Golimumab

Simponi®
50 mg/0.5 mL Solution for Injection (SC) in a pre-filled pen (SmartJect®)
Tumor necrosis factor alpha (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 administration in the following presentation:

Autoinjector/Pre-filled Pen

- Each single-use autoinjector/pre-filled pen contains 50 mg golimumab per 0.5 mL.

For excipients, see List of Excipients.

CLINICAL INFORMATION

INDICATIONS

Rheumatoid arthritis (RA)

Golimumab (Simponi®), by subcutaneous (SC) administration, in combination with methotrexate (MTX), is indicated for:

- Reducing signs and symptoms
- Inducing major clinical response
- Inhibiting the progression of structural damage
- Improving physical function
- Improving health-related quality of life

in adult patients with moderately to severely active rheumatoid arthritis. Golimumab (Simponi®) can be used in patients previously treated with TNF inhibitors.

Psoriatic arthritis (PsA)

Golimumab (Simponi®), by SC administration, alone or in combination with MTX, is indicated for:

- Reducing signs and symptoms
- Improving physical function
- Inhibiting the progression of structural damage
- Improving enthesitis
- Improving psoriasis and psoriatic nail disease
- Improving health-related quality of life

in adult patients with active psoriatic arthritis.

Ankylosing spondylitis (AS)

Golimumab (Simponi®), by SC administration, is indicated for:

- Reducing signs and symptoms
- Improving physical function
- Improving health-related quality of life

in adult patients with active ankylosing spondylitis.

Polyarticular juvenile idiopathic arthritis (pJIA)
Golimumab (Simponi®), by subcutaneous administration, in combination with MTX, is indicated for treatment of polyarticular juvenile idiopathic arthritis in children with a body weight of at least 40 kg, who have responded inadequately to previous therapy with MTX.

Non-radiographic axial spondyloarthritis (nr-Axial SpA)
Golimumab (Simponi®) by SC administration, is indicated for:
- Reducing signs and symptoms
- Improving spinal mobility
- Improving physical function
- Improving health-related quality of life

in adult patients with severe active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to, or are intolerant to, nonsteroidal anti-inflammatory drugs (NSAIDs).

Ulcerative colitis (UC)
Golimumab (Simponi®), by SC administration, is indicated for:
- Reducing signs and symptoms
- Inducing clinical remission
- Inducing mucosal healing
- Improving health-related quality of life
- Maintaining clinical response
- Achieving long-term clinical remission
- Achieving long-term mucosal healing

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

DOSAGE AND ADMINISTRATION
Golimumab (Simponi®) is administered by subcutaneous injection.
Adult patients with:
Rheumatoid arthritis/Psoriatic arthritis/Ankylosing spondylitis/Non-radiographic axial spondyloarthritis
50 mg of Golimumab (Simponi®) given as a subcutaneous injection once a month, on the same date each month.
Ulcerative colitis
Patients with body weight less than 80 kg
Golimumab (Simponi®) given as an initial dose of 200 mg, followed by 100 mg at Week 2, then 50 mg every 4 weeks, thereafter (see ***Pharmacodynamic Properties***, ***Clinical Efficacy***).
Patients with body weight greater than or equal to 80 kg
Golimumab (Simponi®) given as an initial dose of 200 mg, followed by 100 mg at Week 2, then 100 mg every 4 weeks, thereafter (see ***Pharmacodynamic Properties***, ***Clinical Efficacy***).
During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.
Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after 4 doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period.

Golimumab (Simponi®) is intended for use under the guidance and supervision of a physician. 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. Patients should be instructed to inject the full amount of Golimumab (Simponi®) according to the directions provided in **Instructions for Injecting Golimumab Simponi®) Using a Single-Use SmartJect® Autoinjector/Pre-Filled Pen**.

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***).

Polyarticular juvenile idiopathic arthritis
50 mg of Golimumab (Simponi®) administered once a month, on the same date each month, for children with a body weight of at least 40 kilograms.
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.

Elderly (65 years of age and older)
Dose adjustment is not required in elderly patients (see ***Warnings and Precautions***).

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 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 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.

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

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
Although concomitant use of methotrexate results in higher steady-state trough concentrations of Golimumab (Simponi®) in patients with RA, PsA, or AS, 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 Phase 3 clinical trials are available from 6161 golimumab-treated patients including 3090 with rheumatoid arthritis, 634 with psoriatic arthritis, 768 with ankylosing spondylitis, 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 1. 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 1: 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, paresthesia
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, paresthesia)

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 in the RA and PsA studies (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 in the Phase 3 RA, PsA, and AS studies. 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.

Injection site 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 controlled Phase 2 and Phase 3 trials in RA, PsA, AS, severe persistent asthma, nr-Axial SpA, 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 III 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 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 2: 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	Uncommon
	Lichenoid reactions Skin exfoliation	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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Mechanism of action

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

Pharmacodynamic effects

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

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with Golimumab (Simponi®) resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNFα 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 Golimumab (Simponi®) administration and were generally maintained through Week 24.

Clinical efficacy

Rheumatoid arthritis

The efficacy of Golimumab (Simponi®) was demonstrated in three multi-center, randomized, double-blind, placebo-controlled studies in over 1500 patients ≥ 18 years of age with moderately to severely active RA diagnosed according to American College of Rheumatology (ACR) criteria for at least 3 months prior to screening. Patients had at least 4 swollen and 4 tender joints. Golimumab (Simponi®) or placebo were subcutaneously administered every 4 weeks.

RA Study 1 (GO-FORWARD) evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with an anti-TNF agent. Patients were randomized to receive placebo + MTX, Golimumab (Simponi®) 50 mg + MTX, Golimumab (Simponi®) 100 mg + MTX, or Golimumab (Simponi®) 100 mg + placebo. Patients receiving placebo + MTX were switched to Golimumab (Simponi®) 50 mg + MTX after Week 24. At Week 52, patients entered an open-label, long-term extension.

RA Study 2 (GO-AFTER) evaluated 445 patients who were previously treated with one or more of the anti-TNF agents adalimumab, etanercept, or infliximab. Patients were randomized to receive placebo, Golimumab (Simponi®) 50 mg, or Golimumab (Simponi®) 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti-TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

RA Study 3 (GO-BEFORE) evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with an anti-TNF agent. Patients were randomized to receive placebo + MTX,Golimumab (Simponi®) 50 mg + MTX, Golimumab (Simponi®) 100 mg + MTX, or Golimumab (Simponi®) 100 mg + placebo. At Week 52, patients entered an open-label, long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to Golimumab (Simponi®) 50 mg + MTX.

In RA Study 1, the co-primary endpoints were the percentage of patients achieving an ACR 20 response at Week 14 and the improvement from baseline in Health Assessment Questionnaire (HAQ) at Week 24. In RA Study 2, the primary endpoint was the percentage of patients achieving an ACR 20 response at Week 14. In RA Study 3, the co-primary endpoints were the percentage of patients achieving ACR 50 response at Week 24 and the change from baseline in the van der Heijde-modified Sharp (vdH-S) score at Week 52. In addition to the primary endpoint(s), additional assessments of the impact of Golimumab (Simponi®) treatment on the signs and symptoms of arthritis, physical function, and health-related quality of life were performed.

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

Signs and symptoms
Key ACR results for the Golimumab (Simponi®) 50-mg dose at Week 14, Week 24, and Week 52 for RA Study 1, RA Study 2, and RA Study 3 are shown in Table 3 and are described below. Responses were observed at the first assessment (Week 4) after the initial Golimumab (Simponi®) administration.

In RA Study 1, among 89 patients randomized to Golimumab (Simponi®) 50 mg + MTX, 48 were still on this treatment at Week 104. Among those, 40, 33 and 24 patients had ACR 20/50/70 response, respectively at Week 104.

In RA Study 2, the percentage of patients achieving an ACR 20 response was greater for patients receiving Golimumab (Simponi®) than for patients receiving placebo regardless of the reason reported for discontinuation of one or more prior anti-TNF therapies.

Table 3: Key efficacy outcomes from the controlled periods of RA Study 1, RA Study 2, and RA Study 3

	RA Study 1 Active RA despite MTX		**RA Study 2 Active RA, previously treated with one or more anti-TNF agent(s)**		**RA Study 3 Active RA, MTX Naïve**	
	Placebo + MTX	**Golimumab (Simponi®) 50 mg + MTX**	**Placebo**	**Golimumab (Simponi®) 50 mg**	**Placebo + MTX**	**Golimumab (Simponi®) 50 mg + MTX**
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						
Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	16%	31% p=0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p=0.021	NA	NA

Week 24	14%	37%*	4%	16%*	29%	40%
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p=0.008	2%	10% p=0.005	NA	NA
Week 24	5%	20%*	2%	9% p=0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

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

* $p \leq 0.001$

NA: Not Applicable

In RA Study 3, the primary analysis in patients with moderate to severe rheumatoid arthritis (combined Golimumab (Simponi®) 50-mg and 100-mg + MTX groups vs. MTX alone for ACR 50) was not statistically significant at Week 24 (p=0.053). At Week 52 in the overall population, the percentage of patients in the Golimumab (Simponi®) 50-mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 3).

In RA Study 1 and RA Study 2, clinically meaningful and statistically significant responses in Disease Activity Scale (DAS)28 were observed at each prespecified timepoint, at Week 14 and at Week 24 ($p \leq 0.001$). Among patients who remained on the Golimumab (Simponi®) treatment to which they were randomized at study start, DAS28 responses were maintained through Week 104.

In RA Study 3, major clinical response, defined as the maintenance of an ACR 70 response over a continuous 6-month period, was measured. At Week 52, 15% of patients in the Golimumab (Simponi®) 50-mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group (p=0.018). Among 159 patients randomized to Golimumab (Simponi®) 50 mg + MTX, 96 were still on this treatment at Week 104. Among those, 85, 66, and 53 patients had ACR 20/50/70 response, respectively, at Week 104.

Radiographic response

In RA Study 3, the change from baseline in the vdH-S score, a composite score of structural damage that radiographically measures the number and size of joint erosions and the degree of joint space narrowing in hands/wrists and feet, was used to assess the degree of structural damage. Key results for the Golimumab (Simponi®) 50-mg dose at Week 52 are presented in Table 4.

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

Table 4: Radiographic mean (SD) changes from baseline in total vdH-S score at Week 52 in the overall population of GO-BEFORE

	Placebo + MTX	**Golimumab (Simponi®) 50 mg + MTX**
n[a]	160	159
Total Score		
Baseline	19.7 (35.4)	18.7 (32.4)
Change from baseline	1.4 (4.6)	0.7 (5.2)*
Erosion Score		
Baseline	11.3 (18.6)	10.8 (17.4)
Change from baseline	0.7 (2.8)	0.5 (2.1)
JSN Score		
Baseline	8.4 (17.8)	7.9 (16.1)
Change from baseline	0.6 (2.3)	0.2 (2.0)**

[a] n reflects randomized patients.

* p=0.015
** p=0.044

Physical function and health-related quality of life
Physical function and disability were assessed as a separate endpoint in RA Study 1 and RA Study 2 using the disability index of the HAQ. In these studies, Golimumab (Simponi®) demonstrated clinically meaningful and statistically significant improvement in HAQ from baseline vs. control at Week 24. Among patients who remained on the Golimumab (Simponi®) treatment to which they were randomized at study start, improvement in HAQ was maintained through Week 104.

In RA Study 1, 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 Golimumab (Simponi®) vs. placebo at Week 24. Among patients who remained on the Golimumab (Simponi®) treatment to which they were randomized at study start, improvement of the SF-36 physical component was maintained through Week 104. In RA Study 1 and RA Study 2, statistically significant improvements were observed in fatigue as measured by functional assessment of chronic illness therapy-fatigue scale (FACIT-F).

Psoriatic arthritis
The safety and efficacy of Golimumab (Simponi®) were evaluated in a multi-center, randomized, double-blind, placebo-controlled study (GO-REVEAL) in 405 adult patients with active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite non-steroidal anti-inflammatory (NSAID) or DMARD therapy. Patients in this study had a diagnosis of PsA for at least 6 months and had at least mild psoriatic disease. Patients with each sub-type of psoriatic arthritis were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). Previous treatment with an anti-TNF agent was not allowed. Golimumab (Simponi®) or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Golimumab (Simponi®) 50 mg, or Golimumab (Simponi®) 100 mg. Patients receiving placebo were switched to Golimumab (Simponi®) 50 mg after Week 24. Patients entered an open-label, long-term extension at Week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at Week 14 and change from baseline in total PsA modified vdH-S score at Week 24.
In general, no clinically meaningful differences in measures of efficacy were observed between the Golimumab (Simponi®) 50-mg and 100-mg dosing regimens.

Signs and symptoms
Key results for the 50-mg dose at Week 14 and Week 24 are shown in Table 5 and described below.

Table 5: Key efficacy outcomes from PsA study

	Placebo	**Golimumab (Simponi®) 50 mg***
n[a]	113	146
Responders, % of patients		
ACR 20		
Week 14	9%	51%
Week 24	12%	52%
ACR 50		
Week 14	2%	30%

Week 24	4%	32%
ACR 70		
Week 14	1%	12%
Week 24	1%	19%
PASI[b] 75[c]		
Week 14	3%	40%
Week 24	1%	56%

* p<0.05 for all comparisons;

a n reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint

b Psoriasis Area and Severity Index

c Based on the subset of patients with ≥ 3% BSA involvement at baseline, 79 patients (69.9%) in the placebo group and 109 (74.3%) in the Golimumab (Simponi®) 50-mg group.

Responses were observed at the first assessment (Week 4) after the initial Golimumab (Simponi®) administration. Similar ACR 20 responses at Week 14 were observed in patients with polyarticular arthritis with no rheumatoid nodules and asymmetric peripheral arthritis PsA subtypes. The number of patients with other PsA subtypes was too small to allow meaningful assessment. Responses observed in the Golimumab (Simponi®)-treated groups were similar in patients receiving and not receiving concomitant MTX. Among 146 patients randomized to Golimumab (Simponi®) 50 mg, 70 were still on this treatment at Week 104. Of these 70 patients, 64, 46, and 31 patients had an ACR 20/50/70 response, respectively.

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

At Week 24, improvements in parameters of peripheral activity characteristic of psoriatic arthritis (e.g. number of swollen joints, number of painful/tender joints, dactylitis and enthesitis) were seen in the Golimumab (Simponi®)-treated patients. Golimumab (Simponi®) treatment resulted in significant improvement in physical function as assessed by HAQ, as well as significant improvements in health-related quality of life as measured by the physical and mental component summary scores of the SF-36. Among patients who remained on the Golimumab (Simponi®) treatment to which they were randomized at study start, DAS28 and HAQ responses were maintained through Week 104.

Radiographic response

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

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

Ankylosing spondylitis

The safety and efficacy of Golimumab (Simponi®) were evaluated in a multi-center, randomized, double-blind, placebo-controlled study (GO-RAISE) in 356 adult patients with active ankylosing spondylitis (defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥ 4 and

a VAS for total back pain of ≥ 4, on a scale of 0 to 10 cm). Patients enrolled in this study had active disease despite current or previous NSAID or DMARD therapy and had not previously been treated with anti-TNF therapy. Golimumab (Simponi®) or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, Golimumab (Simponi®) 50 mg, and Golimumab (Simponi®) 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ, and/or HCQ). The primary endpoint was the percentage of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

Key results for the 50-mg dose are shown in Table 6 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the Golimumab (Simponi®) 50-mg and 100-mg dosing regimens.

Table 6: Key efficacy outcomes from AS study

	Placebo	**Golimumab (Simponi®) 50 mg***
n[a]	78	138
Responders, % of patients		
ASAS 20		
Week 14	**22%**	**59%**
Week 24	23%	56%
ASAS 40		
Week 14	15%	45%
Week 24	15%	44%
ASAS 5/6		
Week 14	8%	50%
Week 24	13%	49%

* p≤0.001 for all comparisons
[a] n reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint

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

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

Non-radiographic axial spondyloarthritis

The safety and efficacy of Golimumab (Simponi®) were evaluated in a multi-centre, randomised, double-blind, placebo-controlled study (GO-AHEAD) in 197 adult patients with severe active nr-Axial SpA (defined as those patients meeting the ASAS classification criteria of axial spondyloarthritis but did not meet the modified New York criteria for AS). Patients enrolled in this study had active disease (defined as a BASDAI ≥ 4 and a Visual Analogue Scale (VAS) for total back pain of ≥ 4, each on a scale of 0-10 cm) despite current or previous NSAID therapy and had not previously been treated with any biological agents including anti-TNF therapy. Patients

were randomly assigned to placebo or Golimumab (Simponi®) 50 mg administered subcutaneously every 4 weeks. At week 16, patients entered an open label period in which all patients received Golimumab (Simponi®) 50 mg administered subcutaneously every 4 weeks through week 48 with efficacy assessments performed through Week 52 and safety follow-up through Week 60. Approximately 93% of patients who were receiving Golimumab (Simponi®) at the beginning of the open-label extension (Week 16) remained on treatment through the end of the study (Week 52). Analyses were performed on both the All Treated (AT, N = 197) and Objective Signs of Inflammation (OSI, N = 158, defined by elevated CRP and/or evidence of sacroiliitis on MRI at baseline) populations. Placebo-controlled efficacy data were collected and analysed through week 16. The primary endpoint was the proportion of patients achieving ASAS 20 response at week 16. Key results are shown in Table 7 and described below.

Table 7: Key efficacy outcomes from GO-AHEAD at week 16

Improvements in signs and symptoms				
	All treated population (AT)		Objective signs of inflammation population (OSI)	
	Placebo	Golimumab (Simponi®) 50 mg	Placebo	Golimumab (Simponi®) 50 mg
n[a]	100	97	80	78
Responders, % of patients				
ASAS 20	40%	71%**	38%	77%**
ASAS 40	23%	57%**	23%	60%**
ASAS 5/6	23%	54%**	23%	63%**
ASAS Partial Remission	18%	33%*	19%	35%*
ASDAS-C[b] < 1.3	13%	33%*	16%	35%*
BASDAI 50	30%	58%**	29%	59%**
Inhibition of inflammation in sacroiliac (SI) joints as measured by MRI				
	Placebo	Golimumab (Simponi®) 50 mg	Placebo	Golimumab (Simponi®) 50 mg
n[c]	87	74	69	61
Mean change in SPARCC[d] MRI Sacroiliac joint score	-0.9	-5.3**	-1.2	-6.4**

[a] n reflects randomized and treated patients
[b] Ankylosing Spondylitis Disease Activity Score C-Reactive Protein (AT-Placebo, N = 90; AT- Golimumab (Simponi®) 50 mg, N = 88; OSI-Placebo, N = 71; OSI- Golimumab (Simponi®) 50 mg, N = 71)
[c] n reflects number of patients with baseline and week 16 MRI data
[d] SPARCC (Spondyloarthritis Research Consortium of Canada)
** $p < 0.0001$ for Golimumab (Simponi®) *vs* placebo comparisons
* $p < 0.05$ for Golimumab (Simponi®) *vs* placebo comparisons

Statistically significant improvements in signs and symptoms of severe active nr-Axial SpA were demonstrated in patients treated with Golimumab (Simponi®) 50 mg compared to placebo at week 16 (Table 7). Improvements were observed at the first assessment (week 4) after the initial Golimumab (Simponi®) administration. SPARCC score as measured by MRI showed statistically significant reductions in SI joint inflammation at week 16 in patients treated with Golimumab (Simponi®) 50 mg compared to placebo (Table 7). Pain as assessed by the Total Back Pain and Nocturnal Back Pain VAS, and disease activity as measured by ASDAS-C also showed statistically significant improvement from baseline to week 16 in patients treated with Golimumab (Simponi®) 50 mg compared to placebo ($p < 0.0001$). The improvement observed at Week 16 among patients treated with Golimumab (Simponi®) 50 mg continued in those remaining in the study at Week 52.

Statistically significant improvements in spinal mobility as assessed by BASMI (Bath Ankylosing Spondylitis Metrology Index) and in physical function as assessed by the BASFI were demonstrated in Golimumab (Simponi®) 50 mg-treated patients as compared to placebo-treated patients ($p < 0.0001$). Patients treated with Golimumab (Simponi®) experienced significantly more improvements in health-related quality of life as assessed by ASQoL, EQ-5D, and physical and mental components of SF-36, and experienced significantly more improvements in productivity as assessed by greater reductions in overall work impairment and in activity impairment as assessed by the WPAI questionnaire than patients receiving placebo. The improvement observed at Week 16 among patients treated with Golimumab (Simponi®) 50 mg continued in those remaining in the study at Week 52. For all of the endpoints described above, statistically significant results were also demonstrated in the OSI population. Similar improvements in signs and symptoms, spinal mobility, and physical function were observed at week 16 through week 52 among patients remaining in the study and treated with Golimumab (Simponi®) 50 mg.

Ulcerative colitis

The efficacy of Golimumab (Simponi®) was evaluated in two randomized, double-blind, placebo-controlled clinical studies in adult patients.

The induction study (PURSUIT-Induction) evaluated patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12; Endoscopy subscore ≥ 2) who had an inadequate response to or failed to tolerate conventional therapies, or were corticosteroid dependent. In the dose-confirming portion of the study, efficacy was evaluated in 761 patients who were randomized to receive either 400 mg Golimumab (Simponi®) SC at Week 0 and 200 mg at Week 2, 200 mg Golimumab (Simponi®) SC at Week 0 and 100 mg at Week 2, or placebo SC at Week 0 and Week 2. Concomitant stable doses of oral aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted. The efficacy of Golimumab (Simponi®) through Week 6 was assessed in this study.

The results of the maintenance study (PURSUIT-Maintenance) were based on evaluation of 456 patients who achieved clinical response from previous induction with Golimumab (Simponi®). Patients were randomized to receive Golimumab (Simponi®) 50 mg, Golimumab (Simponi®) 100 mg, or placebo administered subcutaneously every 4 weeks. Concomitant stable doses of oral aminosalicylates, and/or immunomodulatory agents were permitted. Corticosteroids were to be tapered at the start of the maintenance study. The efficacy of Golimumab (Simponi®) through Week 54 was assessed in this study. Patients who completed the maintenance study through Week 54 continued treatment in a study extension, with efficacy evaluated through Week 216.

Table 8: Key efficacy outcomes from PURSUIT-Induction and PURSUIT-Maintenance

PURSUIT-Induction			
	Placebo N=251	**Golimumab (Simponi®) 200/100 mg** N=253	
Percentage of patients			
Patients in clinical response at Week 6[a]	30%	51%**	
Patients in clinical remission[b] at Week 6	6%	18%**	
Patients with mucosal healing[c] at Week 6	29%	42%*	
PURSUIT-Maintenance			
	Placebo[d] N=154	**Golimumab (Simponi®) 50 mg** N=151	**Golimumab (Simponi®) 100 mg** N=151
Percentage of patients			

Maintenance of response (Patients in clinical response through Week 54)[e]	31%	47%*	50%**
Sustained remission (Patients in clinical remission at both Week 30 and Week 54)[f]	16%	23%[g]	28%*

N = number of patients

** $p \leq 0.001$

* $p \leq 0.01$

a Defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1.

b Defined as a Mayo score ≤ 2 points, with no individual subscore > 1

c Defined as 0 or 1 on the endoscopy subscore of the Mayo score.

d Golimumab (Simponi®) induction only.

e Patients were assessed for UC disease activity by partial Mayo score every 4 weeks (loss of response was confirmed by endoscopy). Therefore, a patient who maintained response was in a state of continuous clinical response at each evaluation through Week 54.

f A patient had to be in remission at both Week 30 and Week 54 (without demonstrating a loss of response at any timepoint through Week 54) to achieve durable remission.

g In patients weighing less than 80 kg, a greater proportion of patients who received 50-mg maintenance therapy showed sustained clinical remission compared with those who received placebo.

More Golimumab (Simponi®)-treated patients demonstrated sustained mucosal healing (patients with mucosal healing at both Week 30 and Week 54) in the 50-mg group (42%, nominal $p<0.05$) and 100-mg group (42%, $p<0.005$) compared with patients in the placebo group (27%).

Among the 54% of patients (247/456) who were receiving concomitant corticosteroids at the start of PURSUIT-Maintenance, the proportion of patients who maintained clinical response through Week 54 and were not receiving concomitant corticosteroids at Week 54 was greater in the 50–mg group (38%, 30/78) and 100-mg group (30%, 25/82) compared with the placebo group (21%, 18/87). The proportion of patients who eliminated corticosteroids by Week 54 was greater in the 50-mg group (41%, 32/78) and 100-mg group (33%, 27/82) compared with the placebo group (22%, 19/87). Among patients who entered the study extension, the proportion of subjects who remained corticosteroid-free was generally maintained through Week 216.

At Week 6, Golimumab (Simponi®) significantly improved quality of life as measured by change from baseline in a disease specific measure, IBDQ (inflammatory bowel disease questionnaire). Among patients who received Golimumab (Simponi®) maintenance treatment, the improvement in quality of life as measured by IBDQ was maintained through Week 54.

Approximately 63% of patients, who were receiving Golimumab (Simponi®) at the beginning of the study extension (Week 56), remained on treatment through the end of the study (last Golimumab (Simponi®) administration at Week 212).

Immunogenicity

Following SC administration in patients with RA, PsA, or AS, antibodies to Golimumab (Simponi®) nearly all neutralizing *in vitro*, were detected in 5% (105/2115) 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 than patients receiving golimumab without MTX (approximately 3% [41/1262] vs. 8% [64/853], 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 (azathioprine, 6-mercaptopurine, 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).

The presence of antibodies to golimumab may increase the risk of injection site reactions (see ***Warnings and Precautions***). 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.

Pharmacokinetic Properties

Absorption

Following 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.

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

Distribution

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

Elimination

The systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg. Terminal half-life value was estimated to be approximately 12 ± 3 days in healthy subjects and similar values were observed in patients with RA, PsA, AS, or UC.

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 methotrexate, treatment with 50 mg Golimumab (Simponi®) SC every 4 weeks resulted in a median steady-state trough serum concentration of approximately 0.6 ± 0.4 mcg/mL in patients with active RA despite methotrexate therapy, and 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 methotrexate had approximately 30% lower steady-state trough concentrations of Golimumab (Simponi®) than those who received Golimumab (Simponi®) with methotrexate.

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.

Concomitant use of methotrexate reduced the apparent clearance of Golimumab (Simponi®) by 36% after 6-month treatment with SC Golimumab (Simponi®) in patients with RA. However, population PK analysis indicated that concomitant use of NSAIDs, oral corticosteroids, or sulfasalazine did not influence the apparent clearance of Golimumab (Simponi®).

Following induction doses of 200 mg and 100 mg Golimumab (Simponi®) at Week 0 and Week 2, respectively, and maintenance doses of 50 mg or 100 mg Golimumab (Simponi®) subcutaneously every 4 weeks thereafter to patients with UC, serum golimumab concentrations reached steady-state approximately 14 weeks after the start of therapy. Treatment with 50 mg or 100 mg golimumab subcutaneous every 4 weeks during maintenance resulted in a mean steady-state trough serum concentration of approximately 0.9 ± 0.5 mcg/mL and 1.8 ± 1.1 mcg/mL, respectively.

In UC patients treated with 50 mg or 100 mg Golimumab (Simponi®) subcutaneously every 4 weeks, concomitant use of immunomodulators did not have an apparent effect on steady-state trough levels of golimumab.

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

Linearity
Golimumab exhibited approximately dose-proportional pharmacokinetics in patients with RA over the dose range of 0.1 to 10.0 mg/kg following a single intravenous dose. Following a single SC dose in healthy subjects, approximately dose-proportional pharmacokinetics were also observed over a dose range of 50 mg to 400 mg.

Effect of weight on pharmacokinetics
Population pharmacokinetic analyses showed there was a trend toward higher apparent clearance of golimumab with increasing weight.

NON-CLINICAL INFORMATION

Carcinogenesis, Mutagenesis, 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.

PHARMACEUTICAL INFORMATION

LIST OF EXCIPIENTS

L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Sorbitol

Water for injection

INCOMPATIBILITIES
Specific drug compatibility studies have not been conducted.

STORAGE CONDITIONS
Store in a refrigerator (2ºC -8ºC).
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.

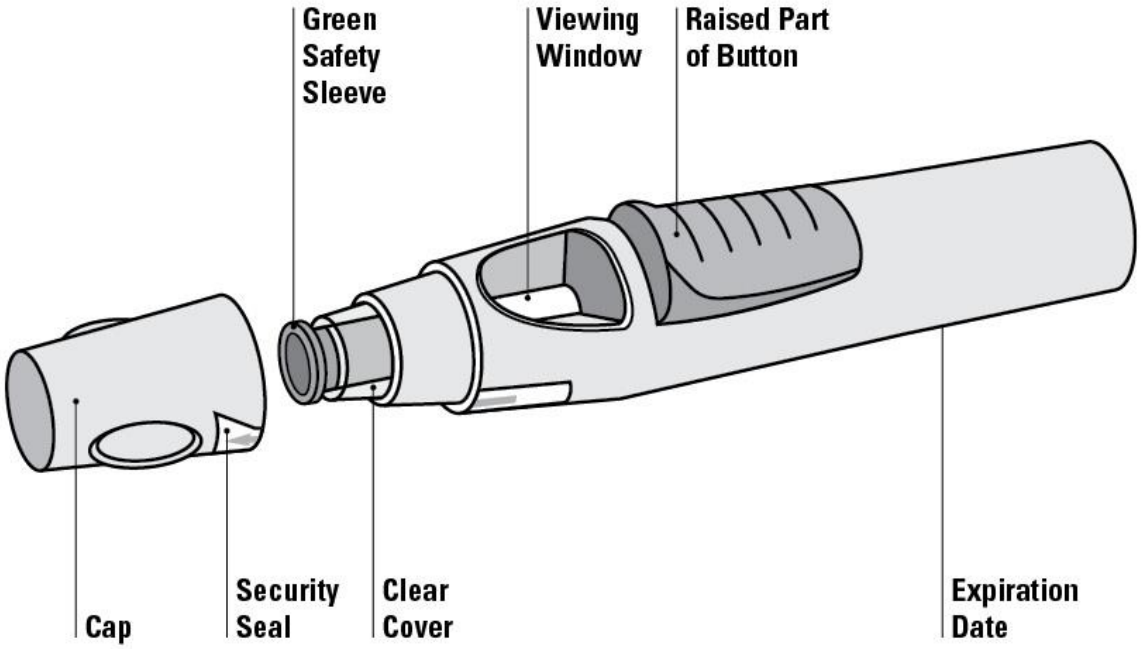
NATURE AND CONTENTS OF CONTAINER
Golimumab (Simponi®) is supplied as a single-use, sterile solution in a Type 1 glass syringe with a fixed stainless steel needle. The syringe is contained in a single-use autoinjector/pre-filled pen. The syringe is stoppered with a coated stopper and the needle is covered with a needle shield to prevent leakage of the solution through the needle and to protect the needle during handling prior to administration. The fixed needle is a 5-bevel, 27G, half-inch stainless steel needle. The needle shields are manufactured using a dry natural rubber containing latex (see ***Warnings and Precautions***).

Golimumab (Simponi®) does not contain preservatives. The solution is clear to slightly opalescent, colorless to light yellow with a pH of approximately 5.5. Each mL of Golimumab (Simponi®) contains 100 mg of golimumab, 0.87 mg L-histidine and L-histidine hydrochloride, 41.0 mg sorbitol, 0.15 mg polysorbate 80, and Water for Injection. There is one strength of Golimumab (Simponi®) available: 50 mg of golimumab in 0.5 mL.

Golimumab (Simponi®) is packaged in a single-use outer carton.

INSTRUCTIONS FOR INJECTING GOLIMUMAB (SIMPONI®) USING A SINGLE-USE SMARTJECT® AUTOINJECTOR / PRE-FILLED PEN
If you would like to self-inject Golimumab (Simponi®), you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your healthcare professional to schedule a training session.

STEP 1: PREPARING TO USE THE AUTOINJECTOR
The diagram below shows what the autoinjector looks like:



DO NOT shake the autoinjector at any time.
DO NOT remove the autoinjector cap from the pen until immediately before the injection.

Check the Expiration Date

- Check the expiration date (indicated as "EXP") on the autoinjector.
- You can also check the expiration date printed on the carton.
- If the expiration date has passed, **DO NOT** use the autoinjector and please contact your doctor, pharmacist, or the local distributor of this medicine for assistance.

Check Security Seal

- Check the security seal around the cap of the autoinjector. If the security seal is broken, **DO NOT** use the autoinjector and please contact your doctor, pharmacist, or the local distributor of this medicine for assistance.

Wait 30 Minutes

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

DO NOT warm the autoinjector in any other way (for example, **DO NOT** warm it in a microwave or in hot water).
DO NOT remove the autoinjector cap while allowing it to reach room temperature.

Assemble Additional Supplies

- Assemble additional supplies you will need for your injection. These include an alcohol swab, a cotton ball or gauze, and a sharps container.

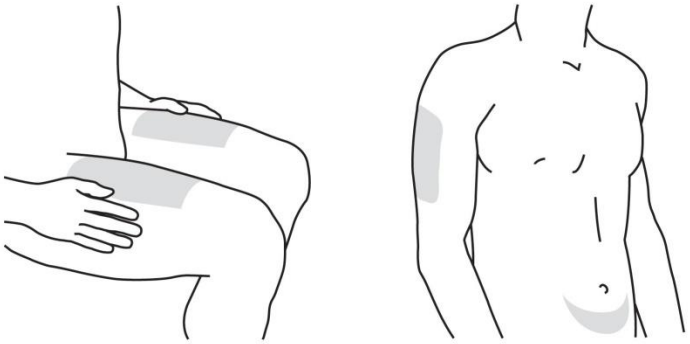
Check the Liquid in the Autoinjector

- Look through the viewing window to make sure that the liquid in the autoinjector is clear to slightly opalescent and colorless to slightly yellow.
- You may also notice an air bubble – this is normal.

DO NOT use if the liquid is discolored, cloudy, or contains particles. If this is the case, please contact your doctor, pharmacist, or the local distributor of this medicine for assistance.

STEP 2: CHOOSING AND PREPARING THE INJECTION SITE
Choose the Injection Site

- The recommended injection site is the front of the middle thighs.
- You can also use the lower abdomen below the belly button, except for the two-inch area directly underneath the belly button.



- If a caregiver is giving you the injection, the caregiver can also use the outer area of the upper arms.
- If multiple injections are required for a single administration, the injections should be administered at different sites on the body.

DO NOT inject into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks.

Preparing the Injection Site

- Thoroughly wash your hands with soap and warm water.
- Wipe the injection site with an alcohol swab.

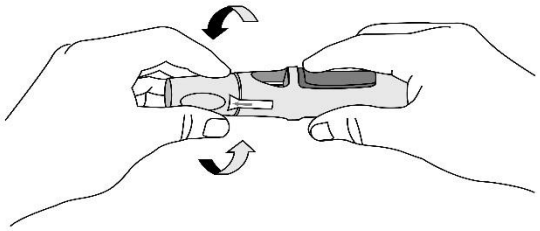
DO NOT touch this area again before giving the injection. Allow the skin to dry before injecting.
DO NOT fan or blow on the clean area.

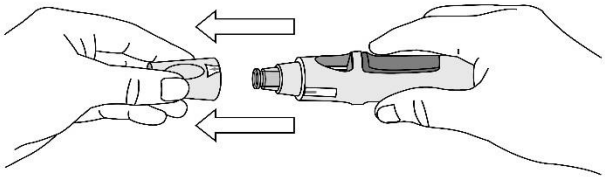
STEP 3: INJECTING THE MEDICATION

Remove the Cap

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

- When you are ready to inject, twist the cap slightly to break the security seal.
- Pull the cap off and immediately place the cap into the trash.

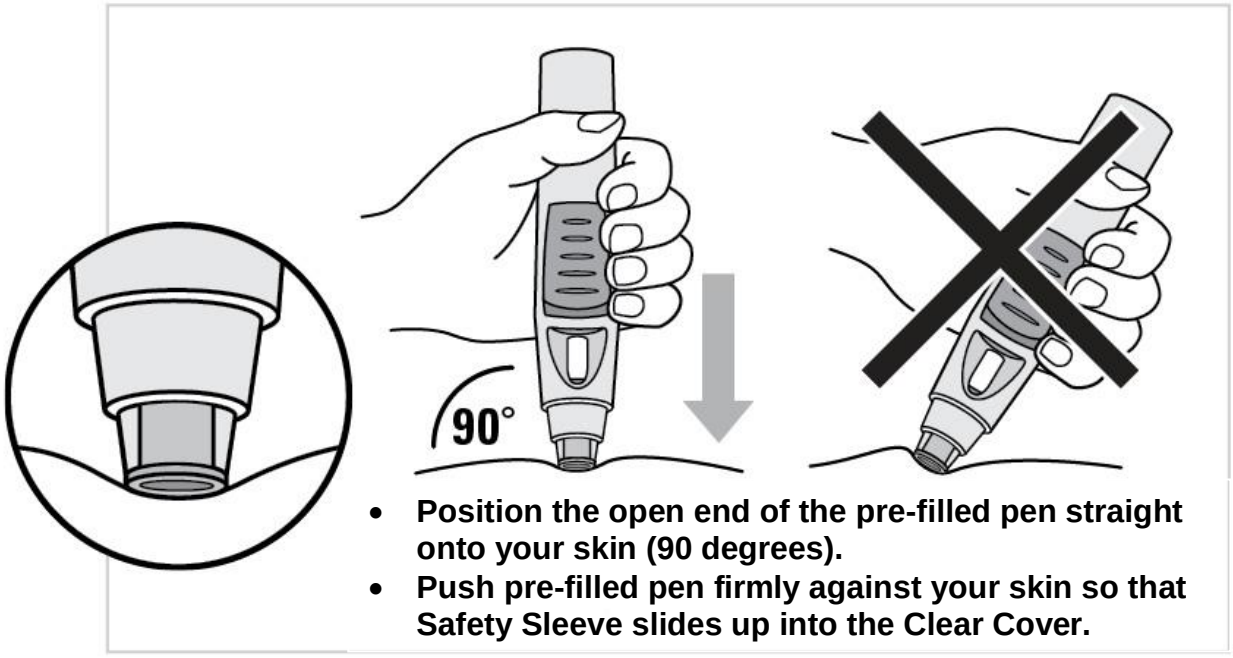




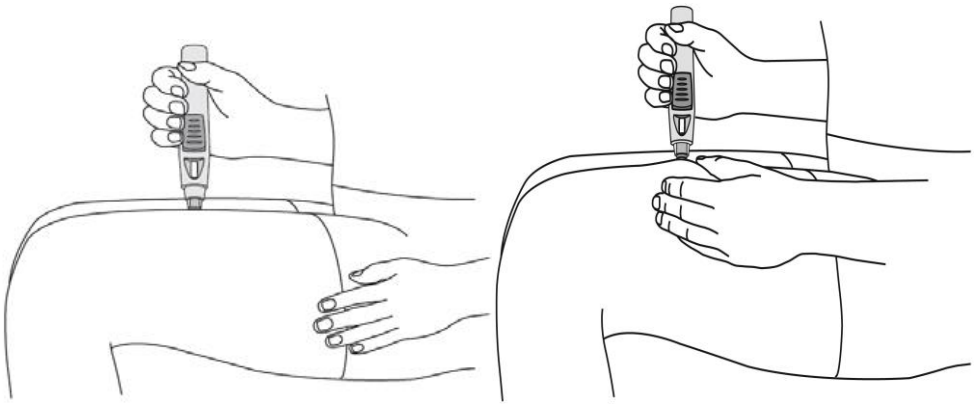
DO NOT put the cap back on because it may damage the needle inside the autoinjector.
Note: **DO NOT** use autoinjector if it is dropped without the cap in place. If you drop the autoinjector without the cap in place, please contact your doctor, pharmacist, or the local distributor of this medicine for assistance.

Push the Autoinjector Against the Skin

- Hold the autoinjector comfortably in your hand. **DO NOT** press the button at this time.
- Push the open end of the autoinjector firmly against the skin at a 90-degree angle.
- **DO NOT** press the button until **after** the autoinjector is pushed firmly against the skin and the Safety Sleeve slides fully into the Clear Cover.

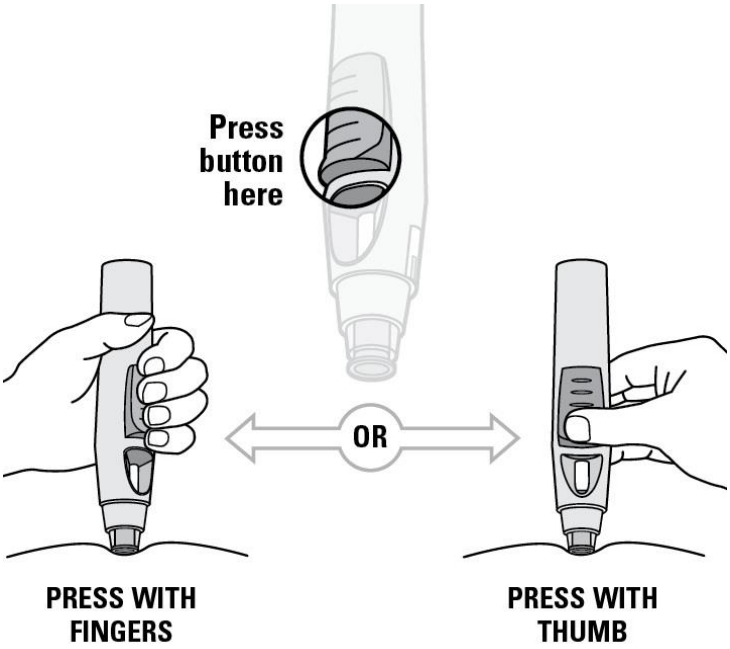


- Injecting without pinching the skin is recommended (left figure). However, if you prefer, you may pinch the skin to create a firmer surface for your injection (right figure).



Press Button to Inject

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

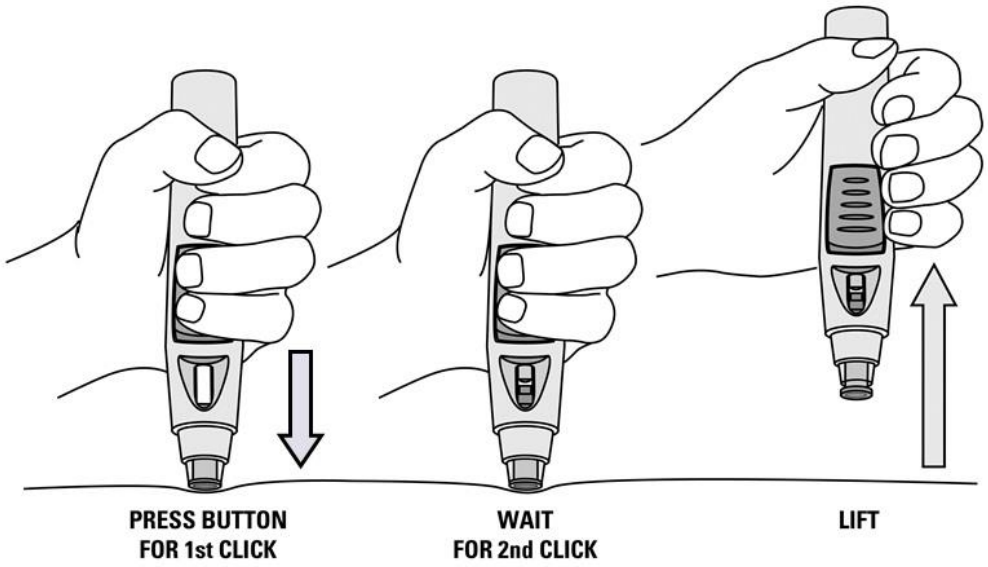


- **You will hear a loud 'click' sound – don't be alarmed.** The first loud 'click' indicates that the needle has been inserted and the injection has started. You may or may not feel a needle prick at this time.

DO NOT lift the autoinjector away from your skin. If you pull the autoinjector away from the skin, you may not get your full dose of medicine.

Wait for Second 'Click'

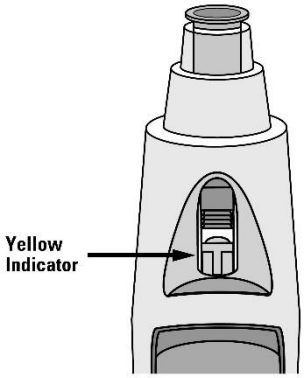
- **Continue to hold the autoinjector against the skin until you hear the second 'click' (it usually take about 3 to 6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound).**
- The second 'click' indicates that the injection is finished and the needle has retracted into the autoinjector. **Note:** If you have a hearing problem and do not hear the second 'click', count 15 seconds from the time you first press the button and then lift the autoinjector from the injection site.
- Lift the autoinjector from the injection site.



STEP 4: AFTER THE INJECTION

Check the Viewing Window

- After injecting, check the viewing window to make sure that the yellow indicator is visible.
- The yellow indicator may not fill the entire viewing window. This is normal.
- This indicates that the autoinjector has worked properly.
- If you do not think you received your injection, check the yellow indicator again to confirm that the dose was delivered.



- If the yellow indicator is not visible in the viewing window, call your doctor, pharmacist, or the local distributor of this medicine for assistance. **DO NOT** administer a second dose without speaking to your doctor.

Disposing of the Autoinjector

- Immediately dispose of the autoinjector in the sharps container.

- Dispose of the sharps container according to your local regulations when the container is full.

Use Cotton Ball or Gauze

- There may be a small amount of blood or liquid at the injection site, which is normal.
- You can press a cotton ball or gauze over the injection site and hold for 10 seconds.

DO NOT rub the injection site.

- You may cover the injection site with a small adhesive bandage, if necessary.

AVAILABILITY
Pre-filled pen (SmartJect®) x 0.5 mL/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 any 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.

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