

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SIMPONI (golimumab) safely and effectively. See full prescribing information for SIMPONI.

SIMPONI (golimumab)

Injection, solution for subcutaneous use

Initial U.S. Approval: 2009

<p>WARNINGS:</p> <p>SERIOUS INFECTIONS <i>See full prescribing information for complete boxed warning</i></p> <ul style="list-style-type: none">• Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial sepsis, invasive fungal, and other opportunistic infections have occurred in patients receiving SIMPONI (5.1).• SIMPONI should be discontinued 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 (5.1).• Monitor all patients for active TB during treatment, even if initial latent TB test is negative (5.1) <p>MALIGNANCY</p> <ul style="list-style-type: none">• Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, of which SIMPONI is a member (5.2)
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-----RECENT MAJOR CHANGES-----

Boxed Warning, MALIGNANCY	11/2009
Warnings and Precautions, Malignancies (5.2)	11/2009

-----INDICATIONS AND USAGE-----

SIMPONI is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- **Moderately to severely active Rheumatoid Arthritis (RA) in adults, in combination with methotrexate (1.1)**
- **Active Psoriatic Arthritis (PsA) in adults, alone or in combination with methotrexate (1.2)**
- **Active Ankylosing Spondylitis in adults (AS) (1.3)**

-----DOSAGE AND ADMINISTRATION-----

Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis (2.1)

- 50 mg administered by subcutaneous injection once a month.

-----DOSAGE FORMS AND STRENGTHS-----

- 50 mg/0.5 mL in a single dose prefilled SmartJect autoinjector (3)
- 50 mg/0.5 mL in a single dose prefilled syringe (3)

-----CONTRAINDICATIONS-----

- None (4)

-----WARNINGS AND PRECAUTIONS-----

- Serious Infections – Do not start SIMPONI during an active infection. If an infection develops, monitor carefully, and stop SIMPONI if infection becomes serious (5.1).
- Invasive fungal infections – For patients who develop a systemic illness on SIMPONI, consider empiric antifungal therapy for those who reside 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 and begin anti-viral therapy (5.1).
- Malignancies – The incidence of lymphoma was seen more often than in the general U.S. population. Cases of other malignancies have been observed among patients receiving TNF-blockers (5.2).
- Heart failure – Worsening, or new onset, may occur. Stop SIMPONI if new or worsening symptoms occur (5.3).
- Demyelinating disease, exacerbation or new onset, may occur (5.4).

-----ADVERSE REACTIONS-----

Most common adverse reactions (incidence > 5%): upper respiratory tract infection, nasopharyngitis (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Centocor Ortho Biotech Inc. at 1-800-457-6399 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Abatacept – increased risk of serious infection (5.1, 5.5, 7.2)
- Anakinra – increased risk of serious infection (5.1, 5.6, 7.2).
- Live vaccines – should not be given with SIMPONI (5.8, 7.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 11/2009

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1 FULL PRESCRIBING INFORMATION

2
3 **WARNINGS**

4 **SERIOUS INFECTIONS**

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

9
10 SIMPONI should be discontinued if a patient develops a serious infection.

11
12 **Reported infections include:**

- 13
- 14 • Active tuberculosis, including reactivation of latent tuberculosis. Patients with
15 tuberculosis have frequently presented with disseminated or extrapulmonary disease.
16 Patients should be tested for latent tuberculosis before SIMPONI use and during
17 therapy. Treatment for latent infection should be initiated prior to SIMPONI use.
 - 18
 - 19 • Invasive fungal infections, including histoplasmosis, coccidioidomycosis, and
20 pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may
21 present with disseminated, rather than localized, disease. Antigen and antibody
22 testing for histoplasmosis may be negative in some patients with active infection.
23 Empiric anti-fungal therapy should be considered in patients at risk for invasive
24 fungal infections who develop severe systemic illness.
 - 25
 - 26 • Bacterial, viral, and other infections due to opportunistic pathogens.
- 27

28 The risks and benefits of treatment with SIMPONI should be carefully considered prior to
29 initiating therapy in patients with chronic or recurrent infection.

30
31 Patients should be closely monitored for the development of signs and symptoms of infection
32 during and after treatment with SIMPONI, including the possible development of
33 tuberculosis in patients who tested negative for latent tuberculosis infection prior to
34 initiating therapy [see Warning and Precautions (5.1)].

35
36 **MALIGNANCY**

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

42 **1.0 INDICATIONS AND USAGE**

43 **1.1 Rheumatoid Arthritis**

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

46 **1.2 Psoriatic Arthritis**

47 SIMPONI, alone or in combination with methotrexate, is indicated for the treatment of adult
48 patients with active psoriatic arthritis.

49 **1.3 Ankylosing Spondylitis**

50 SIMPONI is indicated for the treatment of adult patients with active ankylosing spondylitis.

51 **2.0 DOSAGE AND ADMINISTRATION**

52 **2.1 Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis**

53 The SIMPONI dose regimen is 50 mg administered by subcutaneous (SC) injection once a month.

54 For patients with rheumatoid arthritis (RA), SIMPONI should be given in combination with
55 methotrexate and for patients with psoriatic arthritis (PsA) or ankylosing spondylitis (AS),
56 SIMPONI may be given with or without methotrexate or other non-biologic DMARDs. For
57 patients with RA, PsA, or AS, corticosteroids, non-biologic DMARDs, and/or NSAIDs may be
58 continued during treatment with SIMPONI.

59 **2.2 Monitoring to Assess Safety**

60 Prior to initiating SIMPONI and periodically during therapy, patients should be evaluated for
61 active tuberculosis and tested for latent infection [*see Warnings and Precautions (5.1)*].

62 **2.3 General Considerations for Administration**

63 SIMPONI is intended for use under the guidance and supervision of a physician. After proper
64 training in subcutaneous injection technique, a patient may self inject with SIMPONI if a
65 physician determines that it is appropriate. Patients should be instructed to follow the directions
66 provided in the Medication Guide [*see Medication Guide (17.3)*]. To ensure proper use, allow the
67 prefilled syringe or autoinjector to sit at room temperature outside the carton for 30 minutes prior
68 to subcutaneous injection. Do not warm SIMPONI in any other way.

69 Prior to administration, visually inspect the solution for particles and discoloration through the
70 viewing window. SIMPONI should be clear to slightly opalescent and colorless to light yellow.
71 The solution should not be used if discolored, or cloudy, or if foreign particles are present. Any
72 leftover product remaining in the prefilled syringe or prefilled autoinjector should not be used.
73 NOTE: The needle cover on the prefilled syringe as well as the prefilled syringe in the
74 autoinjector contains dry natural rubber (a derivative of latex), which should not be handled by
75 persons sensitive to latex.

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

78 **3.0 DOSAGE FORMS AND STRENGTHS**

79 **SmartJect™ Autoinjector**

80 Each single dose SmartJect autoinjector contains a prefilled glass syringe (27 gauge ½ inch)
81 providing 50 mg of SIMPONI per 0.5 mL of solution.

82 **Prefilled Syringe**

83 Each single dose prefilled glass syringe (27 gauge ½ inch) contains 50 mg of SIMPONI per 0.5
84 mL of solution.

85 **4.0 CONTRAINDICATIONS**

86 None.

87 **5.0 WARNINGS AND PRECAUTIONS (see Boxed WARNINGS)**

88 **5.1 Serious Infections**

89 Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral,
90 protozoal, or other opportunistic pathogens have been reported in patients receiving TNF-blockers
91 including SIMPONI. Among opportunistic infections, tuberculosis, histoplasmosis, aspergillosis,
92 candidiasis, coccidioidomycosis, listeriosis, and pneumocystosis were the most commonly
93 reported with TNF-blockers. Patients have frequently presented with disseminated rather than
94 localized disease, and were often taking concomitant immunosuppressants such as methotrexate or
95 corticosteroids. The concomitant use of a TNF-blocker and abatacept or anakinra was associated
96 with a higher risk of serious infections; therefore, the concomitant use of SIMPONI and these
97 biologic products is not recommended [*see Warning and Precautions (5.5, 5.6) and Drug*
98 *Interactions (7.2)*].

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

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

108 Patients should be closely monitored for the development of signs and symptoms of infection
109 during and after treatment with SIMPONI. SIMPONI should be discontinued if a patient develops
110 a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection
111 during treatment with SIMPONI should undergo a prompt and complete diagnostic workup
112 appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be
113 initiated, and the patient should be closely monitored.

114 In controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, serious infections
115 were observed in 1.4% of SIMPONI-treated patients and 1.3% of control-treated patients. In the
116 controlled Phase 3 trials through Week 16 in patients with RA, PsA, and AS, the incidence of

117 serious infections per 100 patient-years of follow-up was 5.4 (95% CI: 4.0, 7.2) for the SIMPONI
118 group and 5.3 (95% CI: 3.1, 8.7) for the placebo group. Serious infections observed in SIMPONI-
119 treated patients included sepsis, pneumonia, cellulitis, abscess, tuberculosis, invasive fungal
120 infections, and hepatitis B infection.

121

122 **Tuberculosis**

123 Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients
124 receiving TNF-blockers, including patients who have previously received treatment for latent or
125 active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent
126 infection prior to initiating SIMPONI and periodically during therapy.

127 Treatment of latent tuberculosis infection prior to therapy with TNF-blockers has been shown to
128 reduce the risk of tuberculosis reactivation during therapy. Induration of 5 mm or greater with
129 tuberculin skin testing should be considered a positive test result when assessing if treatment for
130 latent tuberculosis is needed prior to initiating SIMPONI, even for patients previously vaccinated
131 with Bacille Calmette-Guerin (BCG).

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

138 Patients should be closely monitored for the development of signs and symptoms of tuberculosis
139 including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

140 Tuberculosis should be strongly considered in patients who develop a new infection during
141 SIMPONI treatment, especially in patients who have previously or recently traveled to countries
142 with a high prevalence of tuberculosis, or who have had close contact with a person with active
143 tuberculosis.

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

149 **Invasive Fungal Infections**

150 For SIMPONI-treated patients who reside or travel in regions where mycoses are endemic,
151 invasive fungal infection should be suspected if they develop a serious systemic illness.
152 Appropriate empiric antifungal therapy should be considered while a diagnostic workup is being
153 performed. Antigen and antibody testing for histoplasmosis may be negative in some patients
154 with active infection. When feasible, the decision to administer empiric antifungal therapy in
155 these patients should be made in consultation with a physician with expertise in the diagnosis and
156 treatment of invasive fungal infections and should take into account both the risk for severe fungal
157 infection and the risks of antifungal therapy.

158 **Hepatitis B Virus Reactivation**

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

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

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

176 **5.2 Malignancies**

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

186
187 The risks and benefits of TNF-blocker treatment including SIMPONI should be considered prior
188 to initiating therapy in patients with a known malignancy other than a successfully treated non-
189 melanoma skin cancer (NMSC) or when considering continuing a TNF-blocker in patients who
190 develop a malignancy.

191
192 In the controlled portions of clinical trials of TNF-blockers including SIMPONI, more cases of
193 lymphoma have been observed among patients receiving anti-TNF treatment compared with
194 patients in the control groups. During the controlled portions of the Phase 2 trials in RA, and the
195 Phase 3 trials in RA, PsA and AS, the incidence of lymphoma per 100 patient-years of follow-up
196 was 0.21 (95% CI: 0.03, 0.77) in the combined SIMPONI group compared with an incidence of 0
197 (95% CI: 0., 0.96) in the placebo group. In the controlled and uncontrolled portions of these
198 clinical trials in 2347 SIMPONI-treated patients with a median follow-up of 1.4 years, the
199 incidence of lymphoma was 3.8-fold higher than expected in the general U.S. population
200 according to the SEER database (adjusted for age, gender, and race).¹ Patients with RA and other
201 chronic inflammatory diseases, particularly patients with highly active disease and/or chronic
202 exposure to immunosuppressant therapies, may be at higher risk (up to several fold) than the

203 general population for the development of lymphoma, even in the absence of TNF-blocking
204 therapy. Cases of acute and chronic leukemia have been reported with postmarketing TNF-
205 blocker use in rheumatoid arthritis and other indications. Even in the absence of TNF blocker
206 therapy, patients with rheumatoid arthritis may be at a higher risk (approximately 2-fold) than the
207 general population for the development of leukemia.
208

209 During the controlled portions of the Phase 2 trial in RA, and the Phase 3 trials in RA, PsA and
210 AS, the incidence of malignancies other than lymphoma per 100 patient-years of follow-up was
211 not elevated in the combined SIMPONI group compared with the placebo group. In the controlled
212 and uncontrolled portions of these trials, the incidence of malignancies, other than lymphoma, in
213 SIMPONI-treated patients was similar to that expected in the general U.S. population according to
214 the SEER database (adjusted for age, gender, and race).¹

215 In controlled trials of other TNF-blockers in patients at higher risk for malignancies (e.g., patients
216 with COPD, patients with Wegener's granulomatosis treated with concomitant cyclophosphamide)
217 a greater portion of malignancies occurred in the TNF-blocker group compared to the controlled
218 group. In an exploratory 1-year clinical trial evaluating the use of 50, 100 and 200 mg of
219 SIMPONI in 309 patients with severe persistent asthma, 6 patients developed malignancies other
220 than NMSC in the SIMPONI groups compared to none in the control group. Three of the 6
221 patients were in the 200 mg SIMPONI group.

222 **5.3 Congestive Heart Failure**

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

230 **5.4 Demyelinating Disorders**

231 Use of TNF-blockers has been associated with cases of new onset or exacerbation of central
232 nervous system (CNS) demyelinating disorders, including multiple sclerosis (MS). While no trials
233 have been performed evaluating SIMPONI in the treatment of patients with MS, another TNF-
234 blocker was associated with increased disease activity in patients with MS. Therefore, prescribers
235 should exercise caution in considering the use of TNF-blockers including SIMPONI in patients
236 with CNS demyelinating disorders including MS.

237 **5.5 Use with Abatacept**

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

243 **5.6 Use with Anakinra**

244 Concurrent administration of anakinra (an interleukin-1 antagonist) and another TNF-blocker, was
245 associated with a greater portion of serious infections and neutropenia and no additional benefits

246 compared with the TNF-blocker alone. Therefore, the combination of anakinra with TNF-
247 blockers, including SIMPONI, is not recommended [see *Drug Interactions* 7.2].

248 **5.7 Hematologic Cytopenias**

249 There have been post-marketing reports of pancytopenia, leukopenia, neutropenia, aplastic
250 anemia, and thrombocytopenia in patients receiving TNF-blockers. Although, there were no cases
251 of severe cytopenias seen in the SIMPONI clinical trials, caution should be exercised when using
252 TNF-blockers, including SIMPONI, in patients who have significant cytopenias.

253 **5.8 Vaccinations**

254 Patients treated with SIMPONI may receive vaccinations, except for live vaccines. No data are
255 available on the response to live vaccination or the risk of infection, or transmission of infection
256 after the administration of live vaccines to patients receiving SIMPONI. In the Phase 3 PsA study,
257 after pneumococcal vaccination, a similar proportion of SIMPONI-treated and placebo-treated
258 patients were able to mount an adequate immune response of at least a 2-fold increase in antibody
259 titers to pneumococcal polysaccharide vaccine. In both SIMPONI-treated and placebo-treated
260 patients, the proportions of patients with response to pneumococcal vaccine were lower among
261 patients receiving MTX compared with patients not receiving MTX. The data suggest that
262 SIMPONI does not suppress the humoral immune response to the pneumococcal vaccine.

263 **6.0 ADVERSE REACTIONS**

264 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
265 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of
266 another drug and may not reflect the rates observed in clinical practice.

267 **6.1 Clinical Studies Experience**

268 The safety data described below are based on 5 pooled, randomized, double-blind, controlled
269 Phase 3 trials in patients with RA, PsA, and AS (Studies RA-1, RA-2, RA-3, PsA, and AS) [see
270 *Clinical Studies* (14.1, 14.2 and 14.3)]. These 5 trials included 639 control-treated patients and
271 1659 SIMPONI-treated patients including 1089 with RA, 292 with PsA, and 278 with AS. The
272 proportion of patients who discontinued treatment due to adverse reactions in the controlled Phase
273 3 trials through Week 16 in RA, PsA and AS was 2% for SIMPONI-treated patients and 3% for
274 placebo-treated patients. The most common adverse reactions leading to discontinuation of
275 SIMPONI in the controlled Phase 3 trials through Week 16 were sepsis (0.2%), alanine
276 aminotransferase increased (0.2%), and aspartate aminotransferase increased (0.2%).

277 The most serious adverse reactions were:

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

280 Upper respiratory tract infection and nasopharyngitis were the most common adverse reactions
281 reported in the combined Phase 3 RA, PsA and AS trials through Week 16, occurring in 7% and
282 6% of SIMPONI-treated patients as compared with 6% and 5% of control-treated patients,
283 respectively.

284 **Infections**

285 In controlled Phase 3 trials through Week 16 in RA, PsA, and AS, infections were observed in
286 28% of SIMPONI-treated patients compared to 25% of control-treated patients [for Serious
287 Infections, see *Warnings and Precautions* (5.1)].

288 **Liver Enzyme Elevations**

289 There have been reports of severe hepatic reactions including acute liver failure in patients
290 receiving TNF-blockers. In controlled Phase 3 trials of SIMPONI in patients with RA, PsA, and
291 AS through Week 16, ALT elevations $\geq 5 \times$ ULN occurred in 0.2% of control-treated patients and
292 0.7% of SIMPONI-treated patients and ALT elevations $\geq 3 \times$ ULN occurred in 2% of control-
293 treated patients and 2% of SIMPONI-treated patients. Since many of the patients in the Phase 3
294 trials were also taking medications that cause liver enzyme elevations (e.g., NSAIDS, MTX), the
295 relationship between golimumab and liver elevation is not clear.

296 **Autoimmune Disorders and Autoantibodies**

297 The use of TNF-blockers has been associated with the formation of autoantibodies and, rarely,
298 with the development of a lupus-like syndrome. In the controlled Phase 3 trials in patients with
299 RA, PsA, and AS through Week 14, there was no association of SIMPONI treatment and the
300 development of newly positive anti-dsDNA antibodies.

301 **Injection Site Reactions**

302 In controlled Phase 3 trials through Week 16 in RA, PsA and AS, 6% of SIMPONI-treated
303 patients had injection site reactions compared with 2% of control-treated patients. The majority of
304 the injection site reactions were mild and the most frequent manifestation was injection site
305 erythema. In controlled Phase 2 and 3 trials in RA, PsA, and AS, no patients treated with
306 SIMPONI developed anaphylactic reactions.

307 **Psoriasis: New-Onset and Exacerbations**

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

317 **Immunogenicity**

318 Antibodies to SIMPONI were detected in 57 (4%) of SIMPONI-treated patients across the Phase 3
319 RA, PsA and AS trials through Week 24. Similar rates were observed in each of the three
320 indications. Patients who received SIMPONI with concomitant MTX had a lower proportion of
321 antibodies to SIMPONI than patients who received SIMPONI without MTX (approximately 2%
322 versus 7%, respectively). Of the patients with a positive antibody response to SIMPONI in the
323 Phase 2 and 3 trials, most were determined to have neutralizing antibodies to golimumab as
324 measured by a cell-based functional assay. The small number of patients positive for antibodies to
325 SIMPONI limits the ability to draw definitive conclusions regarding the relationship between
326 antibodies to golimumab and clinical efficacy or safety measures.

327 The data above reflect the percentage of patients whose test results were considered positive for
328 antibodies to SIMPONI in an ELISA assay, and are highly dependent on the sensitivity and
329 specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay
330 may be influenced by several factors including sample handling, timing of sample collection,

331 concomitant medications, and underlying disease. For these reasons, comparison of the incidence
332 of antibodies to SIMPONI with the incidence of antibodies to other products may be misleading.

333

334 **Other Adverse Reactions**

335 Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% in the
336 combined SIMPONI groups during the controlled period of the 5 pooled Phase 3 trials through
337 Week 16 in patients with RA, PsA, and AS.

338

Table 1. Adverse Drug Reactions Reported by $\geq 1\%$ of Patients in the Phase 3 Trials of RA, PsA, and AS through Week 16^a

	Placebo \pm DMARDs	SIMPONI \pm DMARDs
Patients treated	639	1659
Adverse Reaction (Preferred Term)		
Upper respiratory tract infection	37 (6%)	120 (7%)
Nasopharyngitis	31 (5%)	91 (6%)
Alanine aminotransferase increased	18 (3%)	58 (4%)
Injection site erythema	6 (1%)	56 (3%)
Hypertension	9 (1%)	48 (3%)
Aspartate aminotransferase increased	10 (2%)	44 (3%)
Bronchitis	9 (1%)	31 (2%)
Dizziness	7 (1%)	32 (2%)
Sinusitis	7 (1%)	27 (2%)
Influenza	7 (1%)	25 (2%)
Pharyngitis	8 (1%)	22 (1%)
Rhinitis	4 (< 1%)	20 (1%)
Pyrexia	4 (< 1%)	20 (1%)
Oral herpes	2 (< 1%)	16 (1%)
Paraesthesia	2 (< 1%)	16 (1%)

339 a Patients may have taken concomitant MTX, sulfasalazine, hydroxychloroquine, low dose corticosteroids (≤ 10 mg
340 of prednisone/day or equivalent), and/or NSAIDs during the trials).

341 **7.0 DRUG INTERACTIONS**

342 **7.1 Methotrexate**

343 For the treatment of RA, SIMPONI should be used with methotrexate (MTX) [*see Clinical Studies*
344 (14.1)]. Since the presence or absence of concomitant MTX did not appear to influence the
345 efficacy or safety of SIMPONI in the treatment of PsA or AS, SIMPONI can be used with or
346 without MTX in the treatment of PsA and AS [*see Clinical Studies (14.1) and Clinical*
347 *Pharmacology (12.3)*].

348 **7.2 Biologic Products for RA, PsA, and/or AS**

349 An increased risk of serious infections has been seen in clinical RA studies of other TNF-blockers
350 used in combination with anakinra or abatacept, with no added benefit; therefore, use of SIMPONI
351 with abatacept or anakinra is not recommended [*see Warnings and Precautions (5.5 and 5.6)*]. A
352 higher rate of serious infections has also been observed in RA patients treated with rituximab who
353 received subsequent treatment with a TNF-blocker. There is insufficient information to provide
354 recommendations regarding the concomitant use of SIMPONI and other biologic products
355 approved to treat RA, PsA, or AS.

356 **7.3 Live Vaccines**

357 Live vaccines should not be given concurrently with SIMPONI [see *Warnings and Precautions*
358 (5.8)].

359 **7.4 Cytochrome P450 Substrates**

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

367 **8.0 USE IN SPECIFIC POPULATIONS**

368 **8.1 Pregnancy**

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

374 An embryofetal developmental toxicology study was performed in which pregnant cynomolgus
375 monkeys were treated subcutaneously with golimumab during the first trimester with doses up to
376 50 mg/kg twice weekly (360 times greater than the maximum recommended human dose-MHRD)
377 and has revealed no evidence of harm to maternal animals or fetuses. Umbilical cord blood
378 samples collected at the end of the second trimester showed that fetuses were exposed to
379 golimumab during gestation. In this study, *in utero* exposure to golimumab produced no
380 developmental defects to the fetus.

381 A pre- and post-natal developmental study was performed in which pregnant cynomolgus
382 monkeys were treated with golimumab during the second and third trimesters, and during lactation
383 at doses up to 50 mg/kg twice weekly (860 times and 310 times greater than the maximal steady
384 state human blood levels for maternal animals and neonates, respectively) and has revealed no
385 evidence of harm to maternal animals or neonates. Golimumab was present in the neonatal serum
386 from the time of birth and for up to six months postpartum. Exposure to golimumab during
387 gestation and during the postnatal period caused no developmental defects in the infants.

388 **8.3 Nursing Mothers**

389 It is not known whether SIMPONI is excreted in human milk or absorbed systemically after
390 ingestion. Because many drugs and immunoglobulins are excreted in human milk, and because of
391 the potential for adverse reactions in nursing infants from SIMPONI, a decision should be made
392 whether to discontinue nursing or to discontinue the drug, taking into account the importance of
393 the drug to the mother.

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

398 **8.4 Pediatric Use**

399 Safety and effectiveness of SIMPONI in pediatric patients less than 18 years of age have not been
400 established.

401 **8.5 Geriatric Use**

402 In the Phase 3 trials in RA, PsA, and AS, there were no overall differences in SAEs, serious
403 infections, and AEs in SIMPONI-treated patients ages 65 or older (N = 155) compared with
404 younger SIMPONI-treated patients. Because there is a higher incidence of infections in the
405 geriatric population in general, caution should be used in treating geriatric patients with
406 SIMPONI.

407 **10.0 OVERDOSAGE**

408 In a clinical study, 5 patients received protocol-directed single infusions of 10 mg/kg of
409 intravenous SIMPONI without serious adverse reactions or other significant reactions. The
410 highest weight patient was 100 kg, and therefore received a single intravenous infusion of 1000
411 mg of SIMPONI. There were no SIMPONI overdoses in the clinical studies.

412 **11.0 DESCRIPTION**

413 SIMPONI (golimumab) is a human IgG1 κ monoclonal antibody specific for human tumor
414 necrosis factor alpha (TNF α) that exhibits multiple glycoforms with molecular masses of
415 approximately 150 to 151 kilodaltons. SIMPONI was created using genetically engineered mice
416 immunized with human TNF, resulting in an antibody with human-derived antibody variable and
417 constant regions. SIMPONI is produced by a recombinant cell line cultured by continuous
418 perfusion and is purified by a series of steps that includes measures to inactivate and remove
419 viruses.

420 The SIMPONI drug product is a sterile solution of the golimumab antibody supplied as either a
421 single dose prefilled syringe (with a passive needle safety guard) or a single dose prefilled
422 autoinjector. The Type 1 glass syringe has a coated stopper. The fixed stainless steel needle (5
423 bevel, 27G, half-inch) is covered with a needle shield to prevent leakage of the solution through
424 the needle and to protect the needle during handling prior to administration. The needle shield is
425 made of a dry natural rubber containing latex.

426 SIMPONI does not contain preservatives. The solution is clear to slightly opalescent, colorless to
427 light yellow with a pH of approximately 5.5. SIMPONI is provided in one strength: 50 mg of the
428 golimumab antibody in 0.5 mL of solution. Each 0.5 mL of SIMPONI contains 50 mg of the
429 golimumab antibody, 0.44 mg of L-histidine and L-histidine monohydrochloride monohydrate,
430 20.5 mg of sorbitol, 0.08 mg of polysorbate 80, and Water for Injection.

431 **12.0 CLINICAL PHARMACOLOGY**

432 **12.1 Mechanism of Action**

433 Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane
434 bioactive forms of human TNF α . This interaction prevents the binding of TNF α to its receptors,
435 thereby inhibiting the biological activity of TNF α (a cytokine protein). There was no evidence of
436 the golimumab antibody binding to other TNF superfamily ligands; in particular, the golimumab
437 antibody did not bind or neutralize human lymphotoxin. Golimumab did not lyse human
438 monocytes expressing transmembrane TNF in the presence of complement or effector cells.

439 Elevated TNF α levels in the blood, synovium, and joints have been implicated in the
440 pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic
441 arthritis, and ankylosing spondylitis. TNF α is an important mediator of the articular inflammation
442 that is characteristic of these diseases. Golimumab modulated the *in vitro* biological effects
443 mediated by TNF in several bioassays, including the expression of adhesion proteins responsible
444 for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of
445 proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF).

446 **12.2 Pharmacodynamics**

447 In clinical studies, decreases in C-reactive protein (CRP), interleukin (IL)-6, matrix
448 metalloproteinase 3 (MMP-3), intercellular adhesion molecule (ICAM)-1 and vascular endothelial
449 growth factor (VEGF) were observed following SIMPONI administration in patients with RA,
450 PsA, and AS.

451 **12.3 Pharmacokinetics**

452 Following subcutaneous (SC) administration of SIMPONI to healthy subjects and patients with
453 active RA, the median time to reach maximum serum concentrations (T_{max}) ranged from 2 to 6
454 days. A SC injection of 50 mg SIMPONI to healthy subjects produced a mean maximum serum
455 concentration (C_{max}) of approximately 2.5 $\mu\text{g/mL}$. SIMPONI exhibited dose-proportional
456 pharmacokinetics (PK) in patients with active RA over the dose range of 0.1 to 10.0 mg/kg
457 following a single intravenous (IV) dose. Following a single IV administration over the same
458 dose range in patients with active RA, mean systemic clearance of SIMPONI was estimated to be
459 4.9 to 6.7 mL/day/kg, and mean volume of distribution ranged from 58 to 126 mL/kg. The
460 volume of distribution for SIMPONI indicates that SIMPONI is distributed primarily in the
461 circulatory system with limited extravascular distribution. Median terminal half-life values were
462 estimated to be approximately 2 weeks in healthy subjects and patients with active RA, PsA or
463 AS. By cross-study comparisons of mean AUC_{inf} values following an IV or SC administration of
464 SIMPONI, the absolute bioavailability of SC SIMPONI was estimated to be approximately 53%.

465 When 50 mg SIMPONI was administered SC to patients with RA, PsA or AS every 4 weeks,
466 serum concentrations appeared to reach steady state by Week 12. With concomitant use of
467 methotrexate (MTX), treatment with 50 mg SIMPONI SC every 4 weeks resulted in a mean
468 steady-state trough serum concentration of approximately 0.4-0.6 $\mu\text{g/mL}$ in patients with active
469 RA, approximately 0.5 $\mu\text{g/mL}$ in patients with active PsA, and approximately 0.8 $\mu\text{g/mL}$ in
470 patients with active AS. Patients with RA, PsA and AS treated with SIMPONI 50 mg and MTX
471 had approximately 52%, 36% and 21% higher mean steady-state trough concentrations of
472 golimumab, respectively compared with those treated with SIMPONI 50 mg without MTX. The
473 presence of MTX also decreased anti-golimumab antibody incidence from 7% to 2% [*see Adverse*
474 *Reactions (6.1)*]. For RA, SIMPONI should be used with MTX. In the PsA and AS trials, the

475 presence or absence of concomitant MTX did not appear to influence clinical efficacy and safety
476 parameters [see *Drug Interactions (7.1) and Clinical Studies (14.1)*].

477 Population PK analyses indicated that concomitant use of NSAIDs, oral corticosteroids, or
478 sulfasalazine did not influence the apparent clearance of SIMPONI.

479 Population PK analyses showed there was a trend toward higher apparent clearance of SIMPONI
480 with increasing weight. However, across the PsA and AS populations, no meaningful differences
481 in clinical efficacy were observed among the subgroups by weight quartile. The RA trial in MTX-
482 experienced and TNF-blocker-naïve patients (Study RA-2) did show evidence of a reduction in
483 clinical efficacy with increasing body weight, but this effect was observed for both tested doses of
484 SIMPONI (50 mg and 100 mg). Therefore, there is no need to adjust the dosage of SIMPONI
485 based on a patient's weight.

486 Population PK analyses suggested no PK differences between male and female patients after body
487 weight adjustment in the RA and PsA trials. In the AS trial, female patients showed 13% higher
488 apparent clearance than male patients after body weight adjustment. Subgroup analysis based on
489 gender showed that both female and male patients achieved clinically significant response at the
490 proposed clinical dose. Dosage adjustment based on gender is not needed.

491 Population PK analyses indicated that PK parameters of SIMPONI were not influenced by age in
492 adult patients. Patients with age ≥ 65 years had apparent clearance of SIMPONI similar to
493 patients with age < 65 years. No ethnicity-related PK differences were observed between
494 Caucasians and Asians, and there were too few patients of other races to assess for PK differences.

495 Patients who developed anti-SIMPONI antibodies generally had lower steady-state serum trough
496 concentrations of SIMPONI.

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

499 **13.0 NONCLINICAL TOXICOLOGY**

500 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

501 Long-term animal studies of golimumab have not been conducted to evaluate its carcinogenic
502 potential. Mutagenicity studies have not been conducted with golimumab. A fertility study
503 conducted in mice using an analogous anti-mouse TNF α antibody showed no impairment of
504 fertility.

505 **14.0 CLINICAL STUDIES**

506 **14.1 Rheumatoid Arthritis**

507 The efficacy and safety of SIMPONI were evaluated in 3 multicenter, randomized, double-blind,
508 controlled trials (Studies RA-1, RA-2, and RA-3) in 1542 patients ≥ 18 years of age with
509 moderately to severely active RA, diagnosed according to the American College of Rheumatology
510 (ACR) criteria, for at least 3 months prior to administration of study agent. Patients were required
511 to have at least 4 swollen and 4 tender joints. SIMPONI was administered subcutaneously at
512 doses of 50 mg or 100 mg every 4 weeks. Double-blinded controlled efficacy data were collected
513 and analyzed through Week 24. Patients were allowed to continue stable doses of concomitant
514 low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs and patients
515 may have received oral MTX during the trials.

516 Study RA-1 evaluated 461 patients who were previously treated (at least 8 to 12 weeks prior to
517 administration of study agent) with one or more doses of a biologic TNF-blocker without a serious
518 adverse reaction. Patients may have discontinued the biologic TNF-blocker for a variety of
519 reasons. Patients were randomized to receive placebo (n = 155), SIMPONI 50 mg (n = 153), or
520 SIMPONI 100 mg (n = 153). Patients were allowed to continue stable doses of concomitant
521 MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the trial. The use of other
522 DMARDs including cytotoxic agents or other biologics was prohibited.

523 Study RA-2 evaluated 444 patients who had active RA despite a stable dose of at least 15
524 mg/week of MTX and who had not been previously treated with a biologic TNF-blocker. Patients
525 were randomized to receive background MTX (n = 133), SIMPONI 50 mg + background MTX (n
526 = 89), SIMPONI 100 mg + background MTX (n = 89), or SIMPONI 100 mg monotherapy (n =
527 133). The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was
528 prohibited.

529 Study RA-3 evaluated 637 patients with active RA who were MTX-naïve and had not previously
530 been treated with a biologic TNF-blocker. Patients were randomized to receive MTX (n = 160),
531 SIMPONI 50 mg + MTX (n = 159), SIMPONI 100 mg + MTX (n = 159), or SIMPONI 100 mg
532 monotherapy (n = 159). For patients receiving MTX, MTX was administered at a dose of 10
533 mg/week beginning at Week 0 and increased to 20 mg/week by Week 8. The use of other
534 DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

535 The primary endpoint in Study RA-1 and Study RA-2 was the percentage of patients achieving an
536 ACR 20 response at Week 14 and the primary endpoint in Study RA-3 was the percentage of
537 patients achieving an ACR 50 response at Week 24.

538 In Studies RA-1, RA-2, and RA-3, the median duration of RA disease was 9.4, 5.7, and 1.2 years;
539 and 99%, 75%, and 54% of the patients used at least one DMARD in the past, respectively.
540 Approximately 77% and 57% of patients received concomitant NSAIDs and low dose
541 corticosteroids, respectively, in the 3 pooled RA trials.

542 **Clinical Response**

543 In the 3 RA trials, a greater percentage of patients treated with the combination of SIMPONI and
544 MTX achieved ACR responses at Week 14 (Studies RA-1 and RA-2) and Week 24 (Studies RA-1,
545 RA-2, and RA-3) versus patients treated with the MTX alone. There was no clear evidence of
546 improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower
547 SIMPONI dose group (50 mg). In Studies RA-2 and RA-3, the SIMPONI monotherapy groups
548 were not statistically different from the MTX monotherapy groups in ACR responses. Table 2
549 shows the proportion of patients with the ACR response for the SIMPONI 50 mg and control
550 groups in Studies RA-1, RA-2, and RA-3. In the subset of patients who received SIMPONI in
551 combination with MTX in Study RA-1, the proportion of patients achieving ACR 20, 50 and 70
552 responses at week 14 were 40%, 18%, and 13%, respectively, in the SIMPONI 50 mg + MTX
553 group (N = 103) compared with 17%, 6%, and 2%, respectively, in the placebo + MTX group (N
554 = 107). Table 3 shows the percent improvement in the components of the ACR response criteria
555 for the SIMPONI 50 mg + MTX and MTX groups in Study RA-2. The percent of patients
556 achieving ACR 20 responses by visit for Study RA-2 is shown in Figure 1. ACR 20 responses
557 were observed in 38% of patients in the SIMPONI 50 mg + MTX group at the first assessment
558 (Week 4) after the initial SIMPONI administration.

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Table 2. Studies RA-1, RA-2, and RA-3 Proportion of Patients with an ACR Response^a

	Study RA-1 Active RA previously treated with one or more doses of TNF-blockers		Study RA-2 Active RA, despite MTX		Study RA-3 Active RA, MTX Naïve	
	Placebo ± DMARDs ^b	SIMPONI 50 mg ± DMARDs ^b	Background MTX	SIMPONI 50 mg + Background MTX	MTX	SIMPONI 50 mg + MTX
N ^c	155	153	133	89	160	159
ACR 20						
Week 14	18%	35%	33%	55%	NA	NA
Week 24	17%	34%	28%	60%	49%	62%
ACR 50						
Week 14	6%	16%	10%	35%	NA	NA
Week 24	5%	18%	14%	37%	29%	40%
ACR 70						
Week 14	2%	10%	4%	13%	NA	NA
Week 24	3%	12%	5%	20%	16%	24% ^d
<p>a Approximately 78% and 58% of the patients received concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and NSAIDs, respectively, during the 3 pooled RA trials.</p> <p>b DMARDs in Study RA-1 included MTX, HCQ, and/or SSZ (about 68%, 8%, and 5% of patients received MTX, HCQ, and SSZ, respectively).</p> <p>c N reflects randomized patients.</p> <p>d Not significantly different from MTX monotherapy.</p> <p>NA Not applicable, as data was not collected at Week 14 in Study RA-3.</p>						

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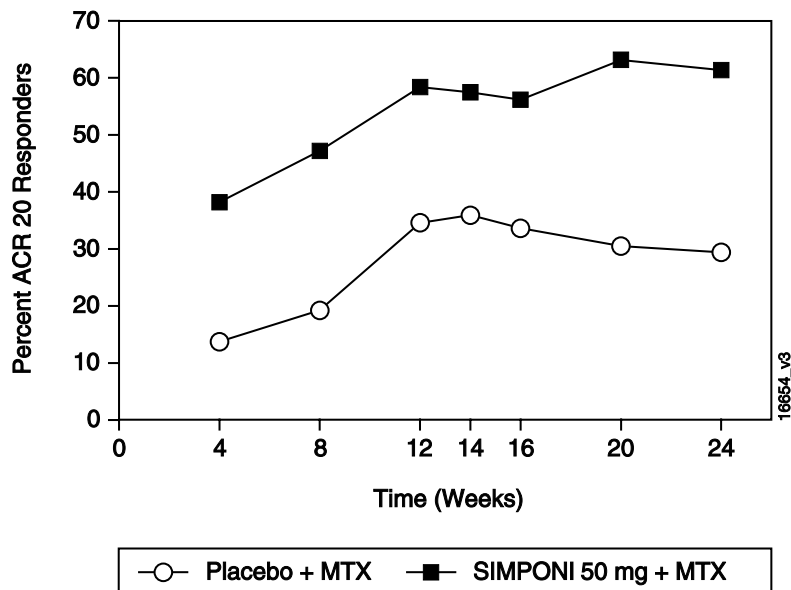
Table 3. Study RA-2 – Median Percent Improvement from Baseline in the Individual ACR Components at Weeks 14^a

	Background MTX	SIMPONI 50 mg + Background MTX
N ^b	133	89
Number of swollen joints (0-66)		
Baseline	12	13
Week 14	38%	62%
Number of tender joints (0-68)		
Baseline	21	26
Week 14	30%	60%
Patient’s assessment of pain (0-10)		
Baseline	5.7	6.1
Week 14	18%	55%
Patient’s global assessment of disease activity (0-10)		
Baseline	5.3	6.0
Week 14	15%	45%
Physician’s global assessment of disease activity (0-10)		
Baseline	5.7	6.1
Week 14	35%	55%
HAQ score (0-3)		
Baseline	1.25	1.38
Week 14	10%	29%
CRP (mg/dl)		
Baseline	0.8	1.0
Week 14	2%	44%
Note: Baseline values are medians. a In Study RA-2, about 70% and 85% of patients received concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs during the trials, respectively. b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary.		

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Figure 1. Study RA - 2 – Percent of Patients Achieving ACR 20 Response by Visit: Randomized Patients*



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* The same patients may not have responded at each timepoint.

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Physical Function Response in Patients with RA

In Studies RA-1 and RA-2, the SIMPONI 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24: 0.25 vs. 0.05 in RA-1, 0.47 vs. 0.13 in RA-2, respectively. Also in Studies RA-1 and RA-2, the SIMPONI 50 mg groups compared to the control groups had a greater proportion of HAQ responders (change from baseline > 0.22) at Week 24: 44% vs. 28%, 65% vs. 35%, respectively.

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14.2 Psoriatic Arthritis

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The safety and efficacy of SIMPONI were evaluated in a multi-center, randomized, double-blind, placebo-controlled trial in 405 adult patients with moderately to severely active PsA (≥ 3 swollen joints and ≥ 3 tender joints) despite NSAID or DMARD therapy (Study PsA). Patients in this study had a diagnosis of PsA for at least 6 months with a qualifying psoriatic skin lesion of at least 2 cm in diameter. Previous treatment with a biologic TNF-blocker was not allowed. Patients were randomly assigned to placebo (n = 113), SIMPONI 50 mg (n = 146), or SIMPONI 100 mg (n = 146) given subcutaneously every 4 weeks. Patients were allowed to receive stable doses of concomitant MTX (≤ 25 mg/week), low dose oral corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited. The primary endpoint was the percentage of patients achieving ACR 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

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Patients with each subtype of PsA were enrolled, including polyarticular arthritis with no rheumatoid nodules (43%), asymmetric peripheral arthritis (30%), distal interphalangeal (DIP) joint arthritis (15%), spondylitis with peripheral arthritis (11%), and arthritis mutilans (1%). The median duration of PsA disease was 5.1 years, 78% of patients received at least one DMARD in

595 the past, and approximately 48% of patients received MTX, and 16% received low dose oral
596 steroids.

597 **Clinical Response in Patients with PsA**

598 SIMPONI ± MTX, compared with placebo ± MTX, resulted in significant improvement in signs
599 and symptoms as demonstrated by the proportion of patients with an ACR 20 response at Week 14
600 in Study PsA (see Table 4). There was no clear evidence of improved ACR response with the
601 higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).
602 ACR responses observed in the SIMPONI-treated groups were similar in patients receiving and
603 not receiving concomitant MTX. Similar ACR 20 responses at Week 14 were observed in patients
604 with different PsA subtypes. However, the number of patients with arthritis mutilans was too
605 small to allow meaningful assessment. SIMPONI 50 mg treatment also resulted in significantly
606 greater improvement compared with placebo for each ACR component in Study PsA (Table 5).
607 Treatment with SIMPONI resulted in improvement in enthesitis and skin manifestations in
608 patients with PsA. However, the safety and efficacy of SIMPONI in the treatment of patients with
609 plaque psoriasis has not been established.

610 The percent of patients achieving ACR 20 responses by visit for Study PsA is shown in Figure 2.
611 ACR 20 responses were observed in 31% of patients in the SIMPONI 50 mg + MTX group at the
612 first assessment (Week 4) after the initial SIMPONI administration.

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Table 4. Study PsA - Proportion of Patients with ACR Responses

	Placebo ± MTX^a	SIMPONI 50 mg ± MTX^a
N ^b	113	146
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 %
a In Study PsA, about 48%, 16%, and 72% of the patients received stable doses of MTX (≤ 25 mg/day), low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and NSAIDs, respectively. b N reflects randomized patients. Bold text indicates primary endpoint		

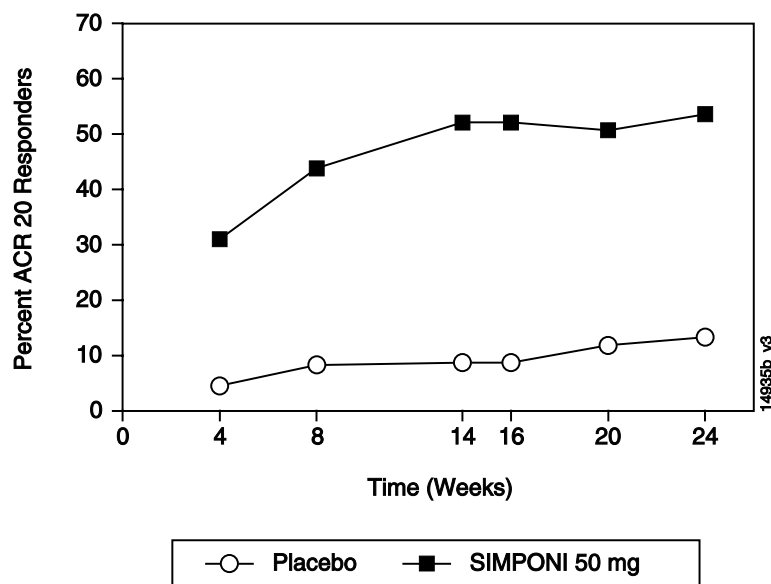
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Table 5. Study PsA - Percent Improvement in ACR Components at Week 14

	Placebo± MTX ^a	SIMPONI 50 mg ± MTX ^a
N ^b	113	146
Number of swollen joints (0-66)		
Baseline	10.0	11.0
Week 14	8 %	60 %
Number of tender joints (0-68)		
Baseline	18.0	19.0
Week 14	0 %	54 %
Patient's assessment of pain (0-10)		
Baseline	5.4	5.8
Week 14	-1 %	48 %
Patient's global assessment of disease activity (0-10)		
Baseline	5.2	5.2
Week 14	2 %	49 %
Physician's global assessment of disease activity (0-10)		
Baseline	5.2	5.4
Week 14	7 %	59 %
HAQ score (0-10)		
Baseline	1.0	1.0
Week 14	0 %	28 %
CRP (mg/dL) (0-10)		
Baseline	0.6	0.6
Week 14	0 %	40 %
Note: Baseline are median values		
a In Study PsA, about 48%, 16%, and 78% of the patients received stable doses of MTX (≤ 25 mg/day), low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day), and NSAIDs, respectively.		
b N reflects randomized patients; actual number of patients evaluable for each endpoint may vary by timepoint		

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Figure 2. Study PsA – Percent of ACR 20 PsA Responders by Visit: Randomized Patients*



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* The same patients may not have responded at each timepoint.

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Physical Function Response in Patients with PsA

In Study PsA, SIMPONI 50 mg demonstrated a greater improvement compared to placebo in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI) score from baseline to Week 24 (0.33 and -0.01, respectively). In addition, the SIMPONI 50 mg group compared to the placebo group had a greater proportion of HAQ responders (≥ 0.3 change from baseline) at Week 24: 43% vs. 22%, respectively.

14.3 Ankylosing Spondylitis

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The safety and efficacy of SIMPONI were evaluated in a multi-center, randomized, double-blind, placebo-controlled trial in 356 adult patients with active ankylosing spondylitis according to modified New York criteria for at least 3 months (Study AS). Patients had symptoms of active disease [defined as a Bath AS Disease Activity Index (BASDAI) ≥ 4 and VAS for total back pain of ≥ 4 , on scales of 0 to 10 cm] despite current or previous NSAID therapy. Patients were excluded if they were previously treated with a biologic TNF-blocker or if they had complete ankylosis of the spine. Patients were randomly assigned to placebo (n = 78), SIMPONI 50 mg (n = 138), or SIMPONI 100 mg (n = 140) administered subcutaneously every 4 weeks. Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine (SSZ), hydroxychloroquine (HCQ), low dose corticosteroids (equivalent to < 10 mg of prednisone a day), and/or NSAIDs during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

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The primary endpoint was the percentage of patients achieving an ASsessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. Placebo-controlled efficacy data were collected and analyzed through Week 24.

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In Study AS, the median duration of AS disease was 5.6 years, median duration of inflammatory back pain was 12 years, 83% were HLA-B27 positive, 24% had prior joint surgery or procedure, and 55% received at least one DMARD in the past. During the trial, the use of concomitant

646 DMARDs and/or NSAIDs was as follows: MTX (20%), SSZ (26%), HCQ (1%), low dose oral
647 steroids (16%), and NSAIDs (90%).

648 **Clinical Response in Patients with AS**

649 In Study AS, SIMPONI ± DMARDs treatment, compared with placebo ± DMARDs, resulted in a
650 significant improvement in signs and symptoms as demonstrated by the proportion of patients with
651 an ASAS 20 response at Week 14 (see Table 6). There was no clear evidence of improved ASAS
652 response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose
653 group (50 mg). Table 7 shows the percent improvement in the components of the ASAS response
654 criteria for the SIMPONI 50 mg ± DMARDs and placebo ± DMARDs groups in Study AS.

655 The percent of patients achieving ASAS 20 responses by visit for Study AS is shown in Figure 3.
656 ASAS 20 responses were observed in 48% of patients in the SIMPONI 50 mg + MTX group at the
657 first assessment (Week 4) after the initial SIMPONI administration.

658 **Table 6. Study AS – Proportion of ASAS Responders at Weeks 14 and 24**

	Placebo ± DMARDs ^a	SIMPONI 50 mg ± DMARDs ^a
N ^b	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%
a During the trial, the concomitant use of stable doses of DMARDs was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively. b N reflects randomized patients. Bold text indicates primary endpoint		

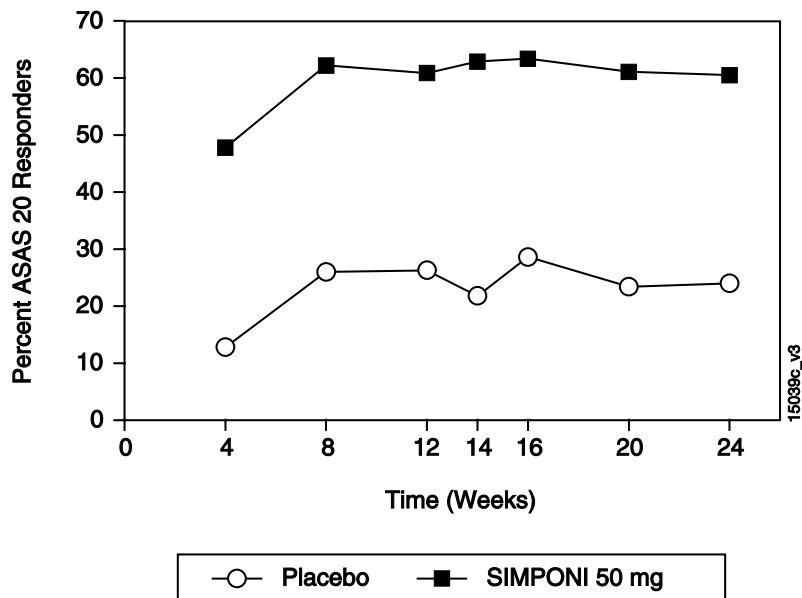
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Table 7. Study AS – Median Percent Improvement in ASAS Components at Week 14

	Placebo ± DMARDs ^a	SIMPONI 50 mg ± DMARDs ^a
N^b	78	138
ASAS components		
Patient global assessment (0-10)		
Baseline	7.2	7.0
Week 14	13%	47%
Total back pain (0-10)		
Baseline	7.6	7.5
Week 14	9%	50%
BASFI (0-10)^c		
Baseline	4.9	5.0
Week 14	-3%	37%
Inflammation (0-10)^d		
Baseline	7.1	7.1
Week 14	6%	59%
a During the trial, the concomitant use of stable doses of DMARDs was as follows: MTX (21%), SSZ (25%), and HCQ (1%). About 16% and 89% of patients received stable doses of low dose oral steroids and NSAIDs during the trial, respectively. b N reflects randomized patients c BASFI is Bath Ankylosing Spondylitis Functional Index d Inflammation is the mean of two patient-reported stiffness self-assessments in the Bath AS Disease Activity Index (BASDAI)		

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Figure 3. Study AS – Percent of AS Patients Achieving ASAS 20 Response by Visit: Randomized Patients*



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* The same patients may not have responded at each timepoint.

668 **15.0 REFERENCES**

669 1. SEER [database online]. US Population Data – 1969-2004. Bethesda, MD: National Cancer
670 Institute. Release date: January 3, 2007. Available at: <http://seer.cancer.gov/popdata/>.

671 **16.0 HOW SUPPLIED/STORAGE AND HANDLING**

672 Each SIMPONI prefilled autoinjector or prefilled syringe is packaged in a light-blocking,
673 cardboard outer carton. SIMPONI is available in packs of 1 prefilled syringe NDC 57894-070-01
674 or 1 prefilled SmartJect autoinjector NDC 57894-070-02.

675 **Prefilled SmartJect Autoinjector**

676 Each single dose SmartJect autoinjector contains a prefilled glass syringe (27 gauge ½ inch)
677 providing 50 mg of SIMPONI per 0.5 mL of solution.

678 **Prefilled Syringe**

679 Each single dose prefilled glass syringe (27 gauge ½ inch) contains 50 mg of SIMPONI per 0.5
680 mL of solution.

681 **Storage and Stability**

682 SIMPONI must be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light. Keep the
683 product in the original carton to protect from light until the time of use. Do not freeze. Do not
684 shake. Do not use SIMPONI beyond the expiration date (EXP) on the carton or the expiration
685 date on the prefilled syringe (observed through the viewing window) or the prefilled SmartJect
686 autoinjector.

687 **17.0 PATIENT COUNSELING INFORMATION**

688 See Medication Guide (17.3)

689 **17.1 Patient Counseling**

690 Patients should be advised of the potential benefits and risks of SIMPONI. Physicians should
691 instruct their patients to read the Medication Guide before starting SIMPONI therapy and to read it
692 each time the prescription is renewed.

693 **Infections**

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

697 **Malignancies**

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

700 **Allergic Reactions**

701 Advise latex-sensitive patients that the needle cover on the prefilled syringe as well as the prefilled
702 syringe in the prefilled SmartJect autoinjector contains dry natural rubber (a derivative of latex).

703 **Other Medical Conditions**

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

707 **17.2 Instruction on Injection Technique**

708 The first self-injection should be performed under the supervision of a qualified healthcare
709 professional. If a patient or caregiver is to administer SIMPONI, he/she should be instructed in
710 injection techniques and their ability to inject subcutaneously should be assessed to ensure the
711 proper administration of SIMPONI [*see Medication Guide (17.3)*].

712 Prior to use, remove the prefilled syringe or the prefilled SmartJect autoinjector from the
713 refrigerator and allow SIMPONI to sit at room temperature outside of the carton for 30 minutes
714 and out of the reach of children.

715 Do not warm SIMPONI in any other way. For example, do not warm SIMPONI in a microwave
716 or in hot water.

717 Do not remove the prefilled syringe needle cover or SmartJect autoinjector cap while allowing
718 SIMPONI to reach room temperature. Remove these immediately before injection.

719 Do not pull the autoinjector away from the skin until you hear a first “click” sound and then a
720 second “click” sound (the injection is finished and the needle is pulled back). It usually takes
721 about 3 to 6 seconds but may take up to 15 seconds for you to hear the second “click” after the
722 first “click”. If the autoinjector is pulled away from the skin before the injection is completed, a
723 full dose of SIMPONI may not be administered.

724 A puncture-resistant container for disposal of needles and syringes should be used. Patients or
725 caregivers should be instructed in the technique of proper syringe and needle disposal, and be
726 advised not to reuse these items.

727 **17.3 Medication Guide**

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730 **MEDICATION GUIDE**
731 **SIMPONI™ (SIM-po-nee)**
732 **(golimumab)**
733

734 Read the Medication Guide that comes with SIMPONI before you start taking it and each time
735 you get a refill. There may be new information. This Medication Guide does not take the place of
736 talking with your doctor about your medical condition or treatment. It is important to remain
737 under your doctor's care while using SIMPONI.

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

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

- 743
- 744 • Your doctor should test you for TB before starting SIMPONI.
 - 745 • Your doctor should monitor you closely for signs and symptoms of TB during treatment with SIMPONI.

746 You should not start taking SIMPONI if you have any kind of infection unless your doctor says it
747 is okay.

748 **Before starting SIMPONI, tell your doctor if you:**

- 749
- 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 use SIMPONI. 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), or Rituxan (rituximab)

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764 **After starting SIMPONI**, call your doctor right away if you have any symptoms of an
765 infection. SIMPONI can make you more likely to get infections or make worse any infection
766 that you have.

767 **Cancer**

- 768 • There have been cases of unusual cancers in children and teenage patients taking TNF-
769 blocking agents.
- 770 • For children and adults taking TNF-blocker medicines, including SIMPONI, the chances of
771 getting lymphoma or other cancers may increase.
- 772 • People with inflammatory diseases including rheumatoid arthritis, psoriatic arthritis, or
773 ankylosing spondylitis, especially those with very active disease, may be more likely to get
774 lymphoma.

775
776 **What is SIMPONI?**

777 SIMPONI is a prescription medicine called a Tumor Necrosis Factor (TNF) blocker. SIMPONI is
778 used in adults:

- 779 • with the medicine methotrexate to treat moderately to severely active rheumatoid arthritis (RA)
- 780 • to treat active psoriatic arthritis (PsA) alone or with methotrexate
- 781 • to treat active ankylosing spondylitis (AS)

782 You may continue to use other medicines that help treat your condition while taking SIMPONI, such
783 as non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as recommended by
784 your doctor.

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

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

- 788 • have an infection (see “What is the most important information I should know about SIMPONI?”).
- 789 • have or have had lymphoma or any other type of cancer.
- 790 • have or had heart failure.
- 791 • have or have had a condition that affects your nervous system, such as multiple sclerosis.
- 792 • have recently received or are scheduled to receive a vaccine. People taking SIMPONI should not
793 receive live vaccines. People taking SIMPONI can receive non-live vaccines.
- 794 • are allergic to rubber or latex. The needle cover on the prefilled syringe and SmartJect autoinjector
795 contains dry natural rubber.
- 796 • are pregnant or planning to become pregnant. It is not known if SIMPONI will harm your unborn
797 baby.
- 798 • are breastfeeding. You and your doctor should decide if you will take SIMPONI or breastfeed.
799 You should not do both without talking to your doctor first.

800 **Tell your doctor about all the medicines you take**, including prescription and non-prescription
801 medicines, vitamins, and herbal supplements. Especially, tell your doctor if you use:

- 802 • ORENCIA (abatacept), KINERET (anakinra), or RITUXAN (rituximab). You should not take
803 SIMPONI while you are also taking ORENCIA or KINERET. Your doctor may not want to give
804 you SIMPONI if you have received RITUXAN recently.

- 805 • Another TNF-blocker medicine. You should not take SIMPONI while you are also taking
806 REMICADE (infliximab), HUMIRA (adalimumab), ENBREL (etanercept), or CIMZIA
807 (certolizumab pegol).

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

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

811 **How should I use SIMPONI?**

- 812 • SIMPONI is given as an injection under the skin (subcutaneous injection or SC).
813 • SIMPONI should be injected one time each month.
814 • If your doctor decides that you or a caregiver may be able to give your injections of SIMPONI at
815 home, you should receive training on the right way to prepare and inject SIMPONI. Do not try to
816 inject SIMPONI yourself until you have been shown the right way to give the injections by your
817 doctor or nurse.
818 • Use SIMPONI exactly as prescribed by your doctor.
819 • SIMPONI comes in a prefilled syringe or SmartJect™ autoinjector. Your doctor will prescribe the
820 type that is best for you.
821 • See the detailed *Patient Instructions for Use* at the end of this Medication Guide for instructions
822 about the right way to prepare and give your SIMPONI injections at home.
823 • Do not miss any doses of SIMPONI. If you forget to use SIMPONI, inject your dose as soon as
824 you remember. Then, take your next dose at your regular scheduled time. In case you are not sure
825 when to inject SIMPONI, call your doctor or pharmacist.

826 **What are the possible side effects with SIMPONI?**

827 SIMPONI can cause serious side effects, including:

828 See “**What is the most important information I should know about SIMPONI?**”

829

830 **Serious Infections**

831

832 **Hepatitis B infection in people who carry the virus in their blood.**

- 833 • If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus can become
834 active while you use SIMPONI. Your doctor may do blood tests before you start treatment with
835 SIMPONI and while you are using SIMPONI. Tell your doctor if you have any of the following
836 symptoms of a possible hepatitis B infection:

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

837

838 **Heart failure, including new heart failure or worsening of heart failure that you already have.**

839 New or worse heart failure can happen in people who use TNF-blocker medicines like SIMPONI.

- 840 • If you have heart failure, your condition should be watched closely while you take SIMPONI.
841 • Call your doctor right away if you get new or worsening symptoms of heart failure while taking
842 SIMPONI (such as shortness of breath or swelling of your lower legs or feet).

843

844 **Nervous System Problems**

845 Rarely, people using TNF-blocker medicine have nervous system problems such as multiple sclerosis.

- 846 • Tell your doctor right away if you get any of these symptoms:
- 847 • vision changes
 - 848 • weakness in your arms or legs
 - 849 • numbness or tingling in any part of your body

850 **Liver Problems**

851 Liver problems can happen in people who use TNF-blocker medicines, including SIMPONI. These
852 problems can lead to liver failure and death. Call your doctor right away if you have any of these
853 symptoms:

- 854 • feel very tired
- 855 • skin or eyes look yellow
- 856 • poor appetite or vomiting
- 857 • pain on the right side of your stomach (abdomen)

858 **Blood Problems**

859 Low blood counts have been seen with other TNF-blockers. Your body may not make enough blood
860 cells that help fight infections or help stop bleeding. Symptoms include fever, bruising or bleeding
861 easily, or looking pale. Your doctor will check your blood counts before and during treatment with
862 SIMPONI.

863 **Common side effects with SIMPONI include:**

- upper respiratory tract infection
- nausea
- abnormal liver tests
- redness at the site of injection
- high blood pressure
- bronchitis
- dizziness
- sinus infection (sinusitis)
- flu
- runny nose
- fever
- cold sores
- numbness or tingling

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865 Other side effects with SIMPONI include:

- 866 • **Immune System Problems.** Rarely, people using TNF-blocker medicines have developed
867 symptoms that are like the symptoms of Lupus. Tell your doctor if you have any of these
868 symptoms:
 - 869 • a rash on your cheeks or other parts of the body
 - 870 • sensitivity to the sun
 - 871 • new joint or muscle pains
 - 872 • becoming very tired
 - 873 • chest pain or shortness of breath
 - 874 • swelling of the feet, ankles, and/or legs

875 • **Psoriasis.** Some people using SIMPONI had new psoriasis or worsening of psoriasis they already
876 had. Tell your doctor if you develop red scaly patches or raised bumps that are filled with pus.
877 Your doctor may decide to stop your treatment with SIMPONI.

878
879 • **Allergic Reactions.** Allergic reactions can happen in people who use TNF-blocker medicines.
880 Call your doctor right away if you have any of these symptoms of an allergic reaction:

- 881 • hives
- 882 • swollen face
- 883 • breathing trouble
- 884 • chest pain

885 These are not all of the side effects with SIMPONI. Tell your doctor about any side effect that bothers
886 you or does not go away. Call your doctor for medical advice about side effects. You may report side
887 effects to the FDA at 1-800-FDA-1088.

888 **How do I store SIMPONI?**

- 889 • Refrigerate SIMPONI at 36°F to 46°F (2°C to 8°C).
- 890 • Do not freeze SIMPONI.
- 891 • Keep SIMPONI in the carton to protect it from light when not being used.
- 892 • Do not shake SIMPONI.

893 **Keep SIMPONI and all medicines out of the reach of children.**

894 **General Information about SIMPONI**

- 895 • Medicines are sometimes prescribed for purposes other than those listed in the Medication Guide.
896 Do not use SIMPONI for a condition for which it was not prescribed.
- 897 • Do not give SIMPONI to other people, even if they have the same condition that you have. It may
898 harm them.
- 899 • This Medication Guide summarizes the most important information about SIMPONI. If you
900 would like more information, talk to your doctor. You can ask your doctor or pharmacist for
901 information about SIMPONI that is written for health professionals. For more information go to
902 www.simponi.com or call 1-800-457-6399.

903 **What are the ingredients in SIMPONI?**

904 Active ingredient: golimumab.

905 Inactive ingredients: L-histidine, L-histidine monohydrochloride monohydrate, sorbitol, polysorbate
906 80, and water for injection. SIMPONI does not contain preservatives.

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**Patient Instructions for Use
SIMPONI™ (SIM-po-nee)
(golimumab)
SmartJect™ autoinjector**

If your doctor decides that you or a caregiver may be able to give your injections of SIMPONI at home, you should receive training on the right way to prepare and inject SIMPONI. **Do not** try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse.

It is important to read, understand, and follow these instructions so that you inject SIMPONI the right way. Call your doctor if you or your caregiver has any questions about the right way to inject SIMPONI.

Important information about your SmartJect autoinjector:

- When the button on the SmartJect autoinjector is pressed to give the dose of SIMPONI you will hear a loud ‘click’ sound. It is very important that you practice injecting SIMPONI with your doctor or nurse so that you are not startled by this click when you start giving the injections to yourself at home.
- If you pull the SmartJect autoinjector away from the skin before the injection is completed, you may not get your full dose of medicine and may lose some of the medicine.

Do not:

- shake the SmartJect autoinjector at any time
- remove the SmartJect autoinjector cap until you get to that step

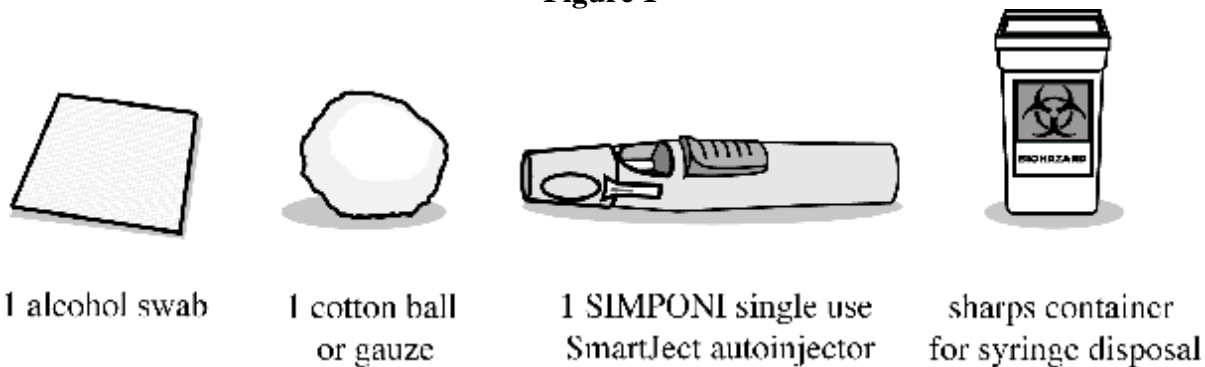
Step 1: Gather and inspect the supplies for your injection

You will need these supplies for an injection of SIMPONI. See Figure 1.

- 1 alcohol swab
- 1 cotton ball or gauze
- 1 SIMPONI prefilled SmartJect autoinjector
- sharps container for autoinjector disposal

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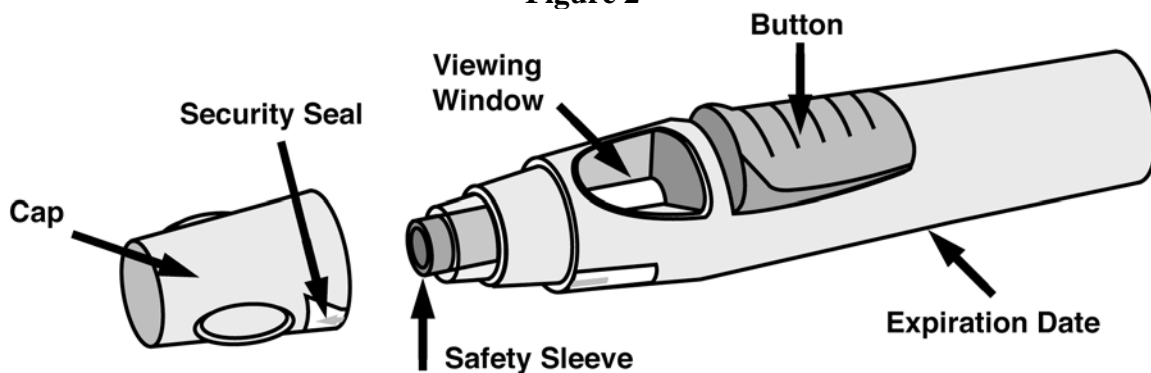
Figure 1



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The figure below shows what the SmartJect autoinjector looks like. See Figure 2.

Figure 2



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1.1 Check Expiration Date

- Check the expiration date (“EXP”) on the SmartJect autoinjector.
- You can also check the expiration date printed on the carton.
- If the expiration date has passed, do not use the SmartJect autoinjector. Call your doctor or pharmacist, or call 1-800-457-6399 for help.

1.2 Check Security Seal

- Check the security seal around the cap of the SmartJect autoinjector. If the security seal is broken, do not use the SmartJect autoinjector.

1.3 Wait 30 minutes

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

Do not warm the SmartJect autoinjector in any other way (For example, **do not** warm it in a microwave or in hot water).

Do not remove the SmartJect autoinjector cap while allowing it to reach room temperature.

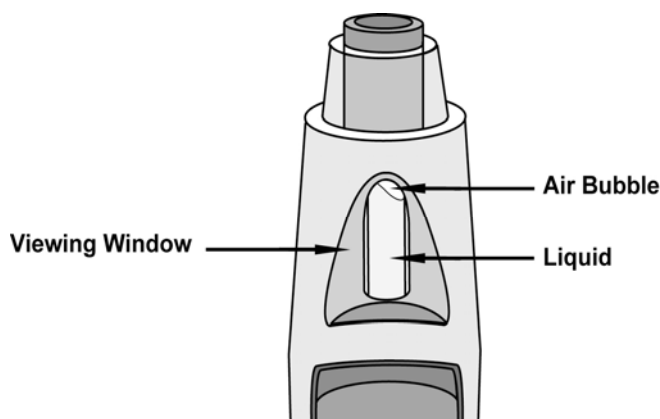


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1.4 Check the Liquid in the SmartJect autoinjector

- Look through the viewing window of the SmartJect autoinjector. See Figure 3. Make sure that the liquid in the prefilled syringe is clear and colorless to slightly yellow in color. You may see a small amount of tiny particles that are white, or that you can see through. Do not inject the liquid if it is cloudy or discolored, or has large particles in it.
- You may also notice an air bubble. This is normal. See Figure 3.

Figure 3



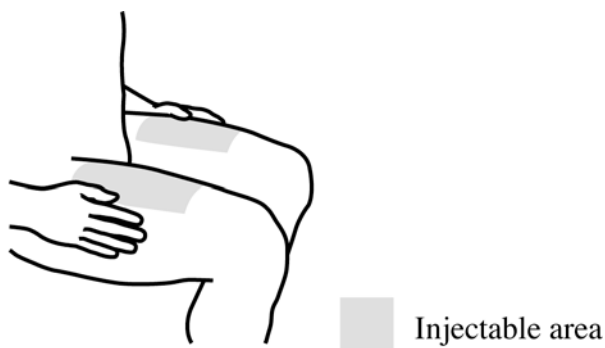
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Step 2: Choose and prepare the injection site

2.1 Choose the Injection Site

- The recommended injection site is the front of your middle thighs. See Figure 4.

Figure 4



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- You can also use the lower part of the abdomen below the navel (belly button), except for the two-inch area directly around the navel. See Figure 5.
- If a caregiver is giving you the injection, the outer area of the upper arms may also be used. See Figure 5.

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Figure 5



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- **Do not** inject into areas where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks.

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2.2 Prepare the Injection Site

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- Wash your hands well 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.

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Step 3: Injecting SIMPONI using the single dose SmartJect autoinjector

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3.1 Remove the Cap

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- Do not remove the cap until you are ready to inject SIMPONI. Inject SIMPONI within 5 minutes after the cap has been removed.
- When you are ready to inject, twist the cap slightly to break the security seal. See Figure 6.

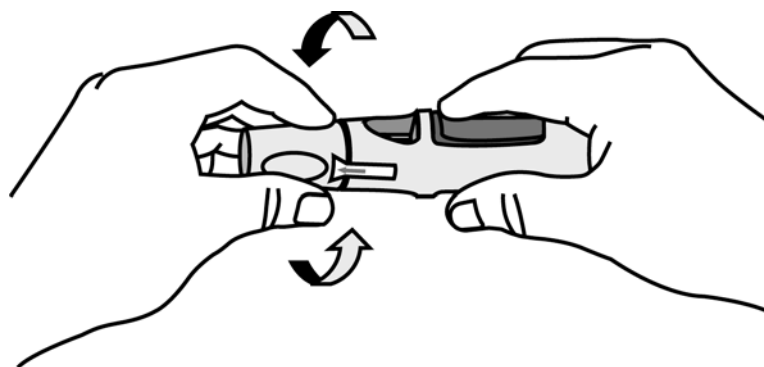
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Figure 6



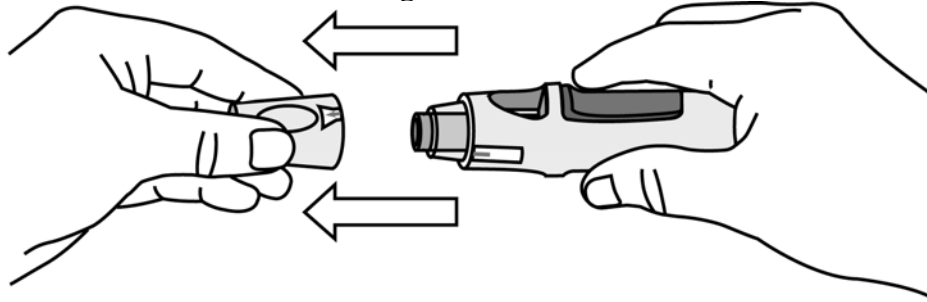
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- Pull the cap off and throw it in the trash right away. See Figure 7.

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Figure 7



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- **Do not** put the cap back on because it may damage the needle inside the SmartJect autoinjector.
- **Do not** use your SmartJect autoinjector if it is dropped without the cap in place.

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3.2 Push the SmartJect autoinjector against the skin

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- Hold the SmartJect autoinjector comfortably in your hand.
- Do not press the button. Push the open end of the SmartJect autoinjector firmly against the skin at **90-degree angle**. See Figure 8.

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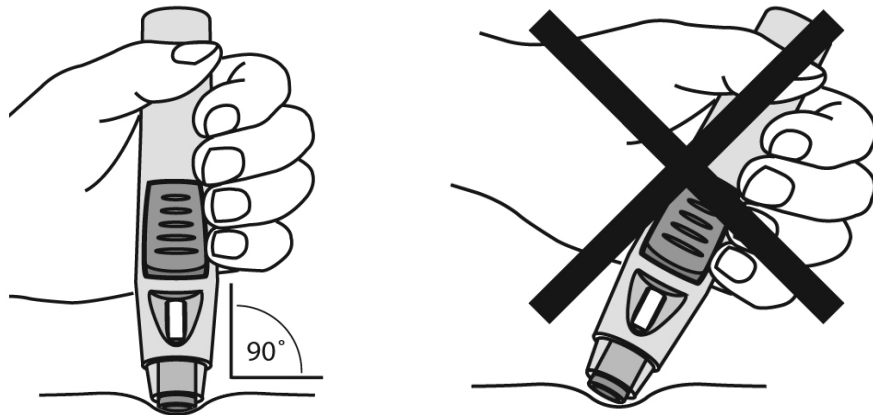
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Figure 8



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- **Use your** free hand to pinch and hold the skin at the injection site. This may make injecting easier.

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3.3 Press button to inject

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- Continue to hold the SmartJect autoinjector firmly against the skin, and press the button with your fingers (see Figure 9) or thumb (see Figure 10). You will not be able to push in the button unless the SmartJect autoinjector is pushed firmly against your skin.

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Figure 9



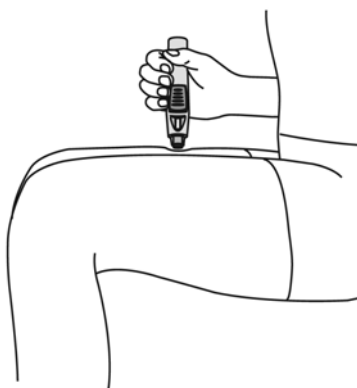
Figure 10



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- After the button is pressed, it will stay pressed in so you do not need to keep pressure on it. See Figure 11.

Figure 11



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- You will hear a loud 'click' sound. This means that the injection has started. Do not pull the SmartJect autoinjector away from your skin. If you pull the SmartJect autoinjector away from the skin, you may not get your full dose of medicine. See Figure 12.
- **Do not** lift the SmartJect autoinjector yet.

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3.4 Wait for Second "Click"

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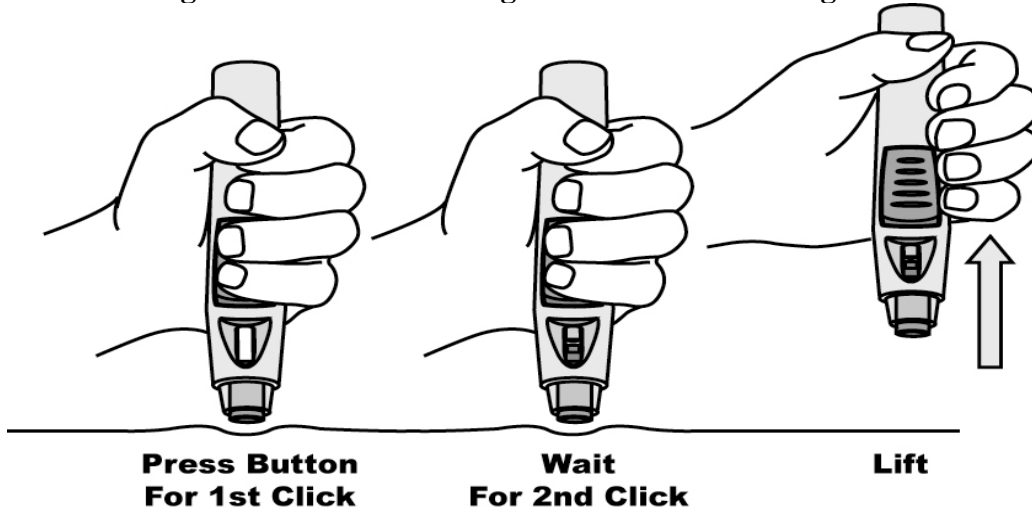
- Keep holding the SmartJect autoinjector against your skin until you hear the second 'click' sound. It usually takes about 3 to 6 seconds, but may take up to 15 seconds for you to hear the second 'click' sound. See Figure 13.
- The second 'click' sound means that the injection is finished and the needle has pulled back (retracted) into the SmartJect autoinjector.
- Lift the SmartJect autoinjector from the injection site. See Figure 14.
- If you have hearing problems, count for 15 seconds from the time you pressed the button and then lift the SmartJect autoinjector from the injection site.

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Figure 12

Figure 13

Figure 14



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1100 **Step 4: After the injection**

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1102 **4.1 Check the Viewing Window**

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- After you finish injecting, check the viewing window to see the yellow indicator. See Figure 15. This means the SmartJect autoinjector has worked the right way.

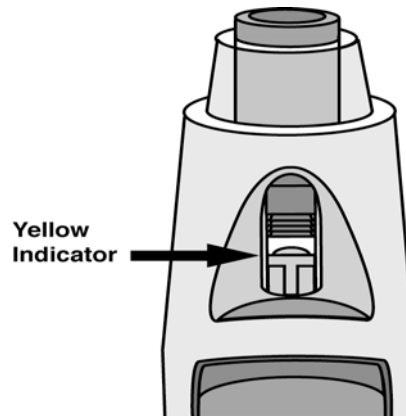
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Figure 15



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- If you do not see the yellow indicator in the viewing window, call 1-800-457-6399 for help.

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1111 **4.2 Dispose of the used SmartJect autoinjector**

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- Place the used SmartJect autoinjector into a closable puncture-resistant container. You may use a sharps container (such as a red biohazard container), a hard plastic container (such as a detergent bottle), or a metal container (such as an empty coffee can). See Figure 16.

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Figure 16



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- Ask your doctor for instructions on the right way to throw away (dispose of) the container. There may be local or state laws about how you should throw away used needles and syringes.
- Do not throw away your used SmartJect autoinjector in household trash. Do not recycle.

1137

1138 **4.3 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 needed.

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Patient Instructions for Use
SIMPONI™
Prefilled Syringe

If your doctor decides that you or a caregiver may be able to give your injections of SIMPONI at home, you should receive training on the right way to prepare and inject SIMPONI. **Do not** try to inject SIMPONI yourself until you have been shown the right way to give the injections by your doctor or nurse.

It is important to read, understand, and follow these instructions so that you inject SIMPONI the right way. Call your doctor if you or your caregiver has any questions about the right way to inject SIMPONI.

Important information about your prefilled syringe:

- Always hold the prefilled syringe by the body of the syringe.

Do not:

- pull back on the plunger at any time.
- shake the SIMPONI prefilled syringe. This may damage the medicine.
- remove the needle cover from the prefilled syringe until you get to that step.
- touch the needle guard activation clips to prevent covering the needle with the needle guard too soon (See Figure 2).
- use SIMPONI if it has been frozen or if it has been kept at a room temperature that is too warm. See the Medication Guide section: “How should I store SIMPONI?”
- use your SIMPONI prefilled syringe if it looks damaged.

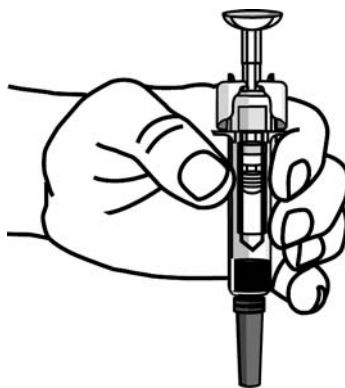
Step 1: Gather the supplies for your injection

You will need these supplies for an injection of SIMPONI. See Figure 1.

- 1 alcohol swab
- 1 cotton ball or gauze
- 1 SIMPONI prefilled syringe
- sharps container for syringe disposal

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1207

Figure 3



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- Look at the liquid through the viewing window of the prefilled syringe. Make sure that the liquid in the prefilled syringe is clear and colorless to slightly yellow in color. You may see a small amount of tiny particles that are white, or that you can see through. Do not inject the liquid if it is cloudy or discolored, or has large particles in it.
- You may also see an air bubble. This is normal.

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Step 3: Choose and prepare the injection site

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3.1 Choose the Injection Site

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- The recommended injection site is the front of your middle thighs. See Figure 4.

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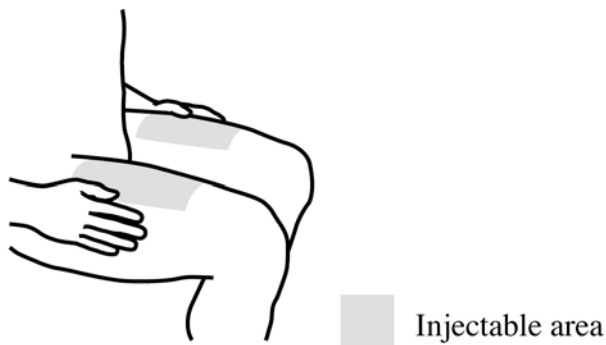
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Figure 4



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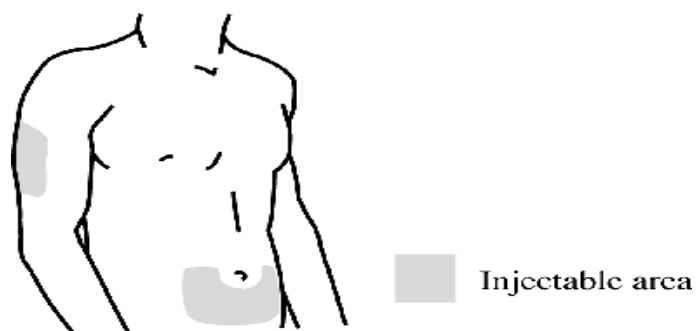
- You can also use the lower part of the abdomen below the navel (belly button), except for the two-inch area directly around the navel. See Figure 5.
- If a caregiver is giving you the injection, the outer area of the upper arms may also be used. See Figure 5.

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Figure 5



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

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3.2 Prepare the Injection Site

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- Wash your hands well with soap and warm water.

1238

- Wipe the injection site with an alcohol swab.

1239

- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.

1240

- **Do not** fan or blow on the clean area.

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Step 4: Inject SIMPONI

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Do not remove the needle cover until you are ready to inject SIMPONI. Inject SIMPONI within 5 minutes after you remove the needle cover.

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4.1 Remove the Needle Cover

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- **Do not** touch the plunger while removing the needle cover.

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- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. See Figure 6.

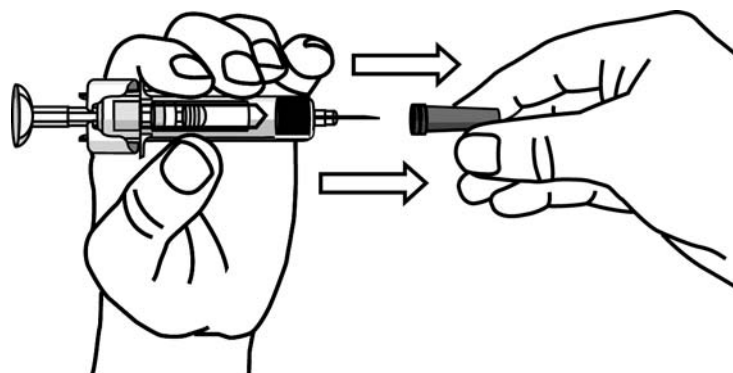
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Figure 6



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- 1257
- Put the needle cover in the trash.
- 1258
- You may see an air bubble in the prefilled syringe. This is normal.
- 1259
- You may also see a drop of liquid at the end of the needle. This is normal.
- 1260
- **Do not** touch the needle or let it touch any surface.
- 1261
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place.
- 1262

4.2 Position the prefilled syringe and inject SIMPONI

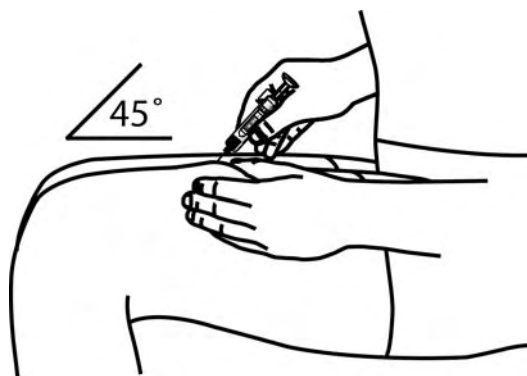
- 1263
- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. See Figure 7.
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Figure 7



- 1269
- **Do not** pull back on the plunger at any time.
- 1270
- Use the other hand to gently pinch the area of skin that you previously cleaned. Hold firmly.
- 1271
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a **45-degree angle**. See Figure 8.
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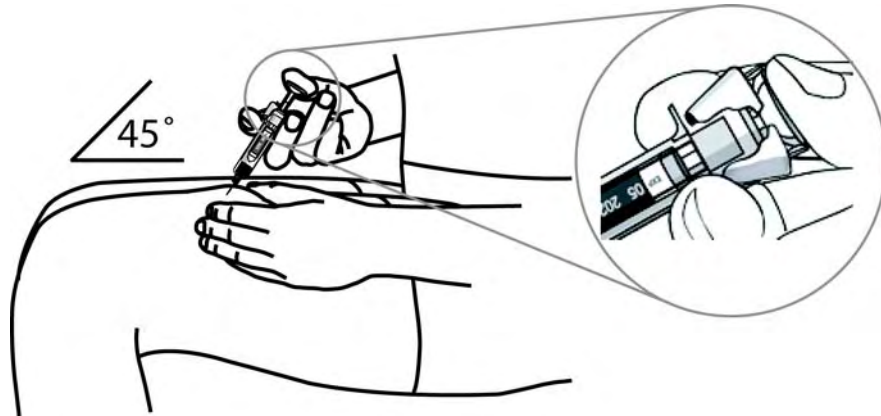
Figure 8



- 1277
- Inject all of the medicine by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. See Figure 9.
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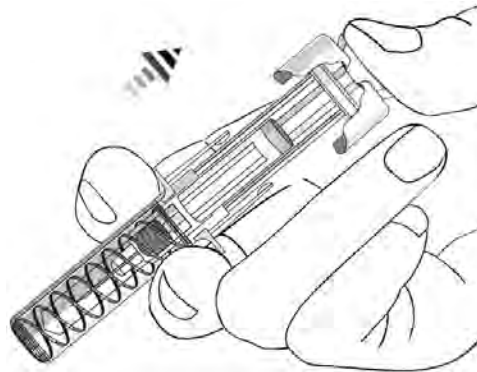
Figure 9



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- When the plunger is pushed as far as it will go, keep pressure on the plunger head. Take the needle out of the skin and let go of the skin.
- Slowly take your thumb off the plunger head. This will let the empty syringe move up until the entire needle is covered by the needle guard. See Figure 10.

Figure 10



1304 **Step 5: After the injection**

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1306 **5.1 Dispose of the used prefilled syringe**

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- 1308 • Place the used prefilled syringe in a closable puncture-resistant container. You may use a sharps
1309 container (such as a red biohazard container), a hard plastic container (such as a detergent bottle),
1310 or a metal container (such as an empty coffee can). For the safety and health of you and others,
1311 needles and used syringes **must never** be re-used. See Figure 11.

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Figure 11



- 1353 • Ask your doctor for instructions on the right way to throw away (dispose of) the container. There
1354 may be local or state laws about how you should throw away used needles and syringes.

- 1355 • Do not throw away your used prefilled syringe in household trash. Do not recycle.

1356

1357 **5.2 Use Cotton Ball or Gauze**

- 1358 • There may be a small amount of blood or liquid at the injection site, which is normal.
- 1359 • You can press a cotton ball or gauze over the injection site and hold for 10 seconds. Do not rub the
1360 injection site.
- 1361 • You may cover the injection site with a small adhesive bandage, if needed.

1362 Manufactured by:
1363 Centocor Ortho Biotech Inc.
1364 Horsham, PA 19044
1365 US License No. 1821
1366
1367 Revised: 11/2009
1368
1369 This Medication Guide has been approved by the U.S. Food and Drug Administration.