

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use STELARA® safely and effectively. See full prescribing information for STELARA®.

STELARA® (ustekinumab) injection, for subcutaneous use
Initial U.S. Approval: 2009

-----RECENT MAJOR CHANGES-----

Contraindications (4) 06/2012
Warnings and Precautions, Hypersensitivity Reactions (5.5) 06/2012

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

STELARA® is a human interleukin-12 and -23 antagonist indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. (1)

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

STELARA® is administered by subcutaneous injection. (2)

- For patients weighing ≤100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. (2.1)
- For patients weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. (2.1)

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

- Injection: 45 mg/0.5 mL in a single-use prefilled syringe (3)
- Injection: 90 mg/1 mL in a single-use prefilled syringe (3)
- Injection: 45 mg/0.5 mL in a single-use vial (3)
- Injection: 90 mg/1 mL in a single-use vial (3)

-----CONTRAINDICATIONS-----

Clinically significant hypersensitivity to ustekinumab or to any of the excipients. (4)

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

- Infections: Serious infections have occurred. Do not start STELARA® during any clinically important active infection. If a serious infection develops, stop STELARA® until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with STELARA®. Initiate treatment of latent TB before administering STELARA®. (5.3)
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Anaphylaxis or other clinically significant hypersensitivity reactions may occur. (5.5)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): One case was reported. If suspected, treat promptly and discontinue STELARA®. (5.6)

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

Most common adverse reactions (incidence >3% and greater than with placebo): Nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)

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

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

- Live vaccines: Live vaccines should not be given with STELARA®. (7.1)
- Concomitant therapy: The safety of concomitant use of STELARA® with immunosuppressants or phototherapy has not been evaluated. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 06/2012

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1 **FULL PRESCRIBING INFORMATION**

2
3 **1 INDICATIONS AND USAGE**

4 STELARA[®] is indicated for the treatment of adult patients (18 years or older) with moderate to severe
5 plaque psoriasis who are candidates for phototherapy or systemic therapy.

6
7 **2 DOSAGE AND ADMINISTRATION**

8 **2.1 Dosing**

9 STELARA[®] is administered by subcutaneous injection.

- 10
- 11 • For patients weighing ≤ 100 kg (220 lbs), the recommended dose is 45 mg initially and 4 weeks
12 later, followed by 45 mg every 12 weeks.
 - 13
 - 14 • For patients weighing > 100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks
15 later, followed by 90 mg every 12 weeks.

16
17 In subjects weighing > 100 kg, 45 mg was also shown to be efficacious. However, 90 mg resulted in
18 greater efficacy in these subjects [*see Clinical Studies (14)*].

19
20 **2.2 General Considerations for Administration**

21 STELARA[®] is for subcutaneous administration under the supervision of a physician.

22
23 Prior to administration, STELARA[®] should be visually inspected for particulate matter and
24 discoloration. STELARA[®] is colorless to light yellow and may contain a few small translucent or
25 white particles. STELARA[®] should not be used if it is discolored or cloudy, or if other particulate
26 matter is present. STELARA[®] does not contain preservatives; therefore, any unused product remaining
27 in the vial and/or syringe should be discarded.

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29 The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The
30 needle cover should not be handled by persons sensitive to latex.

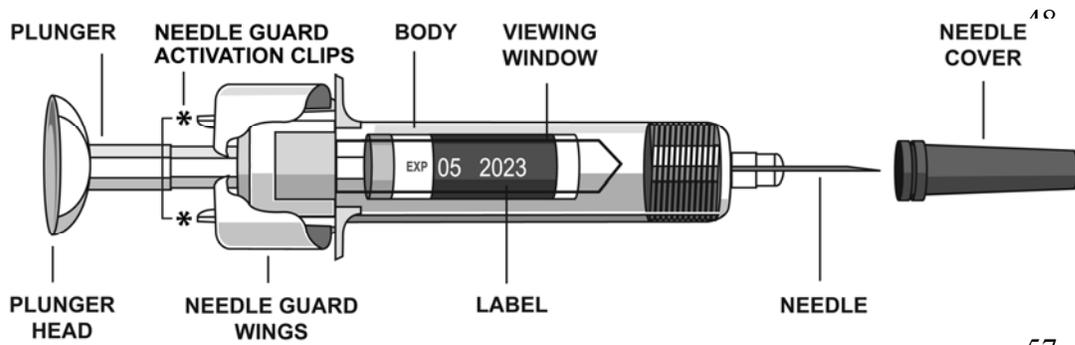
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32 It is recommended that each injection be administered at a different anatomic location (such as upper
33 arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into
34 areas where the skin is tender, bruised, erythematous, or indurated. When using the single-use vial, a
35 27 gauge, ½ inch needle is recommended.

36
37 STELARA[®] should only be administered by a healthcare provider. STELARA[®] should only be
38 administered to patients who will be closely monitored and have regular follow-up visits with a
39 physician.

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41 **2.3 Instructions for Administration of STELARA[®] Prefilled Syringes Equipped with Needle
42 Safety Guard**

43 Refer to the diagram below for the provided instructions.

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45 **To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD
46 ACTIVATION CLIPS at any time during use.**



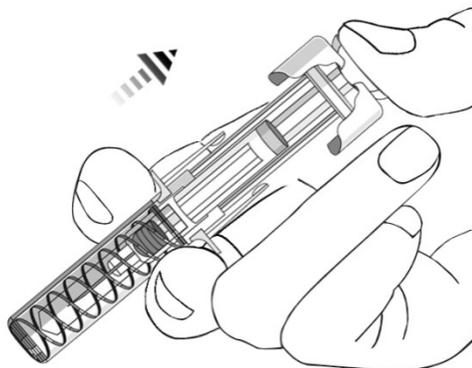
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- 60 • Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place.**
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- 64 • Inject STELARA[®] subcutaneously as recommended [*see Dosage and Administration (2.2)*].
- 65
- 66 • Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is
- 67 completely between the needle guard wings. **Injection of the entire prefilled syringe**
- 68 **contents is necessary to activate the needle guard.**
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- 92 • After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the
- 93 skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up
- 94 until the entire needle is covered by the needle guard, as shown by the illustration below:
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- Used syringes should be placed in a puncture-resistant container.

3 DOSAGE FORMS AND STRENGTHS

STELARA[®] solution is colorless to slightly yellow in appearance and contains 90 mg ustekinumab per mL.

- Injection: 45 mg/0.5 mL in a single-use prefilled syringe
- Injection: 90 mg/1 mL in a single-use prefilled syringe
- Injection: 45 mg/0.5 mL in a single-use vial
- Injection: 90 mg/1 mL in a single-use vial

4 CONTRAINDICATIONS

Clinically significant hypersensitivity to ustekinumab or to any of the excipients [see *Warnings and Precautions* (5.5)].

5 WARNINGS AND PRECAUTIONS

5.1 Infections

STELARA[®] may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving STELARA[®] [see *Adverse Reactions* (6.1)].

STELARA[®] should not be given to patients with any clinically important active infection. STELARA[®] should not be administered until the infection resolves or is adequately treated. Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. Exercise caution when considering the use of STELARA[®] in patients with a chronic infection or a history of recurrent infection.

Serious infections requiring hospitalization occurred in the psoriasis development program. These serious infections included cellulitis, diverticulitis, osteomyelitis, viral infections, gastroenteritis, pneumonia, and urinary tract infections.

5.2 Theoretical Risk for Vulnerability to Particular Infections

Individuals genetically deficient in IL-12/IL-23 are particularly vulnerable to disseminated infections from mycobacteria (including nontuberculous, environmental mycobacteria), salmonella (including nontyphi strains), and Bacillus Calmette-Guerin (BCG) vaccinations. Serious infections and fatal outcomes have been reported in such patients.

It is not known whether patients with pharmacologic blockade of IL-12/IL-23 from treatment with STELARA[®] will be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA[®]. Do not administer STELARA[®] to patients with active tuberculosis. Initiate treatment of latent tuberculosis prior to administering STELARA[®]. Consider anti-tuberculosis therapy prior to initiation of STELARA[®] in patients with a past history of latent or active tuberculosis in whom an adequate

152 course of treatment cannot be confirmed. Patients receiving STELARA[®] should be monitored closely
153 for signs and symptoms of active tuberculosis during and after treatment.

154

155 **5.4 Malignancies**

156 STELARA[®] is an immunosuppressant and may increase the risk of malignancy. Malignancies were
157 reported among subjects who received STELARA[®] in clinical studies [see *Adverse Reactions (6.1)*].
158 In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy [see *Nonclinical*
159 *Toxicology (13)*].

160

161 The safety of STELARA[®] has not been evaluated in patients who have a history of malignancy or who
162 have a known malignancy.

163

164 **5.5 Hypersensitivity Reactions**

165 Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported post-marketing.
166 If an anaphylactic or other clinically significant hypersensitivity reaction occurs, discontinue
167 STELARA[®] and institute appropriate therapy [see *Adverse Reactions (6.3)*].

168

169 **5.6 Reversible Posterior Leukoencephalopathy Syndrome**

170 One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed during the
171 clinical development program which included 3523 STELARA[®]-treated subjects. The subject, who
172 had received 12 doses of STELARA[®] over approximately two years, presented with headache,
173 seizures and confusion. No additional STELARA[®] injections were administered and the subject fully
174 recovered with appropriate treatment.

175

176 RPLS is a neurological disorder, which is not caused by demyelination or a known infectious agent.
177 RPLS can present with headache, seizures, confusion and visual disturbances. Conditions with which
178 it has been associated include preeclampsia, eclampsia, acute hypertension, cytotoxic agents and
179 immunosuppressive therapy. Fatal outcomes have been reported.

180

181 If RPLS is suspected, STELARA[®] should be discontinued and appropriate treatment administered.

182

183 **5.7 Immunizations**

184 Prior to initiating therapy with STELARA[®], patients should receive all immunizations appropriate for
185 age as recommended by current immunization guidelines. Patients being treated with STELARA[®]
186 should not receive live vaccines. BCG vaccines should not be given during treatment with
187 STELARA[®] or for one year prior to initiating treatment or one year following discontinuation of
188 treatment. Caution is advised when administering live vaccines to household contacts of patients
189 receiving STELARA[®] because of the potential risk for shedding from the household contact and
190 transmission to patient.

191

192 Non-live vaccinations received during a course of STELARA[®] may not elicit an immune response
193 sufficient to prevent disease.

194

195 **5.8 Concomitant Therapies**

196 The safety of STELARA[®] in combination with other immunosuppressive agents or phototherapy has
197 not been evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice

198 genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone [see *Nonclinical*
199 *Toxicology (13)*].

200

201 **6 ADVERSE REACTIONS**

202 The following serious adverse reactions are discussed elsewhere in the label:

203

- 204 • Infections [see *Warnings and Precautions (5.1)*]
- 205 • Malignancies [see *Warnings and Precautions (5.4)*]
- 206 • Reversible Posterior Leukoencephalopathy Syndrome [see *Warnings and Precautions (5.6)*]

207

208 **6.1 Clinical Studies Experience**

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

212

213 The safety data reflect exposure to STELARA[®] in 3117 psoriasis subjects, including 2414 exposed for
214 at least 6 months, 1852 exposed for at least one year, 1650 exposed for at least two years, 1129
215 exposed for at least three years, and 619 exposed for at least four years.

216

217 Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in
218 the STELARA[®] groups than the placebo group during the placebo-controlled period of STUDY 1 and
219 STUDY 2 [see *Clinical Studies (14)*].

220

Table 1. Adverse reactions reported by $\geq 1\%$ of subjects through Week 12 in STUDY 1 and STUDY 2

	STELARA [®]		
	Placebo	45 mg	90 mg
Subjects treated	665	664	666
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
Diarrhea	12 (2%)	13 (2%)	13 (2%)
Back pain	8 (1%)	9 (1%)	14 (2%)
Dizziness	8 (1%)	8 (1%)	14 (2%)
Pharyngolaryngeal pain	7 (1%)	9 (1%)	12 (2%)
Pruritus	9 (1%)	10 (2%)	9 (1%)
Injection site erythema	3 (<1%)	6 (1%)	13 (2%)
Myalgia	4 (1%)	7 (1%)	8 (1%)
Depression	3 (<1%)	8 (1%)	4 (1%)

221

222 Adverse reactions that occurred at rates less than 1% in the controlled period of STUDIES 1 and 2
223 through week 12 included: cellulitis, herpes zoster, diverticulitis and certain injection site reactions
224 (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation).

225
226 One case of RPLS occurred during clinical trials [see Warnings and Precautions (5.6)].
227

228 Infections

229 In the placebo-controlled period of clinical studies of psoriasis subjects (average follow-up of 12.6
230 weeks for placebo-treated subjects and 13.4 weeks for STELARA[®]-treated subjects), 27% of
231 STELARA[®]-treated subjects reported infections (1.39 per subject-year of follow-up) compared with
232 24% of placebo-treated subjects (1.21 per subject-year of follow-up). Serious infections occurred in
233 0.3% of STELARA[®]-treated subjects (0.01 per subject-year of follow-up) and in 0.4% of placebo-
234 treated subjects (0.02 per subject-year of follow-up) [see Warnings and Precautions (5.1)].
235

236 In the controlled and non-controlled portions of psoriasis clinical trials (median follow up of 2.6
237 years), representing 6791 subject-years of exposure, 70% of STELARA[®]-treated subjects reported
238 infections (0.98 per subject-years of follow-up). Serious infections were reported in 2% of subjects
239 (0.01 per subject-years of follow-up).
240

241 Malignancies

242 In the controlled and non-controlled portions of psoriasis clinical trials (median follow up of 2.6 years,
243 representing 6791 subject-years of exposure), 1.3% of STELARA[®]-treated subjects reported
244 malignancies excluding non-melanoma skin cancers (0.62 per hundred subject-years of follow-up).
245 Non-melanoma skin cancer was reported in 1.3% of STELARA[®]-treated subjects (0.61 per hundred
246 subject-years of follow-up) [see Warnings and Precautions (5.4)]. The most frequently observed
247 malignancies other than non-melanoma skin cancer during the clinical trials were: prostate, colorectal,
248 melanoma in situ, breast. Malignancies other than non-melanoma skin cancer in STELARA[®]-treated
249 patients during the controlled and uncontrolled portions of studies were similar in type and number to
250 what would be expected in the general U.S. population according to the SEER database (adjusted for
251 age, gender and race).¹
252

253 **6.2 Immunogenicity**

254 The presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab
255 antibodies resulting in inconclusive results due to assay interference. In STUDIES 1 and 2, antibody
256 testing was done at time points when ustekinumab may have been present in the serum. Table 2
257 summarizes the antibody results from STUDY 1 through year 3 and STUDY 2 through year 4.
258

259 **Table 2: Presence of anti-ustekinumab antibodies in STUDY 1 through Year 3 and STUDY 2**
260 **through Year 4.**

Antibody Results	STUDY 1 (N=746)	STUDY 2 (N=1202)
Positive	39 (5%)	65 (5%)
Negative	124(17%)	150 (12%)
Inconclusive	583 (78%)	987 (82%)

261
262 The data reflect the percentage of subjects whose test results were positive for antibodies to
263 ustekinumab in a bridging immunoassay, and are highly dependent on the sensitivity and specificity of
264 the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by
265 several factors, including sample handling, timing of sample collection, concomitant medications and

266 underlying disease. For these reasons, comparison of the incidence of antibodies to ustekinumab with
267 the incidence of antibodies to other products may be misleading.

268

269 **6.3 Post-marketing Experience**

270 Adverse reactions have been reported during post-approval use with STELARA[®]. Because these
271 reactions are reported voluntarily from a population of uncertain size, it is not always possible to
272 reliably estimate their frequency or establish a causal relationship to STELARA[®] exposure.

273 *Immune system disorders:* Serious hypersensitivity reactions (including anaphylaxis and
274 angioedema), other hypersensitivity reactions (including rash and urticaria).

275

276 **7 DRUG INTERACTIONS**

277 Drug interaction studies have not been conducted with STELARA[®].

278

279 **7.1 Live Vaccines**

280 Live vaccines should not be given concurrently with STELARA[®] [*see Warnings and Precautions*
281 (5.7)].

282

283 **7.2 Concomitant Therapies**

284 The safety of STELARA[®] in combination with immunosuppressive agents or phototherapy has not
285 been evaluated [*see Warnings and Precautions* (5.8)].

286

287 **7.3 CYP450 Substrates**

288 The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1,
289 IL-6, IL-10, TNF α , IFN) during chronic inflammation. Thus, STELARA[®], an antagonist of IL-12 and
290 IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA[®] in patients
291 who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index,
292 monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine)
293 should be considered and the individual dose of the drug adjusted as needed [*see Clinical*
294 *Pharmacology* (12.3)].

295

296 **7.4 Allergen Immunotherapy**

297 STELARA[®] has not been evaluated in patients who have undergone allergy immunotherapy.
298 STELARA[®] may decrease the protective effect of allergen immunotherapy (decrease tolerance) which
299 may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution
300 should be exercised in patients receiving or who have received allergen immunotherapy, particularly
301 for anaphylaxis.

302

303 **8 USE IN SPECIFIC POPULATIONS**

304 **8.1 Pregnancy**

305 Pregnancy Category B

306 There are no studies of STELARA[®] in pregnant women. STELARA[®] should be used during
307 pregnancy only if the potential benefit justifies the potential risk to the fetus. No teratogenic effects
308 were observed in the developmental and reproductive toxicology studies performed in cynomolgus
309 monkeys at doses up to 45 mg/kg ustekinumab, which is 45 times (based on mg/kg) the highest
310 intended clinical dose in psoriasis patients (approximately 1 mg/kg based on administration of a 90 mg
311 dose to a 90 kg psoriasis patient).

312
313 Ustekinumab was tested in two embryo-fetal development toxicity studies. Pregnant cynomolgus
314 monkeys were administered ustekinumab at doses up to 45 mg/kg during the period of organogenesis
315 either twice weekly via subcutaneous injections or weekly by intravenous injections. No significant
316 adverse developmental effects were noted in either study.

317
318 In an embryo-fetal development and pre- and post-natal development toxicity study, three groups of 20
319 pregnant cynomolgus monkeys were administered subcutaneous doses of 0, 22.5, or 45 mg/kg
320 ustekinumab twice weekly from the beginning of organogenesis in cynomolgus monkeys to Day 33
321 after delivery. There were no treatment-related effects on mortality, clinical signs, body weight, food
322 consumption, hematology, or serum biochemistry in dams. Fetal losses occurred in six control
323 monkeys, six 22.5 mg/kg-treated monkeys, and five 45 mg/kg-treated monkeys. Neonatal deaths
324 occurred in one 22.5 mg/kg-treated monkey and in one 45 mg/kg-treated monkey. No ustekinumab-
325 related abnormalities were observed in the neonates from birth through six months of age in clinical
326 signs, body weight, hematology, or serum biochemistry. There were no treatment-related effects on
327 functional development until weaning, functional development after weaning, morphological
328 development, immunological development, and gross and histopathological examinations of offsprings
329 by the age of 6 months.

330

331 **8.3 Nursing Mothers**

332 Caution should be exercised when STELARA[®] is administered to a nursing woman. The unknown
333 risks to the infant from gastrointestinal or systemic exposure to ustekinumab should be weighed
334 against the known benefits of breast-feeding. Ustekinumab is excreted in the milk of lactating
335 monkeys administered ustekinumab. IgG is excreted in human milk, so it is expected that STELARA[®]
336 will be present in human milk. It is not known if ustekinumab is absorbed systemically after ingestion;
337 however, published data suggest that antibodies in breast milk do not enter the neonatal and infant
338 circulation in substantial amounts.

339

340 **8.4 Pediatric Use**

341 Safety and effectiveness of STELARA[®] in pediatric patients have not been evaluated.

342

343 **8.5 Geriatric Use**

344 Of the 3117 psoriasis subjects exposed to STELARA[®], a total of 183 were 65 years or older, and 21
345 subjects were 75 years or older. Although no differences in safety or efficacy were observed between
346 older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine
347 whether they respond differently from younger subjects.

348

349 **10 OVERDOSAGE**

350 Single doses up to 4.5 mg/kg intravenously have been administered in clinical studies without dose-
351 limiting toxicity. In case of overdosage, it is recommended that the patient be monitored for any signs
352 or symptoms of adverse reactions or effects and appropriate symptomatic treatment be instituted
353 immediately.

354

355 **11 DESCRIPTION**

356 STELARA[®] is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23
357 cytokines. Using DNA recombinant technology, STELARA[®] is produced in a well characterized

358 recombinant cell line and is purified using standard bio-processing technology. The manufacturing
359 process contains steps for the clearance of viruses. STELARA[®] is comprised of 1326 amino acids and
360 has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

361
362 STELARA[®], for subcutaneous use, is available as: 45 mg of ustekinumab in 0.5 mL and 90 mg of
363 ustekinumab in 1 mL. STELARA[®] is supplied as a sterile solution in a single-use prefilled syringe
364 with a 27 gauge fixed ½ inch needle, or a single-use 2 mL Type I glass vial with a coated stopper. The
365 syringe is fitted with a passive needle guard and a needle cover that is manufactured using a dry
366 natural rubber (a derivative of latex).

367
368 Each 45 mg ustekinumab prefilled syringe also contains: L-histidine and L-histidine
369 monohydrochloride monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg) to fill to a
370 final volume of 0.5 mL.

371
372 Each 90 mg ustekinumab prefilled syringe also contains: L-histidine and L-histidine
373 monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg) to fill to a
374 final volume of 1 mL.

375
376 Each 45 mg ustekinumab vial also contains: L-histidine and L-histidine monohydrochloride
377 monohydrate (0.5 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg) to fill to a final volume of 0.5
378 mL.

379
380 Each 90 mg ustekinumab vial also contains: L-histidine and L-histidine monohydrochloride
381 monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg) to fill to a final volume of 1 mL.

382
383 The STELARA[®] solution is colorless to slightly yellow in appearance and has a pH of 5.7-6.3.
384 STELARA[®] does not contain preservatives.

385

386 **12 CLINICAL PHARMACOLOGY**

387 **12.1 Mechanism of Action**

388 Ustekinumab is a human IgG1κ monoclonal antibody that binds with high affinity and specificity to
389 the p40 protein subunit used by both the interleukin (IL)-12 and IL-23 cytokines. IL-12 and IL-23 are
390 naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural
391 killer cell activation and CD4+ T-cell differentiation and activation. In *in vitro* models, ustekinumab
392 was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the
393 interaction of these cytokines with a shared cell-surface receptor chain, IL-12 β1.

394

395 **12.2 Pharmacodynamics**

396 In a small exploratory study, a decrease was observed in the expression of mRNA of its molecular
397 targets IL-12 and IL-23 in lesional skin biopsies measured at baseline and up to two weeks post-
398 treatment in psoriatic subjects.

399

400 **12.3 Pharmacokinetics**

401 Absorption

402 In psoriasis subjects, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days
403 and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg

404 (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a
405 single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in
406 psoriasis subjects. Following multiple subcutaneous doses of STELARA[®], the steady-state serum
407 concentrations of ustekinumab were achieved by Week 28. The mean (\pm SD) steady-state trough serum
408 concentration ranged from 0.31 ± 0.33 mcg/mL (45 mg) to 0.64 ± 0.64 mcg/mL (90 mg). There was
409 no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously
410 every 12 weeks.

411

412 Distribution

413 Following subcutaneous administration of 45 mg (N=18) and 90 mg (N=21) of ustekinumab to
414 psoriasis subjects, the mean (\pm SD) apparent volume of distribution during the terminal phase (V_z/F)
415 was 161 ± 65 mL/kg and 179 ± 85 mL/kg, respectively. The mean (\pm SD) volume of distribution
416 during the terminal phase (V_z) following a single intravenous administration to subjects with psoriasis
417 ranged from 56.1 ± 6.5 to 82.1 ± 23.6 mL/kg.

418

419 Metabolism

420 The metabolic pathway of ustekinumab has not been characterized. As a human IgG1 κ monoclonal
421 antibody ustekinumab is expected to be degraded into small peptides and amino acids via catabolic
422 pathways in the same manner as endogenous IgG.

423

424 Elimination

425 The mean (\pm SD) systemic clearance (CL) following a single intravenous administration of
426 ustekinumab to psoriasis subjects ranged from 1.90 ± 0.28 to 2.22 ± 0.63 mL/day/kg. The mean
427 (\pm SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following
428 intravenous and subcutaneous administration.

429

430 Weight

431 When given the same dose, subjects weighing >100 kg had lower median serum ustekinumab
432 concentrations compared with those subjects weighing ≤ 100 kg. The median trough serum
433 concentrations of ustekinumab in subjects of higher weight (>100 kg) in the 90 mg group were
434 comparable to those in subjects of lower weight (≤ 100 kg) in the 45 mg group.

435

436 Hepatic and Renal Impairment

437 No pharmacokinetic data are available in patients with hepatic or renal impairment.

438

439 Elderly

440 A population pharmacokinetic analysis (N=106/1937 subjects greater than or equal to 65 years old)
441 was performed to evaluate the effect of age on the pharmacokinetics of ustekinumab. There were no
442 apparent changes in pharmacokinetic parameters (clearance and volume of distribution) in subjects
443 older than 65 years old.

444

445 Drug-Drug Interactions

446 The effects of IL-12 or IL-23 on the regulation of CYP450 enzymes were evaluated in an *in vitro*
447 study using human hepatocytes, which showed that IL-12 and/or IL-23 at levels of 10 ng/mL did not
448 alter human CYP450 enzyme activities (CYP1A2, 2B6, 2C9, 2C19, 2D6, or 3A4). However, the
449 clinical relevance of *in vitro* data has not been established [*see Drug Interactions (7.3)*].

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of STELARA[®]. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

A male fertility study was conducted with only 6 male monkeys per group administered subcutaneous doses of 0, 22.5, or 45 mg/kg ustekinumab twice weekly prior to mating and during the mating period for 13 weeks, followed by a 13-week treatment-free period. Although fertility and pregnancy outcomes were not evaluated in mated females, there were no treatment-related effects on parental toxicity or male fertility parameters.

A female fertility study was conducted in mice using an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, beginning 15 days before cohabitation and continuing through GD 7. There were no treatment-related effects on maternal toxicity or female fertility parameters.

13.2 Animal Toxicology and/or Pharmacology

In a 26-week toxicology study, one out of 10 monkeys subcutaneously administered 45 mg/kg ustekinumab twice weekly for 26 weeks had a bacterial infection.

14 CLINICAL STUDIES

Two multicenter, randomized, double-blind, placebo-controlled studies (STUDY 1 and STUDY 2) enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score ≥ 12 , and who were candidates for phototherapy or systemic therapy. Subjects with guttate, erythrodermic, or pustular psoriasis were excluded from the studies.

STUDY 1 enrolled 766 subjects and STUDY 2 enrolled 1230 subjects. The studies had the same design through Week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of STELARA[®]. Subjects randomized to STELARA[®] received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive STELARA[®] (either 45 mg or 90 mg) at Weeks 12 and 16.

In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.

495 In both studies, subjects in all treatment groups had a median baseline PASI score ranging from
 496 approximately 17 to 18. Baseline PGA score was marked or severe in 44% of subjects in STUDY 1
 497 and 40% of subjects in STUDY 2. Approximately two-thirds of all subjects had received prior
 498 phototherapy, 69% had received either prior conventional systemic or biologic therapy for the
 499 treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving
 500 prior biologic therapy. A total of 28% of study subjects had a history of psoriatic arthritis.

501
 502 Clinical Response

503 The results of STUDY 1 and STUDY 2 are presented in Table 3 below.

504

Table 3. Clinical Outcomes STUDY 1 and STUDY 2

<u>Week 12</u>	<u>STUDY 1</u>			<u>STUDY 2</u>		
		STELARA®			STELARA®	
	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>
Subjects randomized	255	255	256	410	409	411
PASI 75 response	8 (3%)	171 (67%)	170 (66%)	15 (4%)	273 (67%)	311 (76%)
PGA of Cleared or Minimal	10 (4%)	151 (59%)	156 (61%)	18 (4%)	277 (68%)	300 (73%)

505

506 Examination of age, gender, and race subgroups did not identify differences in response to
 507 STELARA® among these subgroups.

508

509 In subjects who weighed <100 kg, response rates were similar with both the 45 mg and 90 mg doses;
 510 however, in subjects who weighed >100 kg, higher response rates were seen with 90 mg dosing
 511 compared with 45 mg dosing (Table 4 below).

Table 4. Clinical Outcomes by Weight STUDY 1 and STUDY 2

	<u>STUDY 1</u>			<u>STUDY 2</u>		
		STELARA®			STELARA®	
	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>	<u>Placebo</u>	<u>45 mg</u>	<u>90 mg</u>
Subjects randomized	255	255	256	410	409	411
PASI 75 response at Week 12*						
≤100 kg	4% 6/166	74% 124/168	65% 107/164	4% 12/290	73% 218/297	78% 225/289
>100 kg	2% 2/89	54% 47/87	68% 63/92	3% 3/120	49% 55/112	71% 86/121
PGA of Cleared or Minimal at Week 12*						
≤100 kg	4% 7/166	64% 108/168	63% 103/164	5% 14/290	74% 220/297	75% 216/289
>100 kg	3% 3/89	49% 43/87	58% 53/92	3% 4/120	51% 57/112	69% 84/121

512 *Patients were dosed with study medication at Weeks 0 and 4.

513
514 Subjects in STUDY 1 who were PASI 75 responders at both Weeks 28 and 40 were re-randomized at
515 Week 40 to either continued dosing of STELARA[®] (STELARA[®] at Week 40) or to withdrawal of
516 therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA[®]
517 treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to
518 placebo (treatment withdrawal after Week 28 dose). The median time to loss of PASI 75 response
519 among the subjects randomized to treatment withdrawal was 16 weeks.

521 **15 REFERENCES**

522 ¹Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov)
523 SEER*Stat Database: Incidence - SEER 6.6.2 Regs Research Data, Nov 2009 Sub (1973-2007) -
524 Linked To County Attributes - Total U.S., 1969-2007 Counties, National Cancer Institute, DCCPS,
525 Surveillance Research Program, Surveillance Systems Branch, released April 2010, based on the
526 November 2009 submission.

527 **16 HOW SUPPLIED/STORAGE AND HANDLING**

528 STELARA[®] does not contain preservatives. STELARA[®] is available in single-use prefilled syringes
529 or single-use vials containing 45 mg or 90 mg of ustekinumab. Each prefilled syringe is equipped
530 with a needle safety guard.

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532
533 The NDC number for the 45 mg prefilled syringe is 57894-060-03.

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535 The NDC number for the 90 mg prefilled syringe is 57894-061-03.

536
537 The NDC number for the 45 mg vial is 57894-060-02.

538
539 The NDC number for the 90 mg vial is 57894-061-02.

540 Storage and Stability

541 STELARA[®] vials and prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Store
542 STELARA[®] vials upright. Keep the product in the original carton to protect from light until the time
543 of use. Do not freeze. Do not shake. STELARA[®] does not contain a preservative; discard any unused
544 portion.

545 **17 PATIENT COUNSELING INFORMATION**

546
547 “See FDA-approved patient labeling (Medication Guide)”

548
549
550 Instruct patients to read the Medication Guide before starting STELARA[®] therapy and to reread the
551 Medication Guide each time the prescription is renewed.

552 Infections

553 Inform patients that STELARA[®] may lower the ability of their immune system to fight infections.
554 Instruct patients of the importance of communicating any history of infections to the doctor, and
555 contacting their doctor if they develop any symptoms of infection.

556
557

558 Malignancies
559 Patients should be counseled about the risk of malignancies while receiving STELARA®.
560
561 Allergic Reactions
562 Advise patients to seek immediate medical attention if they experience any symptoms of serious
563 allergic reactions.
564
565 Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, License No. 1864 at
566 Baxter Pharmaceutical Solutions, Bloomington, IN 47403
567
568 Vial Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, License No. 1864 at Cilag AG,
569 Schaffhausen, Switzerland
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