NAME OF THE MEDICINAL PRODUCT
SIMPONI®

QUALITATIVE AND QUANTITATIVE COMPOSITION
SIMPONI® is a human IgG1κ monoclonal antibody that exhibits multiple glycoforms with predicted molecular masses ranging from 149802 daltons to 151064 daltons. SIMPONI® 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.

SmartJect® Autoinjector / Pre-filled Pen

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

For excipients, see List of Excipients.

PHARMACEUTICAL FORM
Solution for injection

CLINICAL PARTICULARS
Therapeutic Indications
Rheumatoid Arthritis (RA):

SIMPONI®, 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 active rheumatoid arthritis. SIMPONI® can be used in patients previously treated with TNF inhibitors.

Psoriatic Arthritis (PsA):

SIMPONI®, 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):

SIMPONI® is indicated for:

- Reducing signs and symptoms
- Improving physical function
- Improving health related quality of life in adult patients with active ankylosing spondylitis

Posology and Method of Administration
SIMPONI® is administered by subcutaneous injection.

Adult patients with:

Rheumatoid Arthritis / Psoriatic Arthritis / Ankylosing Spondylitis

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

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

SIMPONI® if a physician determines that it is appropriate and with medical follow-up as necessary.

Patients should be instructed to inject the full amount of SIMPONI® according to the directions provided in **INSTRUCTIONS FOR INJECTING SIMPONI® USING A SINGLE-USE SMARTJECT® AUTOINJECTOR / PRE-FILLED PEN**.

Contraindications

None

Special Warnings and Special Precautions for Use

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 SIMPONI®. Some of these serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose them to infections. For patients who have resided in or traveled to regions where histoplasmosis, coccidioidomycosis, or blastomycosis are endemic, the benefits and risks of SIMPONI® treatment should be carefully considered before initiation or continuation of SIMPONI® therapy. In at-risk patients treated with SIMPONI®, an invasive fungal infection should be suspected if they develop a serious systemic illness. Invasive fungal infections may present as disseminated rather than localized disease, and 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 anti-fungal therapy. SIMPONI® should not be given to patients with a clinically important, active infection. Caution should be exercised when considering the use of SIMPONI® in patients with a chronic infection or a history of recurrent infection. Patients should be advised of and avoid exposure to potential risk factors for infection as appropriate.

Tuberculosis

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

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

Tests for latent tuberculosis may yield false negative results, especially in patients who are immunocompromised or severely ill. Prior to initiating SIMPONI®, treatment for latent 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.

Patients receiving SIMPONI® should be monitored closely for signs and symptoms of active tuberculosis during and after treatment, including patients who tested negative for latent tuberculosis infections.

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 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 SIMPONI®, more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with control patients. During the SIMPONI® Phase 2 and Phase 3 clinical trials, the incidence of lymphoma in SIMPONI®-treated patients was higher than expected in the general population. Patients with rheumatoid arthritis and other chronic inflammatory diseases, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF-blocking therapy.

Leukemia

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

Malignancies Other than Lymphoma

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

In an exploratory clinical trial evaluating the use of SIMPONI® in patients with severe persistent asthma, more patients treated with SIMPONI® reported malignancies compared with control patients (See Undesirable Effects). The significance of this finding is unknown.

Skin cancers

Melanoma has been reported in patients treated with TNF blocking agents, including SIMPONI®. Merkel cell carcinoma has been reported in patients treated with other TNF-blocking agents (See Undesirable Effects). 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 SIMPONI®, has been associated with reactivation of hepatitis B virus in patients who are chronic carriers of the virus (i.e. surface antigen positive). Patients should be tested for Hepatitis B Virus (HBV) infection before initiating treatment with immunosuppressants, including SIMPONI®. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Chronic carriers of hepatitis B should be appropriately evaluated and

monitored prior to the initiation of, during treatment with, and for several months following discontinuation of SIMPONI®.

Congestive Heart Failure (CHF)

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

Neurological Events

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 SIMPONI®, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI® should be considered if these disorders develop.

Concurrent Administration of 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 SIMPONI® and anakinra is not recommended.

Concurrent Administration of 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 SIMPONI® and abatacept is not recommended.

Concurrent Administration with other Biological Therapeutics

There is insufficient information regarding the concomitant use of SIMPONI® with other biological therapeutics used to treat the same conditions as SIMPONI®. The concomitant use of SIMPONI® with these biologics is not recommended because of the possibility of an increased risk of infection.

Switching between Biological Therapeutics

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

Hematologic Reactions

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

Vaccinations

Patients treated with SIMPONI® may receive concurrent vaccinations, except for live vaccines. No data are available on the response to vaccination, risk of infection or transmission of infection with the administration of live vaccines to patients receiving SIMPONI®. Psoriatic arthritis patients treated with SIMPONI® in one Phase 3 PsA study were able to mount effective B-cell immune responses to pneumococcal polysaccharide vaccine. Similar numbers of psoriatic arthritis patients receiving SIMPONI® and not receiving SIMPONI® had at least a 2-fold increase in antibody titers. The proportions of

patients with response to pneumococcal vaccine were lower among SIMPONI® and control-treated patients receiving MTX compared with patients not receiving MTX. Overall, the data indicate that SIMPONI® does not suppress the humoral immune response to this vaccine.

Allergic Reactions

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

Special Populations

Pediatric Use

Specific studies of SIMPONI® in pediatric patients have not been conducted.

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 (N=155) who received SIMPONI® were observed compared with younger patients. Because there is a higher incidence of infections in the elderly population in general, caution should be used in treating the elderly.

Hepatic Insufficiency

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

Renal Insufficiency

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

Interactions with Other Medicinal Products and Other Forms of Interaction

Specific drug interaction studies have not been conducted with SIMPONI®.

Concurrent Use of SIMPONI® with other Biological Therapeutics

The combination of SIMPONI® with other biological therapeutics used to treat the same conditions as SIMPONI®, including anakinra and abatacept is not recommended. (See Special Warnings and Special Precautions for Use)

Live Vaccines

Live vaccines should not be given concurrently with SIMPONI®. (See Special Warnings and Special Precautions for Use)

Methotrexate

Although concomitant use of methotrexate results in higher steady-state trough concentrations of SIMPONI® in patients with RA, PsA, or AS, the data do not suggest the need for dose adjustment of either SIMPONI® or methotrexate. (See Pharmacokinetics Properties)

Pregnancy and Lactation

Use during 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 µg/mL) is over 900-fold higher than median steady-state Cmax value (1.71 µg/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 six months postpartum. The mean peak maternal serum concentration obtained in this study (1482 μg/mL) is over 860-fold higher than median steady-state Cmax value (1.71 μg/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 Special Warnings and Special Precautions for Use and Interactions with Other Medicinal Products and Other Forms of Interaction)

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

Use during Lactation

In the pre- and post-natal development study in cynomolgus monkeys (see Use during pregnancy) 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 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.

Undesirable Effects

Safety data from Phase 2 and 3 SC and IV clinical trials are available from 5037 SIMPONI®-treated patients including 2826 with rheumatoid arthritis, 394 with psoriatic arthritis, 353 with ankylosing spondylitis, 1233 with ulcerative colitis, and 231 with severe persistent asthma. Adverse Drug Reactions (ADRs) observed with SIMPONI® are summarized in Table 1. Within the designated system organ classes, the adverse drug 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)

Table 1	Summary of ADRs in Clinical Studies
Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis,laryngitis, and rhinitis)
Common:	Bacterial infections (such as cellulitis). Viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections
Uncommon:	Septic shock, sepsis, lower respiratory tract infection (pneumonia), opportunistic infections (invasive fungal infections, bacterial, atypical mycobacterial and protozoal), abscess, arthritis bacterial
Rare:	Hepatitis B reactivation, Histoplasmosis, coccidioidomycosis, pneumocystosis, tuberculosis, pyelonephritis, 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:	Anemia
Uncommon:	Leukopenia, thrombocytopenia, pancytopenia
Immune System Disorders	
Very common:	autoantibody positive
Common:	Non-serious allergic reactions
Nervous system disorders	
Common:	Dizziness
Uncommon:	Demyelinating disorders (central and peripheral), paresthesia
Cardiac Disorders	
Uncommon:	Congestive heart failure (new onset or worsening)
Vascular disorders	
Common:	Hypertension
Rare:	Vasculitis (systemic)
Gastrointestinal Disorders	
Uncommon:	Constipation
Skin and subcutaneous tissue disorders	
Common:	Rash
Uncommon:	Psoriasis: new onset, palmar/plantar, and pustular, vasculitis (cutaneous), alopecia
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)
*Observed with other TNF-blockers, but not observed in clinical studies with golimumab.	

Infections (See Special Warnings and Special Precautions for Use)
Upper respiratory tract infection was the most common adverse reaction reported in the combined Phase 3 RA, PsA and AS studies through Week 16, occurring in 7.2% of SIMPONI®-treated patients (incidence per patient-year: 0.26; 95% CI: 0.22, 0.31) as compared with 5.8% of control patients (incidence per patient-year: 0.23; 95% CI: 0.17, 0.31). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per patient year of upper respiratory tract infections was 0.17 events; 95% CI: 0.16, 0.19, for SIMPONI® treated patients.
In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in 28.3% of SIMPONI®-treated patients (incidence per patient-year: 1.28; 95% CI: 1.18, 1.38) compared with 24.7% of control patients (incidence per patient-year: 1.17; 95% CI: 1.02, 1.33). In controlled and uncontrolled portions of the studies with a median follow-up of approximately 3 years, the incidence per patient year of infections was 0.96 events; 95% CI: 0.93, 0.99, for SIMPONI® treated patients.
In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections were observed in 1.4% of SIMPONI®-treated patients and 1.3% of control-treated patients. Through Week 16, the incidence of serious infections per patient-year of follow-up was 0.07; 95% CI: 0.05, 0.11 for the SIMPONI® 100 mg group, 0.03; 95% CI: 0.01, 0.07 for the SIMPONI® 50 mg group and 0.04; 95% CI: 0.02, 0.08 for the placebo group. Serious infections observed in SIMPONI®-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections and tuberculosis. In the controlled and uncontrolled portions of the Phase 2 and Phase 3 trials in RA, PsA, and AS with a median follow-up of approximately 3 years, there was a greater incidence of serious infections, including opportunistic infections and TB in patients receiving SIMPONI® 100 mg compared with patients receiving SIMPONI® 50 mg. The incidence per patient-year of all serious infections was 0.05; 95% CI: 0.04, 0.06, in patients receiving SIMPONI® 100 mg and 0.03; 95% CI: 0.02, 0.04, in patients receiving SIMPONI® 50 mg. These results may be confounded by the designs of the Phase 3 studies and different durations of follow-up across treatment groups. ***Malignancies*** (See Special Warnings and Special Precautions for Use)
Lymphoma
The incidence of lymphoma in SIMPONI®-treated patients with RA, PsA and AS during the controlled portions of Phase 2 and 3 clinical trials and through approximately 3 years of follow up was higher than expected in the general population. In the controlled and uncontrolled portions of these trials through a median follow-up of approximately 3 years, a greater incidence of lymphoma was observed in patients receiving SIMPONI® 100 mg compared with patients receiving SIMPONI® 50 mg. These results may be confounded by the small number of events, designs of the Phase 3 studies, and different durations of follow-up across treatment groups. 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 portions of the SIMPONI® Phase 2 and Phase 3 clinical trials in RA, PsA, and AS, the incidence of non-lymphoma malignancies (excluding non-melanoma skin cancer) was similar between the SIMPONI® and the control groups. Through approximately 3 years of follow-up, the incidence of non-lymphoma malignancies was similar to the general population.
In an exploratory clinical trial involving patients with severe persistent asthma, more patients treated with SIMPONI® 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 Special Warnings and Special Precautions for Use)

In the controlled and uncontrolled portions of the Phase 2 RA and the Phase 3 RA, PsA, and AS trials with a median follow-up of approximately 3 years, a greater incidence of demyelination was observed in patients receiving SIMPONI® 100 mg compared with patients receiving SIMPONI® 50 mg. These results may be confounded by the small number of events, designs of the Phase 3 studies, and different durations of follow-up across treatment groups.

Liver Enzyme Elevations

In controlled Phase 3 trials through Week 16, mild ALT elevations (> 1 and < 3 x ULN) occurred in similar proportions of SIMPONI®-treated and control patients in the RA and PsA studies (22.1% to 27.4% of patients); in the AS study, more SIMPONI®-treated patients (25.6%) than control patients (3.9%) had mild ALT elevations. Through approximately 3 years of follow-up, the incidence of mild ALT elevations was similar in SIMPONI-treated and control patients in the RA and PsA studies. In the AS study, the incidence of mild ALT elevations was higher in SIMPONI®-treated patients than in control patients.

In the RA and AS studies through Week 16, ALT elevations ≥ 5 x ULN were uncommon and seen in more SIMPONI®-treated patients (0.4% to 0.9%) than control patients (0.0%). This trend was not observed in the PsA population. Through approximately 3 years of follow-up, the incidence of ALT elevations ≥ 5 x ULN was similar in both SIMPONI®-treated and control patients in the Phase 3 RA, PsA and AS studies. The majority of these elevations were asymptomatic.

Injection Site Reactions

In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 5.8% of SIMPONI® treated patients had injection site reactions compared with 2.2% in control-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 3 trials in RA, PsA, AS and severe persistent asthma, no patients treated with SIMPONI® developed anaphylactic reactions.

Antinuclear Antibodies (ANA) / Anti-double-stranded DNA (dsDNA) Antibodies

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

In Phase 3 trials in RA, PsA, and AS through 1 year of follow up, 4.0% of SIMPONI®-treated patients and 2.6% 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 uncommon.

Post-marketing Experience

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

System Organ Class	Adverse Drug Reaction	Frequency
Neoplasm Benign and Malignant	Melanoma Merkel cell carcinoma	Rare Not known*
Immune System Disorders	Serious Systemic Hypersensitivity Reactions	Rare

	(including anaphylactic reaction) Sarcoidosis	 Very rare
Skin and Subcutaneous Tissue Disorders	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

Pharmacotherapeutic group: Tumour necrosis factor alpha (TNF-α) inhibitors, ATC code: L04AB06

Mechanism of Action

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

Pharmacodynamic Effects

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

Improvement in C-reactive protein (CRP) levels were observed relative to placebo groups and treatment with SIMPONI® resulted in significant reductions from baseline in serum levels of IL-6, ICAM-1, matrix-metalloproteinase (MMP)-3 and vascular endothelial growth factor (VEGF) compared to control treatment. In addition, levels of TNF-α were reduced in RA and AS patients and levels of IL-8 were reduced in PsA patients. These changes were observed at the first assessment (week 4) after the initial SIMPONI® administration and were generally maintained through week 24.

Clinical Efficacy

Rheumatoid Arthritis

The efficacy of SIMPONI® was demonstrated in three multi-centre, 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. 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, SIMPONI® 50 mg + MTX, SIMPONI® 100 mg + MTX or SIMPONI® 100 mg + placebo. Patients receiving placebo + MTX were switched to SIMPONI® 50 mg + MTX after week 24. At week 52, patients entered an open label long-term extension.

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, SIMPONI® 50 mg, or SIMPONI® 100 mg. Patients were allowed to continue concomitant DMARD therapy with MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the study. The stated reasons for discontinuation of prior anti TNF therapies were lack of efficacy (58%), intolerance (13%), and/or reasons other than safety or efficacy (29%, mostly for financial reasons).

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, SIMPONI® 50 mg + MTX, SIMPONI® 100 mg + MTX or SIMPONI® 100 mg + placebo. At week 52, patients entered an open label long-term extension in which patients receiving placebo + MTX who had at least 1 tender or swollen joint were switched to SIMPONI® 50 mg + MTX.

In 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 SIMPONI® treatment on the signs and symptoms of arthritis, physical function and health-related quality of life were performed.

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

Signs and Symptoms

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

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

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

Table 2 Key Efficacy Outcomes from the Controlled Portions of 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	**SIMPONI® 50 mg + MTX**	**Placebo**	**SIMPONI® 50 mg**	**Placebo + MTX**	**SIMPONI® 50 mg + MTX**
n[a]	133	89	150	147	160	159
Responders, % of patients						
ACR 20						

Week 14	**33%**	**55%***	**18%**	**35%***	NA	NA
Week 24	28%	60%*	16%	31% p=0.002	49%	62%
Week 52	NA	NA	NA	NA	52%	60%
ACR 50						
Week 14	10%	35%*	7%	15% p=0.021	NA	NA
Week 24	14%	37%*	4%	16%*	**29%**	**40%**
Week 52	NA	NA	NA	NA	36%	42%
ACR 70						
Week 14	4%	14% p=0.008	2%	10% p=0.005	NA	NA
Week 24	5%	20%*	2%	9% p=0.009	16%	24%
Week 52	NA	NA	NA	NA	22%	28%

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

* $p \leq 0.001$

NA: Not Applicable

In RA Study 3 the primary analysis in patients with moderate to severe rheumatoid arthritis (combined SIMPONI® 50 and 100 mg + MTX groups vs. MTX alone for ACR50) was not statistically significant at week 24 (p=0.053). At week 52 in the overall population, the percentage of patients in the SIMPONI® 50 mg + MTX group who achieved an ACR response was generally higher but not significantly different when compared with MTX alone (see Table 2).

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 time point, at week 14 and at week 24 ($p \leq 0.001$). Among patients who remained on the SIMPONI® treatment to which they were 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 SIMPONI® 50 mg + MTX group achieved a major clinical response compared with 7% of patients in the placebo + MTX group ($p = 0.018$). Among 159 subjects randomized to SIMPONI® 50 mg + MTX, 96 were still on this treatment at week 104. Among those, 85, 66 and 53 patients had ACR 20/50/70 response, respectively, at week 104.

Radiographic Response

In 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 SIMPONI® 50 mg dose at week 52 are presented in Table 3.

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

Table 3 Radiographic Mean (SD) Changes from Baseline in Total vdH-S Score at Week 52 in the Overall Population of GO-BEFORE

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

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

[a] n reflects randomized patients
* p = 0.015
** p = 0.044

Physical Function and Health-Related Quality of Life

Physical function and disability were assessed as a separate endpoint in RA Study 1 and RA Study 2 using the disability index of the HAQ. In these studies, SIMPONI® demonstrated clinically meaningful and statistically significant improvement in HAQ from baseline versus control at week 24. Among patients who remained on the SIMPONI® treatment to which they were 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 SIMPONI® versus placebo at week 24. Among patients who remained on the 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 SIMPONI® were evaluated in a multi-centre, 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. SIMPONI® or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, SIMPONI® 50 mg, or SIMPONI® 100 mg. Patients receiving placebo were switched to SIMPONI® 50 mg after week 24. Patients entered an open label long-term extension at Week 52. Approximately forty-eight percent of patients continued on stable doses of methotrexate (≤ 25 mg/week). The co-primary endpoints were the percentage of patients achieving ACR 20 response at Week 14 and change from baseline in total PsA modified vdH-S score at Week 24.

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

Signs and Symptoms

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

Table 4 Key Efficacy Outcomes from PsA Study		
	Placebo	**SIMPONI® 50 mg***
n[a]	113	146

Responders, % of patients		
ACR 20		
Week 14	**9 %**	**51 %**
Week 24	12 %	52 %
ACR 50		
Week 14	2 %	30 %
Week 24	4 %	32 %
ACR 70		
Week 14	1 %	12 %
Week 24	1 %	19 %
PASI[b] 75[c]		
Week 14	3 %	40 %
Week 24	1 %	56 %

* $p < 0.05$ for all comparisons;

[a] n reflects randomized patients; actual number of patients evaluable for each endpoint may vary by time-point

[b] *Psoriasis Area and Severity Index*

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

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

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

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

SIMPONI® 50 mg treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment at week 24 as measured by change from baseline in total modified vdH-S Score (mean + SD score was 0.27 + 1.3 in the placebo group compared with -0.16 + 1.3 in the SIMPONI® group; p= 0.011). Out of 146 patients who were randomized to SIMPONI® 50 mg, 52 week X-ray data were available for 126 patients, of

whom 77% showed no progression compared to baseline. At week 104, X-ray data were available for 114 patients, and 77% showed no progression from baseline.

Ankylosing Spondylitis

The safety and efficacy of SIMPONI® were evaluated in a multi-centre, 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. SIMPONI® or placebo were administered subcutaneously every 4 weeks. Patients were randomly assigned to placebo, SIMPONI® 50 mg and SIMPONI® 100 mg and were allowed to continue concomitant DMARD therapy (MTX, SSZ and/or HCQ). The primary endpoint was the percentage of patients achieving Ankylosing Spondylitis Assessment Study Group (ASAS) 20 response at week 14. Placebo-controlled efficacy data were collected and analyzed through week 24.

Key results for the 50 mg dose are shown in Table 5 and described below. In general, no clinically meaningful differences in measures of efficacy were observed between the SIMPONI® 50 mg and 100 mg dosing regimens.

Table 5 Key Efficacy Outcomes from AS Study

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

* $p \leq 0.001$ for all comparisons

[a] n reflects randomized patients; actual number of patients evaluable for each endpoint may vary by time-point

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

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

Immunogenicity

Across the Phase III RA, PsA and AS studies through week 52, antibodies to golimumab were detected in 5% (105/2115) of golimumab treated patients and, where tested, nearly all

antibodies were neutralizing *in vitro*. Similar rates were shown across rheumatologic indications. Treatment with concomitant MTX resulted in a lower proportion of patients with antibodies to golimumab than patients receiving golimumab without MTX (approximately 3% [41/1262] versus 8% [64/853], respectively).
The presence of antibodies to golimumab may increase the risk of injection site reactions (see section 4.4). The small number of patients positive for antibodies to golimumab limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.
Because immunogenicity analyses are product- and assay-specific, comparison of antibody rates with those from other products is not appropriate.

Pharmacokinetic Properties

Following SC administration of SIMPONI® to healthy subjects or patients with RA, the time to reach maximum serum concentrations (Tmax) ranged from 2 to 6 days. A SC injection of 50 mg SIMPONI® to healthy subjects produced a mean ± standard deviation maximum serum concentration (Cmax) of 3.2 ±1.4 μg/mL. SIMPONI® 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 (IV) dose. The systemic clearance of SIMPONI® was estimated to be 6.9 ± 2.0 mL/day/kg, and mean volume of distribution was 115 ± 19 mL/kg. The terminal half-life value was estimated to be 12 ± 3 days in healthy subjects and similar half-live values were observed in patients with RA, PsA or AS. Following a single SC injection of 100 mg, the absorption of SIMPONI® was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since SIMPONI® exhibited approximately dose proportional PK following a SC administration, the absolute bioavailability of the SIMPONI® 50 mg dose is expected to be similar to the 100 mg dose.
When 50 mg SIMPONI® was administered SC to patients with RA, PsA or AS every 4 weeks, serum concentrations reached steady state by Week 12. With concomitant use of methotrexate, treatment with 50 mg SIMPONI® SC every 4 weeks resulted in a median steady-state trough serum concentration of approximately 0.6 μg/mL in patients with active RA despite methotrexate therapy, and approximately 0.5 μg/mL in patients with active PsA and approximately 0.6 μg/mL in patients with AS. Patients with RA, PsA or AS who did not receive concomitant use of methotrexate had approximately 30% lower steady-state trough concentrations of SIMPONI® than those who received SIMPONI® with methotrexate. Concomitant use of methotrexate reduced the apparent clearance of SIMPONI® by 36% after 6-month treatment with SC 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 SIMPONI®.
Population pharmacokinetic analyses showed there was a trend toward higher apparent clearance of SIMPONI® with increasing weight.
Patients who developed anti-SIMPONI® antibodies generally had low trough steady-state serum concentrations of SIMPONI®.

Preclinical Safety Data

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 PARTICULARS

List of Excipients
Sorbitol
L-histidine
L-histidine monohydrochloride monohydrate
Polysorbate 80
Water for injection
Incompatibilities
Specific drug compatability studies have not been conducted.
Shelf Life
Observe expiry date on the outer pack.
Special Precautions for Storage
Store in a refrigerator
2ºC to 8ºC
36ºF to 46ºF
Store in original carton until time of use.
Protect from light.
Do not freeze.
Do not shake.
Keep out of reach of children.
Nature and Contents of Container
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 Special Warnings and Special Precautions for Use)
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 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 SIMPONI® available: 50 mg of golimumab in 0.5 mL.
SIMPONI® is available in packs of 1 autoinjector / pre-filled pen and in packages of 3 autoinjector / 3 pre-filled pens. Not all pack sizes may be marketed.
SIMPONI® is packaged in a single-use outer carton.

MANUFACTURED BY
See outer carton.

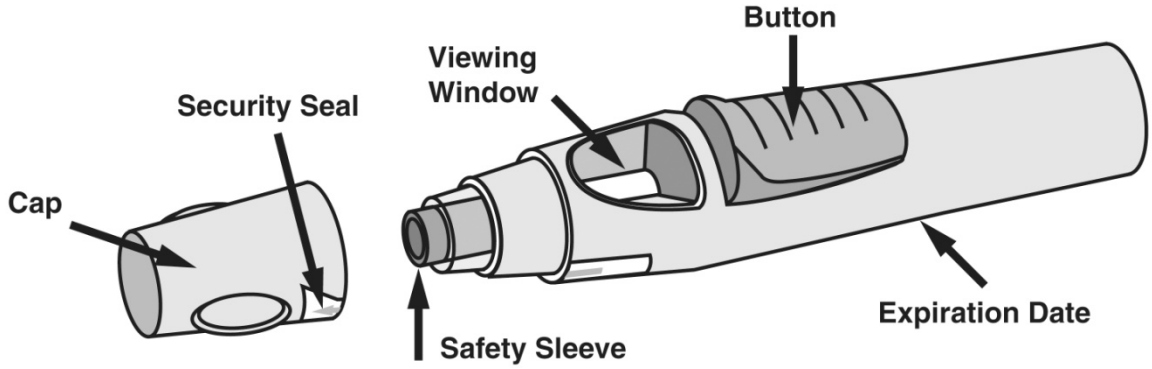
DATE OF REVISION OF THE TEXT
06 August 2012 based on CCDS 27 July 2012

INSTRUCTIONS FOR INJECTING SIMPONI® USING A SINGLE-USE SMARTJECT® AUTOINJECTOR / PRE-FILLED PEN

If you would like to self-inject SIMPONI®, you must be trained by a healthcare professional to prepare an injection and give it to yourself. If you have not been trained, please contact your 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 until instructed to do so

Check Expiration Date

- Check the expiration date (as 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 or 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 or 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 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

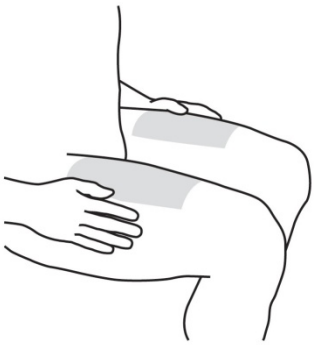
- Look through the viewing window to make sure that the liquid in the autoinjector is clear to slightly opalescent and colorless to slightly yellow
- You may also notice an air bubble – this is normal

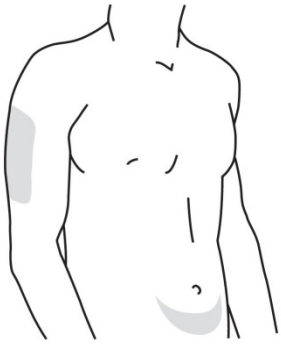
DO NOT use if the liquid is discolored, cloudy or contains particles. If this is the case, please contact your doctor or pharmacist or the local distributor of this medicine for assistance.

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





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

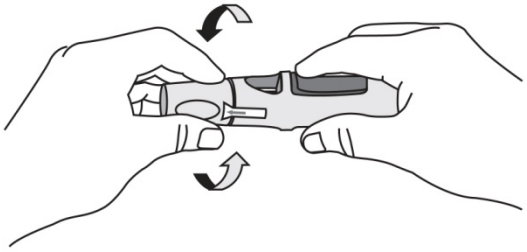
Preparing Injection Site

- 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

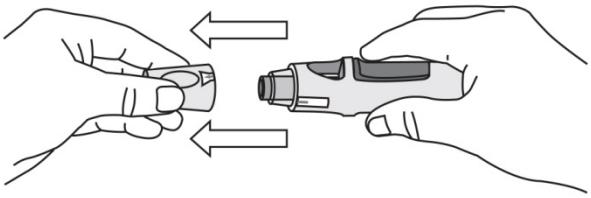
STEP 3: INJECTING THE MEDICINE



Remove the Cap

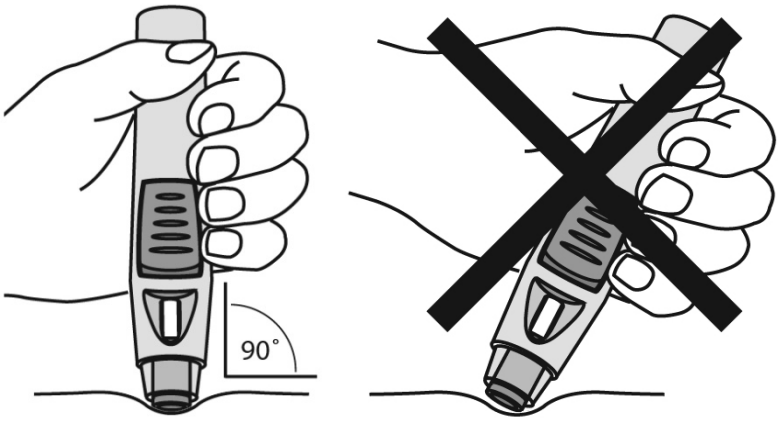
The cap should **NOT** be removed until you are ready to inject the medication. The medication should be injected within 5 minutes after the cap has been removed.

- 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

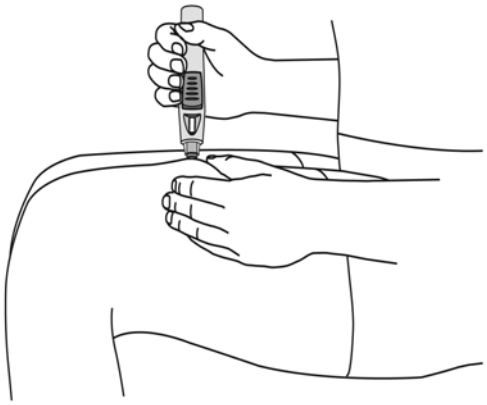
Note: **DO NOT** use autoinjector if it is dropped without the cap in place. If you drop the autoinjector without the cap in place, please contact your doctor, pharmacist or the local distributor of this medicine for assistance.



Push the Autoinjector Against the Skin

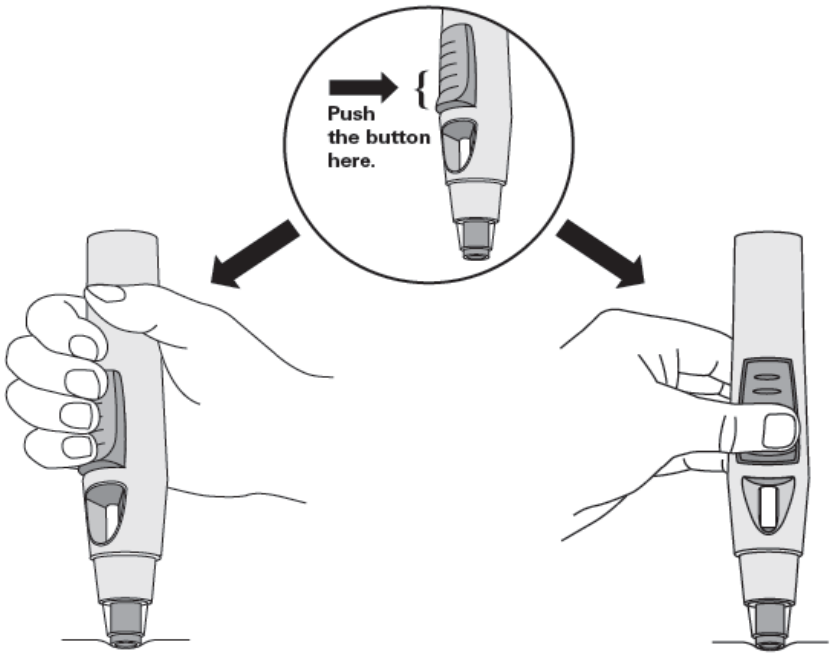
- Hold the autoinjector comfortably in your hand
- Without pressing the button, push the open end of the autoinjector firmly against the skin at a 90-degree angle

Note: Some people find that using their free hand to pinch and hold the skin at the injection site during administration makes injecting easier to make the injection site a firmer, more stable surface for injection.



Press Button to Inject

- Continue to hold the autoinjector firmly against the skin, and press the front raised part of the button. Once the button is pressed, it will remain pressed in so you do not need to keep pressure on it.



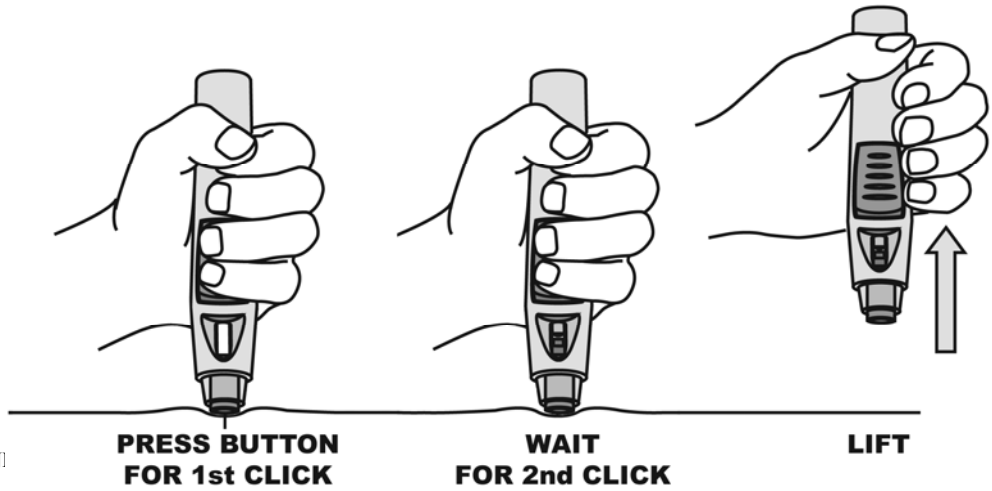
- The first loud 'click' indicates that the needle has been inserted and the injection has started. You may or may not feel a needle prick at this time.

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.
Note: You will not be able to push in the button unless the autoinjector is pushed firmly against the skin

Wait for Second "Click"

- Continue to hold the autoinjector against the skin until you hear the second 'click' (may take up to 15 seconds)
- The second click indicates that the injection is finished and the needle has retracted into the autoinjector
- Lift the autoinjector from the injection site

Note: If you have hearing impairment, count 15 seconds from the time you press the button and then lift the autoinjector from the injection site.

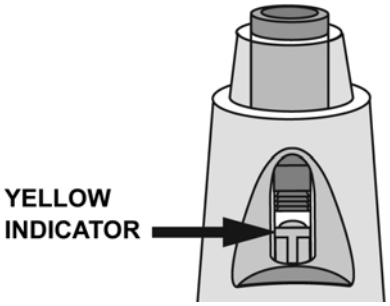


SIMPONI

STEP 4: AFTER THE INJECTION

Check the Viewing Window

- After injecting, check the viewing window to make sure that the yellow indicator is visible
- 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, please contact 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

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 for 10 seconds

DO NOT rub the injection site.

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