GOLIMUMAB

Simponi®
TNF-α inhibitor

FORMULATION

Golimumab is a human IgG1κ monoclonal antibody that exhibits multiple glycoforms with predicted molecular masses ranging from 149802 daltons to 151064 daltons. Golimumab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses.

Golimumab (Simponi®) is available as a solution for injection for subcutaneous (SC) administration in the following presentations:

Autoinjector/Pre-filled pen

- Each 45 mg single-use pre-filled pen for pediatric use contains 45 mg golimumab per 0.45 mL.

The excipients are L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sorbitol and water for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF, which prevents the binding of TNF to its receptors. No binding to other TNF superfamily ligands was observed; in particular, golimumab does not bind or neutralize human lymphotoxin. TNFα is synthesized primarily by activated monocytes, macrophages and T-cells as a transmembrane protein that self-associates to form the bioactive homotrimer and is rapidly released from the cell surface by proteolysis. The binding of TNF to either the p55 or p75 TNF receptors leads to the clustering of the receptor cytoplasmic domains and initiates signaling. TNF has been identified as a key sentinel cytokine that is produced in response to various stimuli and subsequently promotes the inflammatory response through activation of the caspase-dependent apoptosis pathway and the transcription factors nuclear factor (NF)-κB and activator protein-1 (AP-1). TNF also modulates the immune response through its role in the organization of immune cells in germinal centers. Elevated expression of TNF has been linked to chronic inflammatory diseases such as rheumatoid arthritis, as well as spondyloarthropathies such as PsA and AS, and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.

Pharmacodynamic effects

Nonclinical

The binding of human TNF by golimumab was shown to neutralize 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. Consistent with other human IgG1 antibodies, golimumab is capable of binding to Fc receptors and activating complement. However, no golimumab-mediated cell lysis was seen with lipopolysaccharide (LPS)-stimulated human monocytes upon addition of complement or effector cells. In addition, no golimumab-induced apoptosis was detected with LPS-stimulated human peripheral blood mononuclear cells. The effect of golimumab *in vivo* was tested in a human TNF transgenic mouse model of experimental arthritis. Golimumab treatment produced a statistically significant delay in the onset of clinical symptoms compared with untreated mice, as well as a significant reduction in joint pathology.

Immunogenicity
Following SC administration in patients with RA, PsA, or AS, antibodies to Golimumab (Simponi®), nearly all neutralizing *in vitro*, were detected in 5% of Golimumab (Simponi®)-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 (Simponi®) than patients receiving Golimumab (Simponi®) without MTX (approximately 3% vs. 8%, respectively).

Following SC administration in patients with nr-Axial SpA, antibodies to Golimumab (Simponi®), all neutralizing *in vitro*, were detected in 4% of Golimumab (Simponi®)-treated patients through Week 16.

Following SC administration in UC patients, antibodies to Golimumab (Simponi®) were detected in 2.7% of Golimumab (Simponi®)-treated patients through Week 54. Sixty-eight percent of antibody-positive patients had neutralizing antibodies *in vitro*. Treatment with concomitant immunomodulators (AZA, 6-MP and MTX) resulted in a lower proportion of patients with antibodies to Golimumab (Simponi®) than patients receiving Golimumab (Simponi®) without immunomodulators (1.3% vs. 3.4%, respectively).

Following IV administration of Golimumab (Simponi®) in combination with MTX in RA patients, antibodies to golimumab were detected in 4.2% (39/922) of golimumab-treated patients through approximately 1 year. All patients who were positive for antibodies to golimumab had neutralizing antibodies *in vitro*.
The small number of patients positive for antibodies to Golimumab (Simponi®) limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Golimumab (Simponi®) in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Golimumab (Simponi®) with the incidence of antibodies to other products may be misleading.

Clinical Studies
Polyarticular juvenile idiopathic arthritis
The safety and efficacy of Golimumab (Simponi®) was evaluated in a randomized, double-blind, placebo-controlled, withdrawal study (GO KIDS) in 173 children (2 to 17 years of age) with active pJIA with at least 5 active joints and an inadequate response to MTX. Children with polyarticular course JIA (rheumatoid factor positive or negative polyarthritis, extended oligoarthritis, juvenile psoriatic arthritis or systemic JIA with no current systemic symptoms) were included in the study. The baseline median number of active joints was 12, and median CRP was 0.17 mg/dL.

Part 1 of the study consisted of a 16-week open-label phase in which 173 enrolled children received Golimumab (Simponi®) 30 mg/m^2 (maximum 50 mg) subcutaneously every 4 weeks and MTX. The 154 children who achieved an ACR Ped 30 response at week 16 entered Part 2 of the study, the randomized withdrawal phase, and received Golimumab (Simponi®) 30 mg/m^2 (maximum 50 mg) + MTX or placebo + MTX every 4 weeks. After disease flare, children received Golimumab (Simponi®) 30 mg/m^2 (maximum 50 mg) + MTX. At week 48, children entered a long-term extension.

Children in this study demonstrated ACR Ped 30, 50, 70, and 90 responses as early as week 4.

At week 16, 87% of children were ACR Ped 30 responders, and 79%, 66%, and 36% of children were ACR Ped 50, ACR Ped 70, and ACR Ped 90 responders, respectively. At week 16, 34% of children had inactive disease defined as having the presence of all of the following: no joints with active arthritis; no fever, rash, serositis, splenomegaly, hepatomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis; normal ESR (< 20 mm/hour) or CRP (< 1.0 mg/dL); physician global assessment of disease activity (≤ 5 mm on the VAS); duration of morning stiffness < 15 minutes.

At week 16, all ACR Ped components demonstrated clinically relevant improvement from baseline (see Table 1).

Table 1: pJIA study: Improvements from baseline in ACR Ped components at week 16[a]

	Median percent improvement
	Golimumab (Simponi®) 30 mg/m^2 n[b]=173
Physicians global assessment of disease (VAS[c] 0-10 cm)	88%
Subject/parent global assessment of overall well-being (VAS 0-10 cm)	67%
Number of active joints	92%
Number of joints with limited range of motion	80%
Physical function by CHAQ[d]	50%
ESR (mm/h)[e]	33%

[a] baseline = week 0
[b] "n" reflects enrolled patients
[c] VAS: Visual Analogue Scale
[d] CHAQ: Child Health Assessment Questionnaire
[e] ESR (mm/h): erythrocyte sedimentation rate (millimeters per hour)

The primary endpoint, the proportion of children who were ACR Ped 30 responders at week 16 and who did not experience a flare between week 16 and week 48, was not achieved. The majority of children did not experience a flare between week 16 and week 48 (59% in the Golimumab (Simponi®) + MTX and 53% in the placebo + MTX groups, respectively; p = 0.41).

Pre-specified subgroup analyses of the primary endpoint by baseline CRP (≥ 1 mg/dL vs < 1 mg/dL) demonstrated higher flare rates in placebo + MTX vs golimumab + MTX treated subjects among subjects with baseline CRP ≥ 1 mg/dL (87% vs 40% p = 0.0068).

At week 48, 53% and 55% of children in the Golimumab (Simponi®) + MTX group and placebo + MTX group, respectively, were ACR Ped 30 responders, and 40% and 28% of children in the Golimumab (Simponi®) + MTX group and placebo + MTX group, respectively, achieved inactive disease.]

Pharmacokinetic Properties

Absorption

Following a single SC administration of Golimumab (Simponi®) to healthy subjects or patients with RA, the time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6 days. A SC injection of 50 mg Golimumab (Simponi®) to healthy subjects produced a mean ± standard deviation maximum serum concentration (C_{max}) of 3.2 ±1.4 mcg/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 (Simponi®) was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since Golimumab (Simponi®) exhibited approximately dose proportional PK following SC administration, the absolute bioavailability of a Golimumab (Simponi®) 50 mg or 200 mg dose is expected to be similar to the 100 mg dose.

Following a single IV administration of 2 mg/kg Golimumab (Simponi®), a mean C_{max} of 44.4 $\pm$ 11.3 mcg/mL was observed in patients with RA.

Distribution
Following a single IV administration, the mean volume of distribution was estimated to be 115 ± 19 mL/kg in healthy subjects, and 151 ± 61 mL/kg in patients with RA. The volume of distribution for Golimumab (Simponi®) indicates that Golimumab (Simponi®) is distributed primarily in the circulatory system with limited extravascular distribution.

Metabolism
The exact metabolic pathway of Golimumab (Simponi®) is unknown.

Elimination
Following a single IV administration, the systemic clearance of Golimumab (Simponi®) 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 (Simponi®). The terminal half-life was estimated to be 12 $\pm$ 3 days in healthy subjects and similar half-life was observed in patients with RA, PsA, AS, or UC.

After a 6-month treatment with Golimumab (Simponi®) by SC administration in patients with RA, concomitant use of MTX reduced the apparent clearance of Golimumab (Simponi®) by 36%; however, following IV administration, no appreciable effect of MTX on the clearance of Golimumab (Simponi®) was observed. Population PK analysis indicated that concomitant use of NSAIDs, oral corticosteroids, or sulfasalazine did not influence the apparent clearance of Golimumab (Simponi®) following SC administration.

In RA, PsA and AS, population PK analysis indicated that concomitant use of MTX, NSAIDs, oral corticosteroids, or sulfasalazine (SSZ) did not significantly influence the clearance of golimumab following IV administration.

Population PK analyses showed that, following SC administration of Golimumab (Simponi®), patients with higher CRP levels tended to have higher apparent clearance of Golimumab (Simponi®). Patients with higher CRP levels were more likely to have lower trough serum concentrations of Golimumab (Simponi®) following SC administration of Golimumab (Simponi®). In contrast, CRP level showed no effect on the clearance of Golimumab (Simponi®) following IV administrations of 2 mg/kg Golimumab (Simponi®) at Week 0, Week 4, and every 8 weeks thereafter.

Patients who developed anti-Golimumab (Simponi®) antibodies following SC or IV administration generally had low trough steady-state serum concentrations of Golimumab (Simponi®).

Dose linearity
Following a single IV dose in patients with RA, Golimumab (Simponi®) exhibited approximately 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
Serum concentration-time profiles of Golimumab (Simponi®) were generally predictable after single or multiple SC or IV administrations.

When 50 mg Golimumab (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 Golimumab (Simponi®) SC every 4 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4 ± 0.3 mcg/mL in MTX-naïve patients with active RA, approximately 0.6 ± 0.4 mcg/mL in patients with active RA despite MTX therapy, approximately 0.5 ± 0.5 mcg/mL in patients with active RA previously treated with anti-TNFα biologics, approximately 0.5 ± 0.4 mcg/mL in patients with active PsA and approximately 0.8 ± 0.4 mcg/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 (Simponi®) than those who received Golimumab (Simponi®) with MTX.

Steady-state mean trough serum golimumab concentrations in patients with nr-Axial SpA were similar to those observed in patients with AS following subcutaneous administration of 50 mg golimumab every 4 weeks.

When 2 mg/kg Golimumab (Simponi®) was administered IV to patients with RA at Week 0, Week 4 and every 8 weeks thereafter, serum concentrations reached steady-state by Week 12. In patients using concomitant MTX, treatment with 2 mg/kg Golimumab (Simponi®) IV every 8 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4 ± 0.4 mcg/mL in patients with active RA despite MTX therapy. The mean steady-state trough serum concentration in patients with PsA was 0.7 ± 0.6 mcg/mL. The mean steady-state trough serum concentration in patients with AS was 0.8 ± 0.6 mcg/mL.

Following induction doses of 200 mg and 100 mg Golimumab (Simponi®) SC at Week 0 and Week 2 respectively, and maintenance doses of 100 mg Golimumab (Simponi®) 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 (Simponi®) SC every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 1.8 ± 1.1 mcg/mL. Concomitant use of immunomodulators did not have any apparent effect on steady-state trough levels of golimumab when 100 mg Golimumab (Simponi®) 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 (Simponi®) with increasing weight. As a result, patients with heavier weight tend to have lower steady-state trough concentrations of Golimumab (Simponi®) following SC administration of a 50 mg or 100 mg dose; however, across RA, PsA, and AS populations, a treatment benefit from Golimumab (Simponi®) 50 mg was observed for all subgroups by weight quartiles with no meaningful differences in clinical efficacy among these subgroups. Treatment with the recommended dose regimen of Golimumab (Simponi®) 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 (Simponi®) based on a patient's weight.

Following IV administration, patients with higher body weight tended to have slightly higher serum golimumab concentrations than patients with lower body weights when golimumab was administered on a mg/kg (body weight) basis. However, based on population PK analysis, there were no clinically relevant differences in golimumab exposure following IV administration of 2 mg/kg golimumab in patients across a range of different body weights.

Special populations

Pediatric 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 modeling and simulation in children with pJIA confirmed the relationship between golimumab serum exposures and clinical efficacy and supports the dosing regimen of golimumab 50 mg every 4 weeks in children with pJIA of at least 40 kg and 30 mg/m^2 every 4 weeks in children with pJIA weighing less than 40 kg.

Gender

No gender-related pharmacokinetic differences were observed with Golimumab (Simponi®) after correction for patients' body weights.

Ethnicity

No ethnicity-related pharmacokinetic differences were observed between Caucasians and Asians.

Renal or Hepatic Impairment

No pharmacokinetic data are available in patients with impaired renal or hepatic function.

Monthly dosing

The 5 Phase 3 SC studies evaluated the safety and efficacy of Golimumab (Simponi®) at a dosage regimen of every 4 weeks, however a 3 to 7 day window was prospectively allowed. Patients would receive a total of 13 doses over 1 year when Golimumab (Simponi®) is given every 4 weeks instead of 12 doses when given monthly. This results in a calculated monthly dose of 54 mg vs. 50 mg, respectively, and equates to an approximately 8% difference in golimumab exposure.

Non-clinical Information

Carcinogenicity, Mutagenicity, Impairment of Fertility

Long-term animal studies of golimumab have not been conducted to evaluate the carcinogenic potential or its effects on fertility. A fertility study conducted in mice using the analogous anti-mouse TNFα antibody showed no impairment of fertility. Mutagenicity studies have not been conducted with golimumab.

THERAPEUTIC INDICATION

Polyarticular juvenile idiopathic arthritis (pJIA)

Golimumab (Simponi®), by subcutaneous administration, in combination with 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.

DOSAGE AND ADMINISTRATION
Golimumab (Simponi®) is administered by subcutaneous injection.

Polyarticular juvenile idiopathic arthritis (pJIA) in children with body weight less than 40 kg
30 mg/m^2 of Golimumab (Simponi®) 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 2.

A 45 mg/0.45 mL pre-filled pen is available for administration to children with polyarticular juvenile idiopathic arthritis weighing less than 40 kg. Each pre-filled pen is for single use in a single patient, and should be discarded immediately after use.

Table 2: Golimumab (Simponi®) dose in milliliters (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

50 mg of Golimumab (Simponi®) administered once a month, on the same date each month.

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

Method of administration
Golimumab (Simponi®) is intended for use under the guidance and supervision of a physician.

Subcutaneous injection
After proper training in subcutaneous injection technique, a patient may self-inject with Golimumab (Simponi®) if a physician determines that it is appropriate and with medical follow-up as necessary.

At the time of dosing if multiple injections are required, the injections should be administered at different sites on the body (see ***Instructions for Use***).

Comprehensive instructions for the administration of Golimumab (Simponi®) are given in ***Instructions for Use***. Patients should be instructed to inject the full amount of Golimumab (Simponi®) according to the directions provided in the patient information leaflet.

Special populations
Pediatrics (17 years of age and younger)
The safety and efficacy of Golimumab (Simponi®) in pediatric patients aged 17 years and younger for indications other than pJIA have not been established (see Pharmacodynamic Properties).

Renal impairment
Specific studies of Golimumab (Simponi®) have not been conducted in patients with renal impairment.

Hepatic impairment
Specific studies of Golimumab (Simponi®) have not been conducted in patients with hepatic impairment.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Infections
Bacterial (including sepsis and pneumonia), mycobacterial (tuberculosis), invasive fungal and opportunistic infections, including fatalities, have been reported in patients receiving TNF-blocking agents, including Golimumab (Simponi®). Patients have frequently presented with disseminated rather than localized 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 traveled to regions where invasive fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of Golimumab (Simponi®) treatment should be carefully considered before initiation or continuation of Golimumab (Simponi®) therapy. In at-risk patients treated with Golimumab (Simponi®), an invasive fungal infection should be suspected if they develop a serious systemic illness. Antigen and antibody testing may be negative in some patients with active infection. Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed. The decision to administer empiric antifungal therapy should be made, if feasible, 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.

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

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 Golimumab (Simponi®). Treatment of latent tuberculosis infections should be initiated prior to therapy with Golimumab (Simponi®).

Anti-tuberculosis therapy should be considered prior to initiation of Golimumab (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 Golimumab (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 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.

In patients receiving Golimumab (Simponi®), tuberculosis has frequently presented as disseminated or extrapulmonary disease. Cases of active tuberculosis have occurred in patients treated with Golimumab (Simponi®) during and after treatment for latent tuberculosis. Patients receiving Golimumab (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.

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.

Pediatric malignancy

Postmarketing 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 of the reports were lymphomas. 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 Golimumab (Simponi®), more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the Golimumab (Simponi®) Phase 2 and Phase 3 clinical trials in RA, PsA and AS, the incidence of lymphoma in Golimumab (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.

Rare postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with other TNF-blocking agents (see *Adverse Reactions*). This rare 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 Golimumab (Simponi®) should be carefully considered. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF blockers cannot be excluded.

Leukemia

Cases of acute and chronic leukemia have been reported with TNF-blocker use, including Golimumab (Simponi®), 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 leukemia.

Malignancies other than lymphoma

In the controlled portions of the Golimumab (Simponi®) Phase 2 and Phase 3 clinical trials in RA, PsA, AS, and UC, the incidence of non-lymphoma malignancies (excluding nonmelanoma skin cancer) was similar between the Golimumab (Simponi®) and the control groups.

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

Colon dysplasia/carcinoma

It is not known if Golimumab (Simponi®) treatment influences the risk for developing dysplasia or colon cancer. All patients with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma, should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations. In patients with newly diagnosed dysplasia treated with Golimumab (Simponi®), the risks and benefits to the individual patient must be carefully reviewed and consideration should be given to whether therapy should be continued.

Skin cancers

Melanoma and Merkel cell carcinoma have been reported in patients treated with TNF-blocking agents, including Golimumab (Simponi®) (see *Adverse Reactions*). Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

Hepatitis B virus reactivation

As observed with the use of other immunosuppressive drugs, the use of TNF-blocking agents, including Golimumab (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 immunosuppressants, including Golimumab (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. 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 Golimumab (Simponi®).

Congestive heart failure (CHF)

Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNF blockers, including Golimumab (Simponi®). Some cases had a fatal outcome. Golimumab (Simponi®) has not been studied in patients with CHF. Golimumab (Simponi®) should be used with caution in patients with heart failure. If a decision is made to administer Golimumab (Simponi®) to patients with heart failure, they should be closely monitored during therapy, and Golimumab (Simponi®) should be discontinued if new or worsening symptoms of heart failure appear.

Demyelinating disorders

Use of TNF-blocking agents have 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 Golimumab (Simponi®), in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of Golimumab (Simponi®) should be considered if these disorders develop.

Autoimmune processes

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

Concurrent administration of Golimumab (Simponi®) with anakinra

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

Concurrent administration of Golimumab (Simponi®) with abatacept

In clinical studies, concurrent administration of TNF-blocking agents and abatacept have been associated with an increased risk of infections including serious infections compared with TNF-blocking agents alone, without increased clinical benefit. Because of the nature of the adverse events seen with the combination of TNF-blocking agents and abatacept therapy, the combination of Golimumab (Simponi®) and abatacept is not recommended.

Concurrent administration with other biological therapeutics

There is insufficient information regarding the concomitant use of Golimumab (Simponi®) with other biological therapeutics used to treat the same conditions as Golimumab (Simponi®). The concomitant use of Golimumab (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.

Hematologic reactions

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

Live vaccines/therapeutic infectious agents

Patients treated with Golimumab (Simponi®) may receive concurrent vaccinations, except for live vaccines. In patients receiving anti-TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines could result in clinical infections, including disseminated infections.

Other uses of therapeutic infectious agents 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 agents not be given concurrently with Golimumab (Simponi®).

Non-live vaccines

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

Allergic reactions

Latex sensitivity

The needle cover on the pre-filled syringe as well as the pre-filled syringe in the autoinjector/pre-filled pen contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Hypersensitivity reactions

In postmarketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following Golimumab (Simponi®) administration. Some of these reactions occurred after the first administration of Golimumab (Simponi®). If an anaphylactic or other serious allergic reaction occurs, administration of Golimumab (Simponi®) should be discontinued immediately and appropriate therapy instituted.

Special populations

Pediatric use

Vaccinations

If possible, it is recommended that prior to initiating therapy with Golimumab (Simponi®), pediatric patients be brought up to date with all immunizations in agreement with current immunization guidelines.]

INTERACTIONS

Specific drug interaction studies have not been conducted with Golimumab (Simponi®).

Concurrent use of Golimumab (Simponi®) with other biological therapeutics

The combination of Golimumab (Simponi®) with other biological therapeutics used to treat the same conditions as Golimumab (Simponi®), including anakinra and abatacept, is not recommended (see *Warnings and Precautions*).

Live vaccines/therapeutic infectious agents

Live vaccines should not be given concurrently with Golimumab (Simponi®) (see *Warnings and Precautions*).

Therapeutic infectious agents should not be given concurrently with Golimumab (Simponi®) (see *Warnings and Precautions*).

Methotrexate

No significant effect of methotrexate on the clearance of Golimumab (Simponi®) administered intravenously was observed. Following subcutaneous administration, concomitant use of methotrexate resulted in higher steady-state trough concentrations of Golimumab (Simponi®) in patients with RA, PsA, or AS. However, the data do not suggest the need for dose adjustment of either Golimumab (Simponi®) or methotrexate (see *Pharmacokinetic Properties*).

PREGNANCY, BREAST-FEEDING AND FERTILITY

Pregnancy

An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the first trimester at dosages up to 50 mg/kg twice weekly (over 500-fold higher in terms of dose/body weight ratio than the proposed clinical dose of 50 mg every 4 weeks). The mean peak maternal serum concentration obtained in this study (1576 mcg/mL) is over 900-fold higher than median steady-state C_{max} value (1.71 mcg/mL) following 50 mg every 4-week SC dosing in patients with RA, PsA, and AS. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. Fetal serum concentrations were approximately 50% of the maternal serum concentrations. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus.

A pre- and postnatal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters and during lactation. Golimumab was present in the neonatal serum from the time of birth and for up to 6 months postpartum. The mean peak maternal serum concentration obtained in this study (1482 mcg/mL) is over 860-fold higher than median steady-state C_{max} value (1.71 mcg/mL) following 50 mg every 4-week SC dosing in patients with RA, PsA, and AS. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants. However, animal reproductive and developmental studies are not always predictive of human response.

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 infant born by the treated women. Consequently, these infants may be at increased risk of infection. Administration of live vaccines to infants exposed to golimumab *in utero* is not recommended for 6 months following the mother's last golimumab injection during pregnancy (see *Warnings and Precautions* and *Interactions*).

It is not known whether Golimumab (Simponi®) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Golimumab (Simponi®) should be given to a pregnant woman only if clearly needed.

Breast-feeding
In the pre- and postnatal development study in cynomolgus monkeys (see *Pregnancy* above) in which golimumab was administered during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 350-fold lower than the maternal serum concentrations. It is not known whether golimumab is excreted in human milk or absorbed systemically after ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of the potential for adverse reactions in nursing infants from Golimumab (Simponi®), a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and use machines have been performed.

ADVERSE REACTIONS
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of golimumab based on the comprehensive assessment of the available adverse event information. A causal relationship with golimumab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
Safety data from Phase 2 and 3 clinical trials are available from 6161 golimumab-treated patients including 3090 with rheumatoid arthritis, 634 with PsA, 768 with AS, 1245 with ulcerative colitis, 231 with severe persistent asthma, and 193 with active non-radiographic axial spondyloarthritis (nr-Axial SpA). Adverse reactions observed with golimumab are summarized in Table 3.

In general, the overall safety profile was similar for patients receiving golimumab via the SC or IV routes of administration.

Within the designated system organ classes, the adverse reactions are listed under headings of frequency, using the following convention:

Very common	(≥ 1/10)
Common	(frequent) (≥ 1/100, < 1/10)
Uncommon	(infrequent) (≥ 1/1000, < 1/100)
Rare	(≥1/10000, < 1/1000, including isolated reports)
Not known	(cannot be estimated from the available data)

Table 3: Summary of golimumab adverse reactions in clinical studies

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis, and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (pneumonia), viral infections (such as influenza and

	herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis
Rare:	Histoplasmosis, coccidioidomycosis, tuberculosis, opportunistic infections (invasive fungal infections, bacterial, atypical mycobacterial and protozoal), hepatitis B reactivation, pneumocystosis, arthritis bacterial, bursitis infective
Neoplasm benign and malignant	
Rare:	Lymphoma, leukemia
Not known:	Pediatric malignancy
Investigations	
Common:	Alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon:	Neutrophil count decreased
Blood and lymphatic system disorders	
Common:	Leukopenia (including neutropenia), anemia
Uncommon:	Thrombocytopenia, pancytopenia
Immune system disorders	
Common:	Autoantibody positive, non-serious allergic reactions
Nervous system disorders	
Common:	Dizziness, paraesthesia
Rare:	Demyelinating disorders (central and peripheral)
Cardiac disorders	
Rare:	Congestive heart failure (new onset or worsening)
Vascular disorders	
Common:	Hypertension
Rare:	Vasculitis (systemic)
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Interstitial lung disease
Gastrointestinal disorders	
Uncommon:	Constipation
Skin and subcutaneous tissue disorders	
Common:	Rash, alopecia
Uncommon:	Psoriasis: new onset or worsening, palmar/plantar, and pustular
Rare:	Vasculitis (cutaneous)
Musculoskeletal and connective tissue disorders	
Rare	Lupus-like syndrome
General disorders and administration site conditions	
Common:	Pyrexia, injection site reaction (injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation, paraesthesia)

The data described below reflect adverse reactions from the SC Phase 2 and 3 clinical trials, except for administration reactions which includes both SC and IV data. Throughout this section, median duration of follow-up (approximately 4 years) is generally presented for all golimumab use. Where golimumab 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.

Infections **(see *Warnings and Precautions*)**
In the controlled period of pivotal trials, upper respiratory tract infection was the most common adverse reaction reported in 12.6% of golimumab-treated patients (incidence per patient-year: 0.61; 95% CI: 0.55, 0.67) compared with 11.0% of control patients (incidence per patient-year: 0.55; 95% CI: 0.46, 0.64). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 4 years, the incidence per patient-year of upper respiratory tract infections was 0.35 events; 95% CI: 0.34, 0.36, for golimumab-treated patients.

In the controlled period of pivotal trials, infections were observed in 23.0% of golimumab-treated patients (incidence per patient-year: 1.32; 95% CI: 1.23, 1.41) compared with 20.2% of control patients (incidence per patient-year: 1.22; 95% CI: 1.09, 1.36). In controlled and uncontrolled portions of the trials with a median follow-up of approximately 4 years, the incidence per patient-year of infections was 0.81 events; 95% CI: 0.79, 0.83, for golimumab-treated patients.

Serious infections observed in golimumab-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections, and tuberculosis. In the controlled period of RA, PsA, ulcerative colitis, AS, and nr-Axial SpA trials, serious infections were observed in 1.2% of golimumab-treated patients and 1.2% of control-treated patients. The incidence of serious infections per patient-year of follow-up in the controlled period of RA, PsA, AS, and nr-Axial SpA trials was 0.07; 95% CI: 0.05, 0.11 for the golimumab 100-mg group, 0.03; 95% CI: 0.01, 0.06 for the golimumab 50-mg group and 0.04; 95% CI: 0.02, 0.07 for the placebo group. In the controlled period of UC trials of golimumab induction, serious infections were observed in 0.8% of golimumab-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 patient-year of all serious infections was 0.04; 95% CI: 0.04, 0.05, in patients receiving golimumab 100 mg and 0.03; 95% CI: 0.02, 0.03, 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 **(see *Warnings and Precautions*)**
Lymphoma: The incidence of lymphoma in golimumab-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 up 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 RA Study 2, 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 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 significance of this finding in the asthma population is unknown.

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

Demyelinating disorders **(see *Warnings and Precautions*)**
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. 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 ULN) occurred in similar proportions of golimumab-treated and control patients (22.1% to 27.4% of patients); in the AS and nr-Axial SpA studies, more golimumab-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 golimumab-treated and control patients.

In the controlled period of the UC pivotal trials of golimumab induction, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of golimumab-treated and control patients (7.8% 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 golimumab.

In the controlled period of RA and AS pivotal trials, ALT elevations ≥ 5 x ULN were uncommon and seen in more golimumab-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. 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 golimumab-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 golimumab induction, ALT elevations ≥ 5 x ULN occurred in similar proportions of golimumab-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 golimumab.

Administration reactions
In the controlled periods of the pivotal trials, 5.4% of golimumab-treated patients had injection site reactions compared with 2.0% in control-treated patients. The majority of the injection site reactions were mild and moderate and the most frequent manifestation was injection site erythema.

In the controlled pivotal IV trials in RA through Week 16, 2.5% of placebo-treated subjects and 3.3% of golimumab-treated subjects had an infusion reaction. No serious infusion reactions were reported.

In controlled Phase 2 and/or 3 trials in RA, PsA, AS, nr-Axial SpA, severe persistent asthma, and Phase 2/3 trials in UC, no patients treated with golimumab developed anaphylactic reactions deemed to be related to golimumab.

Antinuclear antibodies (ANA)/anti-double-stranded DNA (dsDNA) antibodies
In the controlled and uncontrolled periods of the pivotal trials through 1 year of follow-up, 3.5% of golimumab-treated patients and 2.3% of control patients were newly ANA-positive (at titers of 1:160 or

greater). The frequency of anti-dsDNA antibodies at 1 year of follow-up in patients anti-dsDNA negative at baseline was 1.1% (see *Warnings and Precautions*).

Pediatric population
Polyarticular juvenile idiopathic arthritis
The safety of golimumab 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.

Postmarketing experience
The frequencies provided below reflect reporting rates of adverse reactions from the worldwide postmarketing experience with golimumab. Precise estimates of incidence cannot be made due to voluntary reporting from a population of uncertain size. These adverse 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 (≥ 1/10000 and < 1/1000), Very rare (< 1/10000, including isolated reports), and Not known (cannot be estimated from the available data).

Table 4: Golimumab postmarketing adverse reactions

System Organ Class	Adverse Reaction	Frequency
Neoplasm benign and malignant	Melanoma Merkel cell carcinoma Hepatosplenic T-cell lymphoma*	Rare Not known
Immune system disorders	Serious systemic hypersensitivity reactions (including anaphylactic reaction) Sarcoidosis	Rare
Skin and subcutaneous tissue disorders	Bullous skin reactions Lichenoid reactions Skin exfoliation	Uncommon Rare

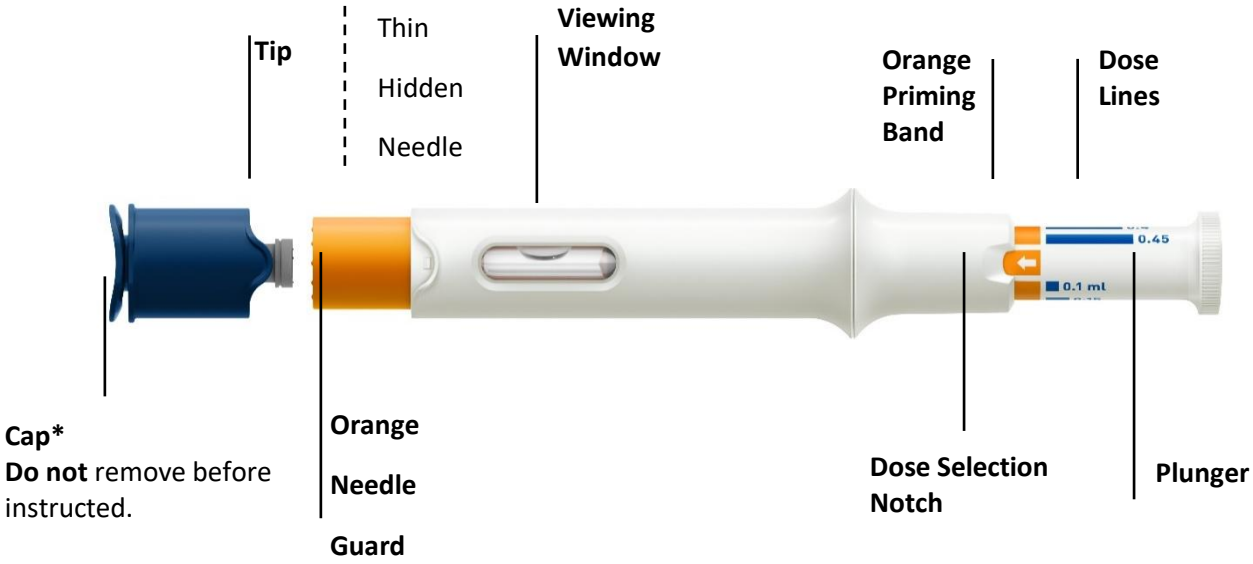
* Observed with other TNF-blocking agents.

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

INCOMPATIBILITIES
Specific drug compatability studies have not been conducted.

INSTRUCTIONS FOR USE

Your pre-filled pen at-a-glance



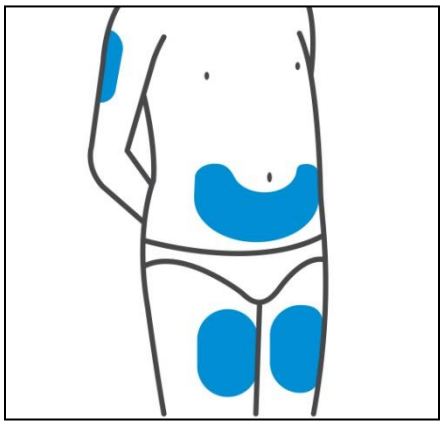
IMPORTANT:

Do not press on the orange needle guard before the injection. It will lock, and you will not receive the dose.

Do not lift the pre-filled pen from the skin during the injection. The orange needle guard will lock, and you will

***CHOKING HAZARD! Keep out of reach of children.**

1. Prepare for your injection

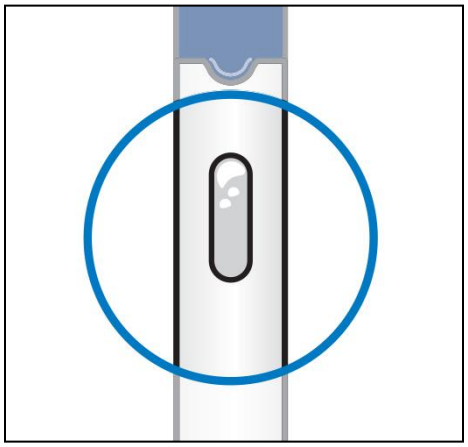


Choose injection site
Select from the following areas for your injection:

- **Front of thighs** (recommended)
- Lower abdomen
  Do not use the 5-centimeter area around your belly-button.
- Back of upper arms (if a caregiver is giving you the injection)

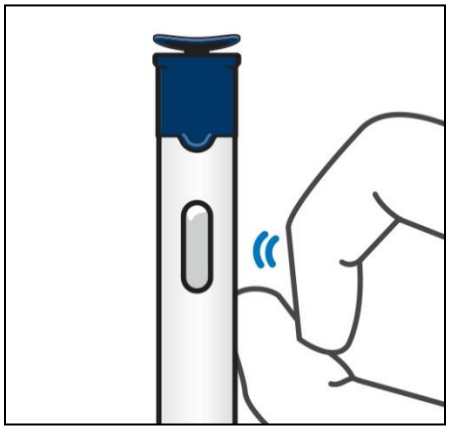
Choose a different site within your preferred area for each injection.
Do not inject into skin that is tender, bruised, red, scaly, hard or has scars.

Clean injection site
Wash your hands well with soap and warm water.
Wipe your chosen injection site with an alcohol swab and allow it to dry.
Do not touch, fan, or blow on the injection site after you have cleaned it.

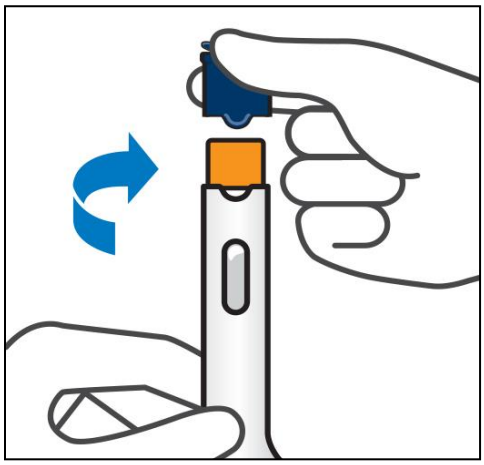


Inspect liquid
Take the pre-filled pen out of the carton.
Check the liquid in the viewing window. It should be clear to slightly opalescent (having pearl-like shine) and colorless to light yellow and may contain a few small translucent or white particles of protein. You may also see one or more air bubbles. This is normal.

Do not inject if the liquid is the wrong color, cloudy or has large particles. If you are uncertain, call your doctor or pharmacist for a new pre-filled pen.



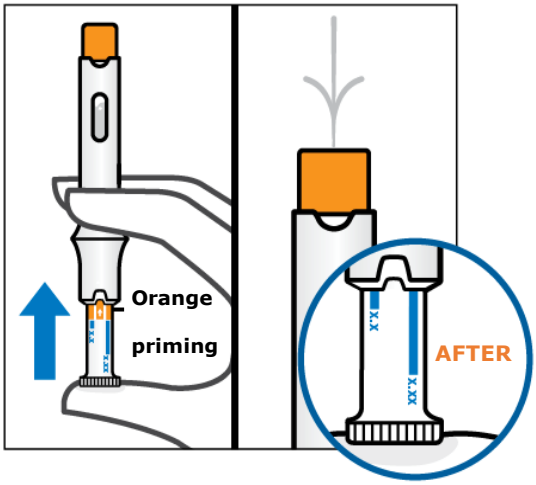
Tap air bubbles to top
Hold the pre-filled pen upright with the blue cap pointing up.
Tap the pre-filled pen gently with your finger near the viewing window. This will cause any air bubbles to rise to the top.



Remove cap
Keep holding the pre-filled pen upright, then twist and pull the cap to remove.

IMPORTANT: **Do not** press on the orange needle guard before the injection. It will lock, and you will not receive the dose.

Inject within 5 minutes of removing the cap.
Do not put the cap back on, this may damage the hidden needle.
Do not use the pre-filled pen if it is dropped without the cap on.
Call your doctor or pharmacist for a new pre-filled pen.

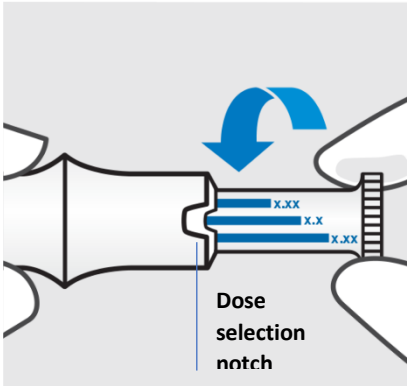


Remove air bubbles*
Keep holding the pre-filled pen upright.
Gently, press the plunger up with your thumb until it stops. Liquid will squirt out. This is normal.

The orange priming band will disappear.

**Removing air bubbles helps make sure the right dose is given.*
After you remove the air bubbles, you may see a line inside the viewing window. This is normal.

2. Inject Golimumab (Simponi®) using the pre-filled pen

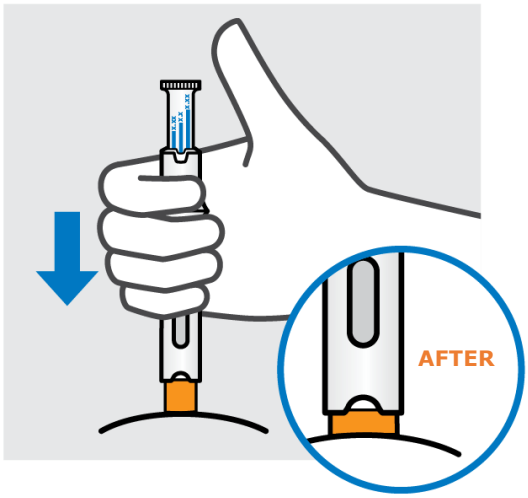


Set prescribed dose
Turn plunger until the dose line for your prescribed dose lines up with the dose selection notch. The pre-filled pen is now ready to use.

Dose selections:

0.1 mL
0.15 mL
0.2 mL
0.25 mL
0.3 mL

0.35 mL
0.4 mL
0.45 mL

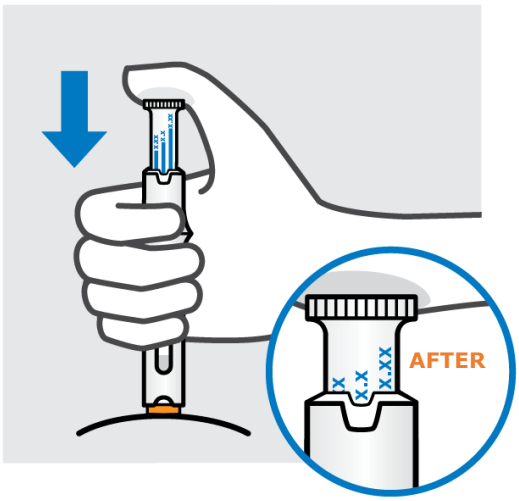


Insert needle and hold in place

IMPORTANT: **Do not** lift the pre-filled pen from the skin during the injection. The orange needle guard will lock, and you will not receive the full dose.

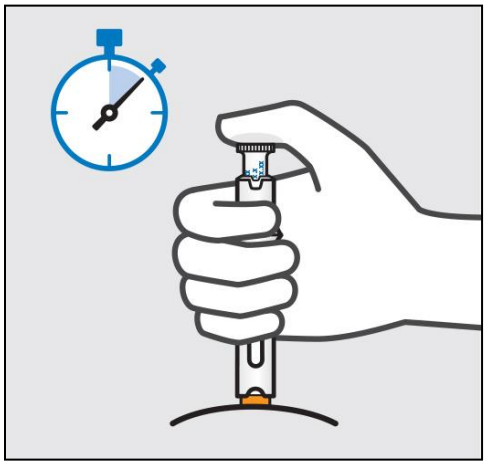
Do not press the plunger while inserting the needle.

Push and hold the pre-filled pen tip against the skin so the orange needle guard pushes up until it stops. Some orange will still be showing.



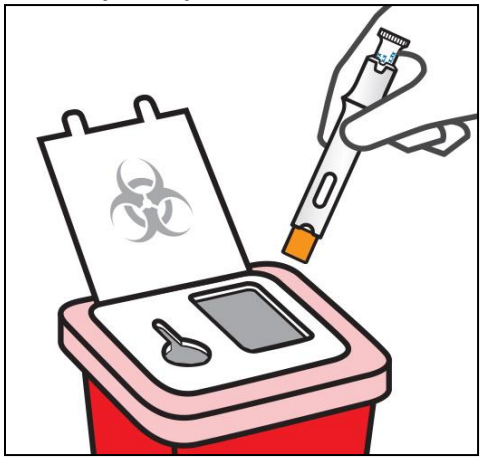
Inject Golimumab (Simponi®)
Keep pushing the pre-filled pen against the skin.
Gently, press the plunger until it stops.
If a small dose is set, the plunger will only move a short distance.
The dose you delivered can be confirmed by viewing the dose selection notch.

Do not lift the pre-filled pen up yet.

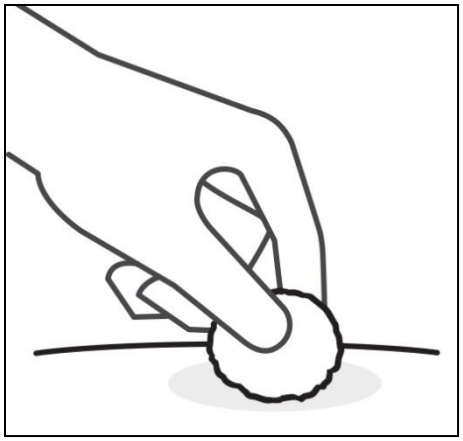


Keep holding, then lift
Keep pushing the pre-filled pen against the skin for approximately 5 seconds.
It is normal to see some drug still visible in the viewing window.
Lift the pre-filled pen away from the skin.
The orange needle guard will extend and lock.

3. After your injection



Throw the used pre-filled pen away
Put your used pre-filled pen in a sharps disposal container right away after use.
Make sure you dispose of the bin as instructed by your doctor or nurse when the container is full.



Check injection site
There may be a small amount of blood or liquid at the injection site.
Hold pressure on your skin with a cotton ball or gauze pad until any bleeding stops.
Do not rub the injection site.
If needed, cover injection site with a bandage. Your injection is now complete!

STORAGE CONDITIONS
Store in a refrigerator (2-8°C).
Store in original carton until time of use. Protect from light. Do not freeze. Do not shake. Keep out of the sight and reach of children.

AVAILABILITY
1 pre-filled pen/Box of 1's

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Patient must seek medical attention immediately at the first sign of adverse drug reaction. For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Questions or comments? Email us at Janssendrugsafety_Phil@its.jnj.com.

REGISTRATION NUMBER
BR-1349

DATE OF FIRST AUTHORIZATION
27 May 2021

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Version : *31 July 2019*