sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. The needle shields are manufactured from dry natural rubber containing latex (see PRECUATIONS, “Allergic reactions”). SIMPONI is available in packs of 1 or 3* pre-filled syringe(s).

SIMPONI SmartJect injector pen

SIMPONI is supplied as a sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. This syringe is contained in a single-use pre-filled pen called “SmartJect”. The needle shields are manufactured from dry natural rubber containing latex (see PRECAUTIONS, “Allergic reactions”). SIMPONI is available in packs of 1 or 3* pre-filled pen(s).

* Not currently supplied in Australia.

Storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Do not shake. Keep the pre-filled pen/syringe in the outer carton in order to protect it from light.

NAME AND ADDRESS OF SPONSOR

JANSSEN CILAG Pty Ltd
1-5 Khartoum Road
Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334

NZ Office: Auckland New Zealand
Telephone: 0800 800 806

Attachment 1: Product information for AusPAR Simponi and Simponi Smartject injector; golimumab (rmc); Janssen-Cilag Pty Ltd PM-2012-01202-3-3 Date of Finalisation 16 August 2013. This Product Information was approved at the time this AusPAR was published.

POISON SCHEDULE OF MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

13 November 2009

DATE OF MOST RECENT AMENDMENT

12 June 2013