SIMPONI ARIA- golimumab solution
Janssen Biotech, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SIMPONI® ARIA® safely and effectively. See full prescribing information for SIMPONI ARIA.

SIMPONI ARIA
(golimumab) injection, for intravenous use
Initial U.S. Approval: 2009

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal (such as histoplasmosis), and other opportunistic infections have occurred in patients receiving SIMPONI ARIA (5.1).**
- **Discontinue SIMPONI ARIA if a patient develops a serious infection or sepsis (5.1).**
- **Perform test for latent TB; if positive, start treatment for TB prior to starting SIMPONI ARIA (5.1).**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1).**
- **Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member (5.2).**

RECENT MAJOR CHANGES

Dosage and Administration (2.3)	02/2014
Warnings and Precautions (5.1, 5.2, 5.9)	12/2014

INDICATIONS AND USAGE

SIMPONI ARIA is a tumor necrosis factor (TNF) blocker indicated for the treatment of adult patients with moderately to severely active Rheumatoid Arthritis (RA) in combination with methotrexate (1.1)

DOSAGE AND ADMINISTRATION

- 2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks (2.1)
- Dilution of supplied SIMPONI ARIA solution with 0.9% w/v sodium chloride is required prior to administration (2.3)

DOSAGE FORMS AND STRENGTHS

- Injection: 50 mg/4 mL (12.5 mg/mL) in a single use vial (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Serious infections – Do not start SIMPONI ARIA during an active infection. If an infection develops, monitor carefully, and stop SIMPONI ARIA if infection becomes serious (5.1).
- Invasive fungal infections – For patients who develop a systemic illness on SIMPONI ARIA, consider empiric antifungal therapy for those who reside in or travel to regions where mycoses are endemic (5.1).
- Hepatitis B reactivation – Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop SIMPONI ARIA and begin anti-viral therapy (5.1).
- Malignancies – More cases of lymphoma have been observed among patients receiving TNF-blockers compared with patients in the control groups. Cases of other malignancies have been observed among patients receiving TNF-blockers (5.2).
- Heart failure – Worsening, or new onset, may occur. Stop SIMPONI ARIA if new or worsening symptoms occur (5.3).
- Demyelinating disease, exacerbation or new onset, may occur (5.4).
- Hypersensitivity reactions: Serious systemic hypersensitivity reactions including anaphylaxis may occur (5.10).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3%) are: upper respiratory tract infection, viral infection, bronchitis,

hypertension, and rash (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- Biologics, including abatacept and anakinra: Increased risk of serious infection (5.1, 5.5, 5.6, 5.7, 7.2)
- Live vaccines should not be given with SIMPONI ARIA (5.9, 7.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with SIMPONI ARIA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

Discontinue SIMPONI ARIA if a patient develops a serious infection.

Reported infections with TNF-blockers, of which SIMPONI ARIA is a member, include:

- **Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Test patients for latent tuberculosis before SIMPONI ARIA use and during therapy. Initiate treatment for latent tuberculosis prior to SIMPONI ARIA use.**
- **Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized, disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Consider empiric anti-fungal therapy in patients at risk for invasive fungal infections who develop severe systemic illness.**
- **Bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria.**

Consider the risks and benefits of treatment with SIMPONI ARIA prior to initiating therapy in patients with chronic or recurrent infection.

Monitor patients closely for the development of signs and symptoms of infection during and after treatment with SIMPONI ARIA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

MALIGNANCY

Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI ARIA is a member *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

SIMPONI ARIA, in combination with methotrexate, is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

2 DOSAGE AND ADMINISTRATION

2.1 Rheumatoid Arthritis

The SIMPONI ARIA dosage regimen is 2 mg per kg given as an intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.

SIMPONI ARIA should be given in combination with methotrexate. Other non-biologic DMARDs, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with SIMPONI ARIA.

The efficacy and safety of switching between intravenous and subcutaneous formulations and routes of administration have not been established.

2.2 Evaluation for Tuberculosis and Hepatitis B Prior to Dosage

Prior to initiating SIMPONI ARIA and periodically during therapy, evaluate patients for active tuberculosis and test for latent infection *[see Warnings and Precautions (5.1)]*. Prior to initiating SIMPONI ARIA, test patients for hepatitis B viral infection *[see Warnings and Precautions (5.1)]*.

2.3 Important Administration Instructions

SIMPONI ARIA solution for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

1. Calculate the dosage and the number of SIMPONI ARIA vials needed based on the recommended dosage of 2 mg/kg and the patient's weight. Each 4 mL vial of SIMPONI ARIA contains 50 mg of golimumab.
2. Check that the solution in each vial is colorless to light yellow. The solution may develop a few fine translucent particles, as golimumab is a protein. Do not use if opaque particles, discoloration or other foreign particles are present.
3. Dilute the total volume of the SIMPONI ARIA solution with 0.9% w/v sodium chloride for infusion to a final volume of 100 mL. For example, this can be accomplished by withdrawing a volume of the 0.9% w/v sodium chloride solution from the 100-mL infusion bag or bottle equal to the total volume of SIMPONI ARIA. Slowly add the total volume of SIMPONI ARIA solution to the 100-mL infusion bag or bottle. Gently mix. Discard any unused solution remaining in the vials.
4. Prior to infusion, visually inspect the diluted SIMPONI ARIA solution for particulate matter or discoloration. Do not use if these exist.
5. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein-binding filter (pore size 0.22 micrometer or less).
6. Do not infuse SIMPONI ARIA concomitantly in the same intravenous line with other agents. No physical biochemical compatibility studies have been conducted to evaluate the use of SIMPONI ARIA with other intravenous agents in the same intravenous line.
7. Infuse the diluted solution over 30 minutes.
8. Once diluted, the infusion solution can be stored for 4 hours at room temperature.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg of golimumab per 4 mL of solution (12.5 mg of golimumab per mL) in each single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Patients treated with SIMPONI ARIA are at increased risk for developing serious infections involving various organ systems and sites that may lead to hospitalization or death.

Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis have been reported with TNF-blockers. Patients have frequently presented with disseminated rather than localized disease. The concomitant use of a TNF-blocker and abatacept or anakinra was associated with a higher risk of serious infections; therefore, the concomitant use of SIMPONI ARIA and these biologic products is not recommended *[see Warnings and Precautions (5.5, 5.6) and Drug Interactions (7.2)]*.

Treatment with SIMPONI ARIA should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection. Consider the risks and benefits of treatment prior to initiating SIMPONI ARIA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis; or
- with underlying conditions that may predispose them to infection.

Monitoring

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with SIMPONI ARIA. Discontinue SIMPONI ARIA if a patient develops a serious infection, an opportunistic infection, or sepsis. For patients who develop a new infection during treatment with SIMPONI ARIA, perform a prompt and complete diagnostic workup appropriate for an immunocompromised patient and initiate appropriate antimicrobial therapy and closely monitor them.

Tuberculosis

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving TNF-blockers, including patients who have previously received treatment for latent or active tuberculosis. Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating SIMPONI ARIA and periodically during therapy.

Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to reduce the risk of tuberculosis reactivation during therapy. Prior to initiating SIMPONI ARIA, assess if treatment for latent tuberculosis is needed; An induration of 5 mm or greater is a positive tuberculin skin test, even for patients previously vaccinated with Bacille Calmette-Guerin (BCG).

Consider anti-tuberculosis therapy prior to initiation of SIMPONI ARIA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Cases of active tuberculosis have occurred in patients treated with the subcutaneous formulation of golimumab during and after treatment for latent tuberculosis. Monitor patients for the development of

signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy, patients who are on treatment for latent tuberculosis, or patients who were previously treated for tuberculosis infection.

Consider tuberculosis in the differential diagnosis in patients who develop a new infection during SIMPONI ARIA treatment, especially in patients who have previously or recently traveled to countries with a high prevalence of tuberculosis, or who have had close contact with a person with active tuberculosis.

Invasive Fungal Infections

If patients develop a serious systemic illness and they reside or travel in regions where mycoses are endemic, consider invasive fungal infection in the differential diagnosis. Consider appropriate empiric antifungal therapy and take into account both the risk for severe fungal infection and the risks of antifungal therapy while a diagnostic workup is being performed. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. To aid in the management of such patients, consider consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections.

Hepatitis B Virus Reactivation

The use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic hepatitis B carriers (i.e., surface antigen positive). In some instances, HBV reactivation occurring in conjunction with TNF-blocker therapy has been fatal. The majority of these reports have occurred in patients who received concomitant immunosuppressants.

All patients should be tested for HBV infection before initiating TNF-blocker therapy. For patients who test positive for hepatitis B surface antigen, consultation with a physician with expertise in the treatment of hepatitis B is recommended before initiating TNF-blocker therapy. The risks and benefits of treatment should be considered prior to prescribing TNF-blockers, including SIMPONI ARIA, to patients who are carriers of HBV. Adequate data are not available on whether anti-viral therapy can reduce the risk of HBV reactivation in HBV carriers who are treated with TNF-blockers. Patients who are carriers of HBV and require treatment with TNF-blockers should be closely monitored for clinical and laboratory signs of active HBV infection throughout therapy and for several months following termination of therapy.

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

5.2 Malignancies

Malignancies in Pediatric Patients

Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blocking agents (initiation of therapy ≤ 18 years of age), of which SIMPONI ARIA is a member. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of malignancies, including rare malignancies that are usually associated with immunosuppression, and malignancies that are not usually observed in children and adolescents. The malignancies occurred after a median of 30 months (range 1 to 84 months) after the first dose of TNF-blocker therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources, including registries and spontaneous post-marketing reports. Use of SIMPONI ARIA in patients under 18 years of age has not been established.

Malignancies in Adult Patients

The risks and benefits of TNF-blocker treatment including SIMPONI ARIA should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who develop a malignancy.

In the controlled portions of clinical trials of TNF-blockers including the subcutaneous formulation of golimumab more cases of lymphoma have been observed among patients receiving anti-TNF treatment compared with patients in the control groups. Patients with RA 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. Cases of acute and chronic leukemia have been reported with post-marketing TNF-blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the general population for the development of leukemia.

Rare post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF-blocking agents. This rare type of T-cell lymphoma has a very aggressive disease course and is usually fatal. Nearly all of the reported TNF-blocker associated 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. A risk for the development for hepatosplenic T-cell lymphoma in patients treated with TNF-blockers cannot be excluded.

Melanoma has been reported in patients treated with TNF-blocking agents, including the subcutaneous formulation of golimumab. Merkel cell carcinoma has been reported in patients treated with TNF-blocking agents. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer.

In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients with COPD, patients with Wegener's granulomatosis treated with concomitant cyclophosphamide) a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled group. In an exploratory clinical trial evaluating the use of the subcutaneous formulation of golimumab in patients with severe persistent asthma, more patients treated with golimumab reported malignancies compared with control patients. The significance of this finding is unknown.

During the controlled portion of the Phase 3 trial in RA for SIMPONI ARIA, the incidence of malignancies other than lymphoma and NMSC per 100-patient-years of follow-up was 0.56 (95% CI: 0.01, 3.11) in the SIMPONI ARIA group compared with an incidence of 0 (95% CI: 0.00, 3.79) in the placebo group.

5.3 Congestive Heart Failure

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

5.4 Demyelinating Disorders

Use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with rare cases of new onset or exacerbation of central nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS) and peripheral demyelinating disorders, including Guillain-Barré syndrome. Cases of central demyelination, MS, optic neuritis, and peripheral demyelinating polyneuropathy have rarely been

reported in patients treated with the subcutaneous formulation of golimumab. Prescribers should exercise caution in considering the use of TNF-blockers, including SIMPONI ARIA, in patients with central or peripheral nervous system demyelinating disorders. Discontinuation of SIMPONI ARIA should be considered if these disorders develop.

5.5 Use with Abatacept

In controlled trials, the concurrent administration of another TNF-blocker and abatacept was associated with a greater proportion of serious infections than the use of a TNF-blocker alone; and the combination therapy, compared to the use of a TNF-blocker alone, has not demonstrated improved clinical benefit in the treatment of RA. Therefore, the combination of TNF-blockers including SIMPONI ARIA and abatacept is not recommended *[see Drug Interactions (7.2)]*.

5.6 Use with Anakinra

Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was associated with a greater portion of serious infections and neutropenia and no additional benefits compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-blockers, including SIMPONI ARIA, is not recommended *[see Drug Interactions (7.2)]*.

5.7 Switching Between Biological Disease Modifying Antirheumatic Drugs (DMARDs)

Care should be taken when switching from one biologic product to another biologic product since overlapping biological activity may further increase the risk of infection.

5.8 Hematologic Cytopenias

There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic anemia, and thrombocytopenia in patients receiving TNF-blockers. In clinical studies, cases of pancytopenia, leukopenia, neutropenia, and thrombocytopenia have also occurred in SIMPONI ARIA-treated patients. Caution should be exercised when using TNF-blockers, including SIMPONI ARIA, in patients who have or have had significant cytopenias.

5.9 Vaccinations/Therapeutic Infectious Agents

Live Vaccines

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

Therapeutic Infectious Agents

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 SIMPONI ARIA.

5.10 Hypersensitivity Reactions

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

6 ADVERSE REACTIONS

The most serious adverse reactions were:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Malignancies *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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.

The safety data described below are based on one, randomized, double-blind, controlled Phase 3 trial in patients with RA receiving SIMPONI ARIA by intravenous infusion (Trial 1). The protocol included provisions for patients taking placebo to receive treatment with SIMPONI ARIA at Week 16 or Week 24 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Comparisons between placebo and SIMPONI ARIA were based on the first 24 weeks of exposure.

Trial 1 included 197 control-treated patients and 463 SIMPONI ARIA-treated patients (which includes control-treated patients who switched to SIMPONI ARIA at Week 16). The proportion of patients who discontinued treatment due to adverse reactions in the controlled phase of Trial 1 through Week 24 was 3.5% for SIMPONI ARIA-treated patients and 0.5% for placebo-treated patients. Upper respiratory tract infection was the most common adverse reaction reported in the trial through Week 24 occurring in 6.5% of SIMPONI ARIA-treated patients as compared with 7.6% of control-treated patients, respectively.

Infections

Serious infections observed in SIMPONI ARIA-treated patients included sepsis, pneumonia, cellulitis, abscess, opportunistic infections, tuberculosis (TB), and invasive fungal infections. Cases of TB included pulmonary and extrapulmonary TB. The majority of the TB cases occurred in countries with a high incidence rate of TB *[see Warnings and Precautions (5.1)]*.

In the controlled phase of Trial 1 through Week 24, infections were observed in 27% of SIMPONI ARIA-treated patients compared with 24% of control-treated patients, and serious infections were observed in 0.9% of SIMPONI ARIA-treated patients and 0.0% of control-treated patients. Through Week 24, the incidence of serious infections per 100 patient-years of follow-up was 2.2 (95% CI 0.61, 5.71) for the SIMPONI ARIA group, and 0 (0.00, 3.79) for the placebo group. In the controlled and uncontrolled portions of Trial 1, 958 total patient-years of follow-up with a median follow-up of approximately 92 weeks, the incidence per 100 patient-years of all serious infections was 4.07 (CI: 2.90, 5.57) in patients receiving SIMPONI ARIA *[see Warnings and Precautions (5.1)]*. In the controlled and uncontrolled portions of Trial 1, in SIMPONI ARIA treated patients, the incidence of active TB per 100 patient-years was 0.31 (95% CI: 0.06; 0.92) and the incidence of other opportunistic infections per 100 patient-years was 0.42 (95% CI: 0.11, 1.07).

Malignancies

One case of malignancy other than lymphoma and NMSC with SIMPONI ARIA was reported through Week 24 during the controlled phase of Trial 1. In the controlled and uncontrolled portions through approximately 92 weeks, the incidence of malignancies per 100 patient-years, other than lymphoma and NMSC, in SIMPONI ARIA-treated patients was 0.31 (CI: 0.06, 0.92) and the incidence of NMSC was 0.1 (95% CI: 0.00, 0.58).

Liver Enzyme Elevations

There have been reports of severe hepatic reactions including acute liver failure in patients receiving TNF-blockers.

In the controlled phase of Trial 1, through Week 24, ALT elevations ≥ 5 × ULN occurred in 0.8% of SIMPONI ARIA-treated patients and 0% of control-treated patients and ALT elevations ≥ 3 × ULN

occurred in 2.3% of SIMPONI ARIA-treated patients and 2.5% of control-treated patients.

Since many of the patients in the Phase 3 trial were also taking medications that cause liver enzyme elevations (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], methotrexate [MTX], or isoniazid prophylaxis), the relationship between SIMPONI ARIA and liver enzyme elevation is not clear.

Autoimmune Disorders and Autoantibodies

The use of TNF-blockers, of which SIMPONI ARIA is a member, has been associated with the formation of autoantibodies and, rarely, with the development of a lupus-like syndrome.

At Week 20 in Trial 1, 17% of SIMPONI ARIA-treated patients and 13% of control patients were newly ANA-positive (at titers of 1:160 or greater). Of these patients, one SIMPONI ARIA-treated patient and no control-treated patients had newly positive anti-dsDNA antibodies.

Administration Reactions

In the controlled phase of Trial 1 through Week 24, 1.1% of SIMPONI ARIA infusions were associated with an infusion reaction compared with 0.2% of infusions in the control group. The most common infusion reaction in SIMPONI ARIA treated patients was rash. No serious infusion reactions were reported.

Immunogenicity

Antibodies to SIMPONI ARIA were detected in 13 (3%) golimumab-treated patients following IV administration of SIMPONI ARIA in combination with MTX through Week 24 of Trial 1.

All patients who were positive for antibodies to golimumab had neutralizing antibodies based on an in vitro cell-based assay. The small number of patients positive for antibodies to SIMPONI ARIA limits the ability to draw definitive conclusions regarding the relationship between antibodies to golimumab and clinical efficacy or safety measures.

The data above reflect the percentage of patients whose test results were considered positive for antibodies to SIMPONI ARIA in an ELISA assay. The ELISA assay is subject to interference by co-present golimumab and thus the results are an underestimate of the rate of product immunogenicity and are in addition highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SIMPONI ARIA with the incidence of antibodies to other products may be misleading.

Other Adverse Reactions

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% in the SIMPONI ARIA + MTX group with a higher incidence than in the placebo + MTX group during the controlled period of Trial 1 through Week 24.

Table 1: Adverse Drug Reactions Reported by ≥ 1% of SIMPONI ARIA-Treated Patients and with a Higher Incidence than Placebo-Treated Patients in Trial 1 through Week 24

	Placebo + MTX	**SIMPONI ARIA + MTX**
Patients treated	197	463
Adverse Reaction		
Infections and Infestations		
Upper respiratory tract infection (such as upper respiratory tract infection, nasopharyngitis, pharyngitis, laryngitis, and	12%	13%

rhinitis)		
Viral infections (such as influenza and herpes)	3%	4%
Bacterial infections	0%	1%
Bronchitis	1%	3%
Vascular disorders		
Hypertension	2%	3%
Skin and subcutaneous disorders		
Rash	1%	3%
General disorders and administration site conditions		
Pyrexia	1%	2%
Blood and lymphatic disorders		
Leukopenia	0%	1%

Other and less common clinical trial adverse drug reactions

Adverse drug reactions that do not appear in Table 1 or that occurred <1% in SIMPONI ARIA -treated patients during Trial 1 through Week 24 that do not appear in the Warnings and Precautions section included the following events listed by system organ class:

Infections and Infestations: Superficial fungal infection, sinusitis, abscess, lower respiratory tract infection (pneumonia), pyelonephritis

Investigations: Alanine aminotransferase increased, aspartate aminotransferase increased, neutrophil count decreased

Nervous system disorders: Dizziness, paresthesia

Gastrointestinal disorders: Constipation

6.2 Post-marketing Experience

There is no post-marketing experience available for SIMPONI ARIA. The following adverse reactions have been identified during post-approval use of the subcutaneous formulation of golimumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to golimumab exposure.

Neoplasm Benign and Malignant: Melanoma *[see Warnings and Precautions (5.2)]*

Immune System Disorders: Serious systemic hypersensitivity reactions (including anaphylactic reaction) *[see Warnings and Precautions (5.10)]*, sarcoidosis

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease

Skin and subcutaneous tissue disorders: Skin exfoliation, bullous skin reactions

7 DRUG INTERACTIONS

7.1 Methotrexate

SIMPONI ARIA should be used with methotrexate (MTX) *[see Clinical Studies (14)]*. Following IV administration, concomitant administration of methotrexate decreases the clearance of SIMPONI ARIA by approximately 9% based on population PK analysis. In addition, concomitant administration of methotrexate decreases the SIMPONI ARIA clearance by reducing the development of anti-golimumab antibodies.

7.2 Biologic Products for RA

An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI ARIA with other biologic products, including abatacept or anakinra is not recommended *[see Warnings and Precautions (5.5 and 5.6)]*. A higher rate of serious infections has also been observed in RA patients treated with rituximab who received subsequent treatment with a TNF-blocker. The concomitant use of SIMPONI ARIA with biologics approved to treat RA is not recommended because of the possibility of an increased risk of infection.

7.3 Live Vaccines/Therapeutic Infectious Agents

Live vaccines should not be given concurrently with SIMPONI ARIA *[see Warnings and Precautions (5.9)]*.

Therapeutic infectious agents should not be given concurrently with SIMPONI ARIA *[see Warnings and Precautions (5.9)]*.

Infants born to women treated with SIMPONI ARIA during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI ARIA *in utero* is not recommended for 6 months following the mother's last SIMPONI ARIA infusion during pregnancy *[see Use in Specific Populations (8.1)]*.

7.4 Cytochrome P450 Substrates

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα) during chronic inflammation. Therefore, it is expected that for a molecule that antagonizes cytokine activity, such as golimumab, the formation of CYP450 enzymes could be normalized. Upon initiation or discontinuation of SIMPONI ARIA in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) is recommended and the individual dose of the drug product may be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B – There are no adequate and well-controlled studies of SIMPONI ARIA in pregnant women. Because animal reproduction and developmental studies are not always predictive of human response, it is not known whether SIMPONI ARIA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. SIMPONI ARIA should be used during pregnancy only if clearly needed.

An embryofetal developmental toxicology study was performed in which pregnant cynomolgus monkeys were treated subcutaneously with golimumab during the first trimester with doses up to 50 mg/kg twice weekly (200 times greater than the maximum recommended human dose-MRHD) and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood samples collected at the end of the second trimester showed that fetuses were exposed to golimumab during gestation. In this study, *in utero* exposure to golimumab produced no developmental defects to the fetus.

A pre- and post-natal developmental study was performed in which pregnant cynomolgus monkeys were treated with golimumab during the second and third trimesters, and during lactation at doses up to 50 mg/kg twice weekly (33 times and 12 times greater than the maximal steady state human blood levels for maternal animals and neonates, respectively) and has revealed no evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum from the time of birth and for up to six months postpartum. Exposure to golimumab during gestation and during the postnatal period caused no developmental defects in the infants.

IgG antibodies are known to cross the placenta during pregnancy and have been detected in the serum of

infants born to patients treated with these antibodies. Since SIMPONI ARIA is an IgG antibody, infants born to women treated with SIMPONI ARIA during their pregnancy may be at increased risk of infection for up to 6 months. Administration of live vaccines to infants exposed to SIMPONI ARIA *in utero* is not recommended for 6 months following the mother's last SIMPONI ARIA infusion during pregnancy *[see Warnings and Precautions (5.10)]*.

8.3 Nursing Mothers

It is not known whether SIMPONI ARIA 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 ARIA, 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.

In the pre- and post-natal development study in cynomolgus monkeys in which golimumab was administered subcutaneously during pregnancy and lactation, golimumab was detected in the breast milk at concentrations that were approximately 400-fold lower than the maternal serum concentrations.

8.4 Pediatric Use

Safety and effectiveness of SIMPONI ARIA in pediatric patients less than 18 years of age have not been established. Malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with other TNF-blocking agents *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

In Trial 1 in RA, the number of patients ages 65 or older was too small to make comparisons with younger SIMPONI ARIA -treated patients. Because there is a higher incidence of infections in the geriatric population in general, caution should be used in treating geriatric patients with SIMPONI ARIA.

10 OVERDOSAGE

In a clinical study, 5 patients received single infusions of up to 1000 mg of SIMPONI ARIA without serious adverse reactions or other significant reactions.

11 DESCRIPTION

SIMPONI ARIA (golimumab) is a human IgG1 monoclonal antibody specific for human tumor necrosis factor alpha (TNFα) that exhibits multiple glycoforms with molecular masses of approximately 150 to 151 kilodaltons. SIMPONI ARIA was created using genetically engineered mice immunized with human TNF, resulting in an antibody with human-derived antibody variable and constant regions. SIMPONI ARIA 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.

The SIMPONI ARIA drug product is a sterile concentrated solution of the golimumab antibody supplied in a 4 mL glass vial for intravenous infusion.

SIMPONI ARIA does not contain preservatives, natural rubber or latex. The solution is colorless to light yellow with a pH of approximately 5.5. Each 4 mL vial of SIMPONI ARIA contains 50 mg golimumab, 9.5 mM L-histidine, 4.5% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive

forms of human TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα (a cytokine protein). There was no evidence of the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab antibody did not bind or neutralize human lymphotoxin. Golimumab did not lyse human monocytes expressing transmembrane TNF in the presence of complement or effector cells.

Elevated TNFα levels in the blood, synovium, and joints have been implicated in the pathophysiology of rheumatoid arthritis. TNFα is an important mediator of the articular inflammation that is characteristic of RA. Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF). The clinical relevance of these findings is unknown.

12.2 Pharmacodynamics

Following treatment with SIMPONI ARIA in patients with RA, decreases from baseline were observed in tissue inhibitor of metalloproteinases 1 (TIMP-1), matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-3 (MMP-3), resistin, interleukin-6 (IL-6), macrophage inflammatory protein-1 (MIP-1b), vascular endothelial growth factor (VEGF), serum amyloid A (SAA), S100A12, and high sensitivity C-Reactive protein (hsCRP). Conversely, increases from baseline were observed in tartrate-resistant acid phosphatase (TRAP-5b). The clinical relevance of this information is not known.

12.3 Pharmacokinetics

Absorption

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, a mean C_{max} of 44.4 ±11.3 µg/mL was observed in patients with RA. Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.

Distribution

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the mean volume of distribution was estimated to be 115 ± 19 mL/kg in healthy subjects, and 151 ± 61 mL/kg in patients with RA. The volume of distribution of golimumab may indicate that golimumab is distributed primarily in the circulatory system with limited extravascular distribution.

Elimination

The elimination pathways for golimumab have not been characterized.

Following a single intravenous administration of 2 mg/kg SIMPONI ARIA, the systemic clearance of golimumab was estimated to be 6.9 ± 2.0 mL/day/kg in healthy subjects and 7.6 ± 2.0 mL/day/kg in patients with RA. The mean terminal half-life was estimated to be 12 ± 3 days in healthy subjects and the mean terminal half-life in RA patients was 14 ± 4 days.

When 2 mg/kg SIMPONI ARIA was administered intravenously to patients with RA at weeks 0, 4 and every 8 weeks thereafter, serum concentrations reached steady state by Week 12. Following IV administration, concomitant administration of methotrexate decreases the clearance of SIMPONI ARIA by approximately 9% based on population PK analysis. In addition, concomitant administration of methotrexate decreases the SIMPONI ARIA clearance by reducing the development of anti-golimumab antibodies. With concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4 ± 0.4 µg/mL in patients with active RA despite MTX therapy.

Population PK analysis indicated that concomitant use of NSAIDs, oral corticosteroids or sulfasalazine did not influence the apparent clearance of SIMPONI following SC administration.

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

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

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.

Effect of weight on pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic potential. Mutagenicity studies have not been conducted with golimumab. A fertility study conducted in mice using an analogous anti-mouse TNFα antibody administered by the intravenous route at doses up to 40 mg/kg once per week showed no impairment of fertility.

14 CLINICAL STUDIES

The efficacy and safety of SIMPONI ARIA were evaluated in one multicenter, randomized, double-blind, controlled trial (Trial 1) in 592 patients ≥ 18 years of age with moderately to severely active RA despite concurrent MTX therapy and had not previously been treated with a biologic TNF-blocker. Patients were diagnosed according to the American College of Rheumatology (ACR) criteria, at least 3 months prior to administration of study agent and were required to have at least 6 swollen and 6 tender joints. Patients were randomized to receive either SIMPONI ARIA 2 mg/kg (n=395) or placebo (n=197) over a 30 minute intravenous infusion at Weeks 0, 4 and every 8 weeks thereafter in addition to their weekly maintenance MTX dose (15–25 mg). All patients receiving placebo + MTX received SIMPONI ARIA + MTX after Week 24, but the trial remained blinded until all patients had completed 108 weeks of treatment. Efficacy data were collected and analyzed through Week 52. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

The primary endpoint in Trial 1 was the percentage of patients achieving an ACR 20 response at Week 14. In Trial 1, the majority of subjects were women (82%) and were Caucasian (80%) with a median age of 52 years and a median weight of 70 kg. Median disease duration was 4.7 years, and 50% of the patients used at least one DMARD other than MTX in the past. At baseline, 81% of patients received concomitant NSAIDs and 81% of patients received low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day). The median baseline DAS28-CRP was 5.9 and the median van der Heijde-Sharp score at baseline was 28.5.

Clinical Response

A greater percentage of patients treated with the combination of SIMPONI ARIA + MTX achieved ACR 20 at Week 14 and ACR50 at Week 24 versus patients treated with the placebo + MTX as shown in Table 2. The percent of patients achieving ACR 20 responses by visit for Trial 1 is shown in Figure 1.

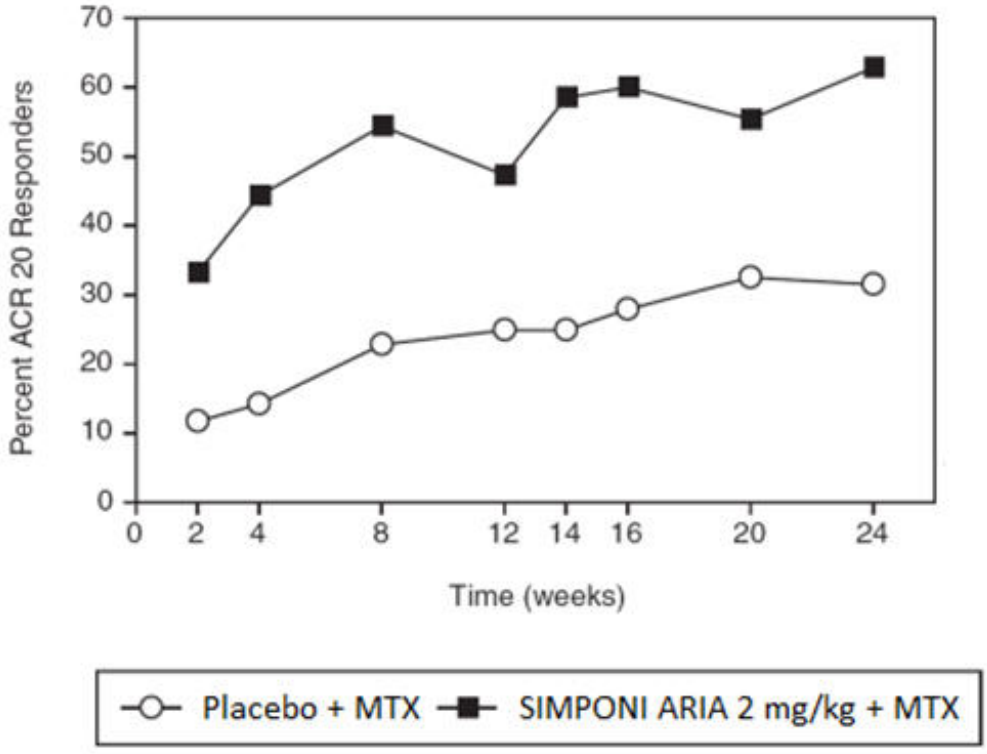
Table 2: Trial 1 – Proportion of Patients with an ACR Response

Trial 1 Active RA, despite MTX			
	Placebo + MTX	**SIMPONI ARIA + MTX**	**95% CI***
N†	197	395	
ACR 20			
Week 14	25%	59%	25.9, 41.4
Week 24	32%	63%	23.3, 39.4
ACR 50			
Week 14	9%	30%	15.3, 27.2
Week 24	13%	35%	15.1, 28.4
ACR 70			
Week 14	3%	12%	5.3, 13.4
Week 24	4%	18%	8.8, 18.1

* For difference in proportions

† N reflects randomized patients.

Figure 1: Trial 1 – Percent of Patients Achieving ACR 20 Response Over Time: Randomized Patients



The analysis is based on the intent-to-treat population. Last observation carried forward was performed for missing data. Patients who discontinued treatment due to lack of efficacy were counted as non-responders, as were patients who started prohibited medication or failed to achieve at least a 10% improvement in joint counts at Week 16.

The improvement in all components of the ACR response criteria for the SIMPONI ARIA + MTX group was greater compared to the placebo + MTX group in Trial 1 as shown in Table 3.

Table 3: Trial 1 – Components of ACR Response at Week 14

	Trial 1 Active RA, despite MTX	
	Placebo + MTX	**SIMPONI ARIA + MTX**
N*	197	395
Number of swollen joints (0–66)		
Baseline	15	15
Week 14	11	6
Number of tender joints (0–68)		
Baseline	26	26
Week 14	20	13
Patient's assessment of pain (0–10)		
Baseline	6.5	6.5
Week 14	5.6	3.9
Patient's global assessment of disease activity (0–10)		
Baseline	6.5	6.5
Week 14	5.5	4.0
Physician's global assessment of disease activity (0–10)		
Baseline	6.3	6.2
Week 14	4.9	3.1
HAQ score (0–3)		
Baseline	1.6	1.6
Week 14	1.4	1.1
CRP (mg/dL) (0–1)		
Baseline	2.2	2.8
Week 14	1.8	0.9

Note: All values are means.

* N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.

At Week 14, a greater proportion of patients treated with SIMPONI ARIA + MTX achieved a low level of disease activity as measured by a DAS28-CRP less than 2.6 compared with the placebo + MTX group (15% compared to 5%; 95% confidence interval for difference [6.3%,15.5%]).

Radiographic Response

In Trial 1, structural joint damage was assessed radiographically and expressed as a change in van der Heijde-Modified Sharp Score (vdH-S) and its components, the erosion score and Joint Space Narrowing (JSN) score, at Week 24 compared to baseline. The SIMPONI ARIA + MTX treatment group inhibited the progression of structural damage compared with placebo + MTX, as assessed by total vdH-S score as shown in Table 4.

Table 4: Trial 1 – Radiographic Change From Baseline at Week 24

	Placebo + MTX (N=197)*	**SIMPONI ARIA + MTX (N=395)*,†**
	Mean	**Mean**
Change Total vdH-S Score	1.1	0.03‡
Change Erosion Score	0.5	-0.1
Change JSN Score	0.6	0.1

* N reflects randomized patients
† p-value is displayed only for the major secondary endpoint
‡ p≤0.001

At Week 24, a greater proportion of patients in the SIMPONI ARIA + MTX group (71%) had no progression of structural damage (change in the total vdH-S score ≤ 0), compared to 57% of patients in the placebo + MTX group. At Week 52, the mean change from baseline in total vdH-S score was 1.2 in patients originally randomized to placebo + MTX who crossed over to SIMPONI ARIA + MTX at Week 16 or 24, and 0.1 in patients originally randomized to SIMPONI ARIA + MTX who remained on active treatment.

Physical Function Response in Patients with RA

Physical function was assessed by the disability index of the Health Assessment Questionnaire (HAQ-DI). At Week 14, the SIMPONI ARIA + MTX group showed greater mean improvement in the HAQ-DI compared with placebo + MTX (0.5 compared to 0.2; 95% confidence interval for difference [0.2, 0.4]).

16 HOW SUPPLIED/STORAGE AND HANDLING

SIMPONI ARIA is available in packs of 1 vial NDC 57894-350-01

Vial

Each single-use vial contains 50 mg of SIMPONI ARIA per 4 mL of solution.

Storage and Stability

SIMPONI ARIA must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) and protected from light. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Do not use SIMPONI ARIA beyond the expiration date (EXP) on the vial label.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Advise patients of the potential benefits and risks of SIMPONI ARIA. Instruct patients to read the Medication Guide before starting SIMPONI ARIA therapy and to read it each time the prescription is renewed.

Infections

Inform patients that SIMPONI ARIA may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection, including tuberculosis, invasive fungal infections, and hepatitis B reactivation.

Malignancies

Patients should be counseled about the risk of lymphoma and other malignancies while receiving SIMPONI ARIA.

Other Medical Conditions

Advise patients to report any signs of new or worsening medical conditions such as congestive heart failure, demyelinating disorders, autoimmune diseases, liver disease, cytopenias, or psoriasis.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
US License No. 1864 at

Cilag AG
Schaffhausen, Switzerland

MEDICATION GUIDE

SIMPONI® ARIA®
(SIM-puh-nee AHR-ee-uh**)**
(golimumab)
For Infusion

Read the Medication Guide for SIMPONI ARIA before each infusion. There may be new information. This Medication Guide does not take the place of talking with your doctor about your medical condition or treatment. It is important to remain under your doctor's care while receiving SIMPONI ARIA.

What is the most important information I should know about SIMPONI ARIA?

SIMPONI ARIA is a medicine that affects your immune system. SIMPONI ARIA can lower the ability of your immune system to fight infections. Some people have serious infections while taking SIMPONI ARIA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that spread throughout their body. Some people have died from these serious infections.

- Your doctor should test you for TB and hepatitis B before starting SIMPONI ARIA.
- Your doctor should monitor you closely for signs and symptoms of TB during treatment with SIMPONI ARIA.

You should not receive SIMPONI ARIA if you have any kind of infection unless your doctor says it is okay.

Before receiving SIMPONI ARIA, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweat, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinate more often than normal
  - feel very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live, have lived, or traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, blastomycosis). These infections may happen or become more severe if you receive SIMPONI ARIA. Ask your doctor if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B.
- use the medicine ORENCIA (abatacept), KINERET (anakinra), ACTEMRA (tocilizumab) or RITUXAN (rituximab).

After receiving SIMPONI ARIA, call your doctor right away if you have any symptoms of an infection. SIMPONI ARIA can make you more likely to get infections or make worse any infection that you have.

Cancer

- For children and adults receiving TNF-blocker medicines, including SIMPONI ARIA, the chances of getting cancer may increase.
- There have been cases of unusual cancers in children and teenage patients taking TNF-blocking agents.
- People with inflammatory diseases including rheumatoid arthritis especially those with very active disease, may be more likely to get lymphoma.
- Some people receiving TNF-blocker medicines developed a rare type of cancer called hepatosplenic T-cell lymphoma. This type of cancer often results in death. Most of these people were male teenagers or young men. Also, most people were being treated for Crohn's disease or ulcerative colitis with a TNF-blocker and another medicine called IMURAN® (azathioprine) or PURINETHOL® (6-mercaptopurine, 6-MP).
- Some people treated with SIMPONI ARIA developed skin cancer. If any changes in the appearance of your skin or growths on your skin occur during or after your treatment with SIMPONI ARIA, tell your doctor.
- You should see your doctor periodically for skin examinations, especially if you have a history of skin cancer.

What is SIMPONI ARIA?

SIMPONI ARIA is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker. SIMPONI ARIA is used with the medicine methotrexate to treat adults with moderately to severely active rheumatoid arthritis (RA).

SIMPONI ARIA is not for children under 18 years of age.

What should I tell my doctor before starting treatment with SIMPONI ARIA?

SIMPONI ARIA may not be right for you. Before receiving SIMPONI ARIA, tell your doctor about all your medical conditions, including if you:

- have an infection (see "What is the most important information I should know about SIMPONI ARIA?")
- have or have had lymphoma or any other type of cancer.
- have or had heart failure
- have or have had a condition that affects your nervous system, such as multiple sclerosis or Guillain-Barré syndrome
- have a skin problem called psoriasis
- have recently received or are scheduled to receive a vaccine. People receiving SIMPONI ARIA should not receive live vaccines or treatment with a weakened bacteria (such as BCG for bladder cancer). People receiving SIMPONI ARIA can receive non-live vaccines.
- have a baby and you received SIMPONI ARIA during your pregnancy. Tell your baby's doctor before your baby receives any vaccine. Your baby may have an increased chance of getting an infection for up to 6 months after birth.
- are pregnant or planning to become pregnant. It is not known if SIMPONI ARIA will harm your unborn baby.
- are breastfeeding. It is not known if SIMPONI ARIA passes into your breast milk. You and your doctor should decide if you will receive SIMPONI ARIA or breastfeed. You should not do both without talking to your doctor first.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your doctor if you:

- use ORENCIA (abatacept) or KINERET (anakinra). You should not receive SIMPONI ARIA while you are also taking ORENCIA (abatacept) or KINERET (anakinra).

- use other TNF-blocker medicines, including REMICADE (infliximab), HUMIRA (adalimumab), ENBREL (etanercept), or CIMZIA (certolizumab pegol).
- receive RITUXAN (rituximab) or ACTEMRA (tocilizumab).

Ask your doctor if you are not sure if your medicine is one listed above.

Keep a list of all your medications with you to show your doctor and pharmacist each time you get a new medicine.

How should I receive SIMPONI ARIA?

- SIMPONI ARIA is prepared and given by a healthcare provider through a needle placed in your vein (infusion). The infusion is usually given in your arm and should take 30 minutes.
- Your doctor will decide how much SIMPONI ARIA you will receive based on your weight. Your usual schedule for receiving SIMPONI ARIA after your first treatment should be:
  - 4 weeks after your first treatment
  - every 8 weeks after that
- If you forget or miss an appointment to receive SIMPONI ARIA, make another appointment as soon as possible.
- You may continue to use other medicines for your treatment while taking SIMPONI ARIA, such as non-steroidal anti-inflammatory drugs (NSAIDs), prescription steroids, and pain relief medicines.

What are the possible side effects of SIMPONI ARIA?

SIMPONI ARIA can cause serious side effects, including:

- See "**What is the most important information I should know about SIMPONI ARIA?"**
- **Hepatitis B infection in people who carry the virus in their blood**. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become active while you receive SIMPONI ARIA. Your doctor should do blood tests before you start treatment with SIMPONI ARIA and while you are receiving SIMPONI ARIA. Tell your doctor if you have any of the following symptoms of a possible hepatitis B infection:

  - feel very tired
  - clay-colored bowel movements
  - dark urine
  - fevers
  - skin or eyes look yellow
  - little or no appetite
  - vomiting
  - muscle aches
  - chills
  - stomach discomfort
  - skin rash

- **Heart failure, including new heart failure or worsening of heart failure that you already have.** New or worse heart failure can happen in people who use TNF-blocker medicines including SIMPONI ARIA.
  - If you have heart failure, your condition should be watched closely while you receive SIMPONI ARIA.
  - Call your doctor right away if you get new or worsening symptoms of heart failure while receiving SIMPONI ARIA (such as shortness of breath, swelling of your lower legs or feet, or sudden weight gain).
- **Nervous System Problems**
  Rarely, people using TNF-blocker medicines, including SIMPONI ARIA, have nervous system problems such as multiple sclerosis or Guillain-Barré syndrome.
  Tell your doctor right away if you get any of these symptoms:
  - vision changes
  - weakness in your arms or legs
  - numbness or tingling in any part of your body

- **Liver Problems**
  Liver problems can happen in people who use TNF-blocker medicines, including SIMPONI ARIA. These problems can lead to liver failure and death. Call your doctor right away if you have any of these symptoms:
  - feel very tired
  - skin or eyes look yellow
  - poor appetite or vomiting
  - pain on the right side of your stomach (abdomen)
- **Blood Problems**
  Low blood counts have been seen with TNF-blockers, including SIMPONI ARIA. Your body may not make enough blood cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding easily, or looking pale. Your doctor will check your blood counts before and during treatment with SIMPONI ARIA.
- **Allergic Reactions**
  Allergic reactions can happen in people who use TNF-blocker medicines including SIMPONI ARIA. Some reactions may be serious and can be life threatening. Some of these reactions can happen after receiving your first dose of SIMPONI ARIA. Call your doctor right away if you have any of these symptoms of an allergic reaction:
  - hives
  - swollen face
  - breathing trouble
  - chest pain

The most common side effects of SIMPONI ARIA include:
- upper respiratory infection (runny nose, sore throat, and hoarseness or laryngitis)
- viral infections such as flu and cold sores in the mouth
- bronchitis
- high blood pressure
- rash

Other side effects with SIMPONI ARIA include:
- **Immune System Problems.** Rarely, people using TNF-blocker medicines have developed symptoms that are like the symptoms of Lupus. Tell your doctor if you have any of these symptoms:
  - a rash on your cheeks or other parts of the body
  - sensitivity to the sun
  - new joint or muscle pains
  - becoming very tired
  - chest pain or shortness of breath
  - swelling of the feet, ankles, or legs

These are not all of the side effects with SIMPONI ARIA. Tell your doctor about any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

General Information about SIMPONI ARIA

Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide. Do not use SIMPONI ARIA for a condition for which it was not prescribed.

This Medication Guide summarizes the most important information about SIMPONI ARIA. If you would like more information, talk to your doctor. You can ask your doctor or pharmacist for information about SIMPONI ARIA that is written for health professionals.

For more information go to www.SimponiAria.com or call 1-800-JANSSEN (1-800-526-7736).

What are the ingredients in SIMPONI ARIA?

Active ingredient: golimumab

Inactive ingredients: L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sorbitol, and water for injection. SIMPONI ARIA does not contain preservatives, natural rubber or latex.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
US License No. 1864 at
Cilag AG
Schaffhausen, Switzerland

Approved: December 2014

PRINCIPAL DISPLAY PANEL - 4 mL Vial Carton

NDC 57894-350-01

Simponi® ARIA™
golimumab

50 mg/4 mL

(12.5 mg/mL)

For intravenous infusion

Single-use vial.
Discard unused portion.

Rx Only

Provide the enclosed Medication Guide to each patient.

SIMPONI ARIA

golimumab solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:57894-350
Route of Administration	INTRAVENOUS	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
golimumab (golimumab)	golimumab	50 mg in 4 mL

Inactive Ingredients	
Ingredient Name	**Strength**
sorbitol	180 mg in 4 mL
histidine monohydrochloride monohydrate	6.42 mg in 4 mL
histidine	1.14 mg in 4 mL
polysorbate 80	0.6 mg in 4 mL
water	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:57894-350-01	1 in 1 CARTON		
1		4 mL in 1 VIAL, SINGLE-USE; Combination Product Type = C112160		
2	NDC:57894-350-89	1 in 1 CARTON		
2		4 mL in 1 VIAL, SINGLE-USE; Combination Product Type = C112160		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125433	07/19/2013	

Labeler - Janssen Biotech, Inc. (099091753)

Establishment

Name	Address	ID/FEI	Business Operations
Cilag AG		483237103	MANUFACTURE(57894-350), ANALYSIS(57894-350), LABEL(57894-350), PACK(57894-350)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Biologics		987061921	API MANUFACTURE(57894-350), ANALYSIS(57894-350)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Biologics, B.V.		409612918	API MANUFACTURE(57894-350), ANALYSIS(57894-350)

Establishment

Name	Address	ID/FEI	Business Operations
Anderson Brecon		053217022	LABEL(57894-350), PACK(57894-350)

Revised: 12/2014 Janssen Biotech, Inc.