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

----------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----------

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

----------CONTRAINDICATIONS----------

None (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) evaluation: 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 serious allergic 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: 04/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

STELARA® is 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing

STELARA® is administered by subcutaneous injection.

- 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.

- 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.

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

The safety and efficacy of STELARA® have not been evaluated beyond two years.

2.2 General Considerations for Administration

STELARA® is intended for subcutaneous administration under the supervision of a physician.

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

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

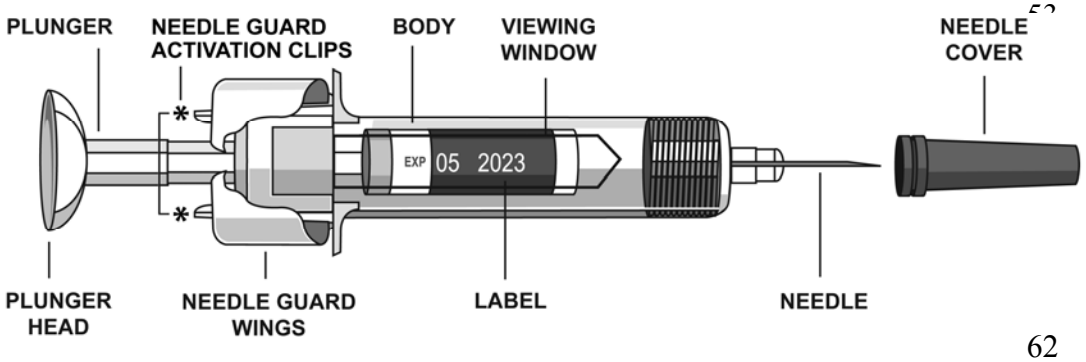
It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated. When using the single-use vial,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

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

2.3 Instructions for Administration of STELARA® Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

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

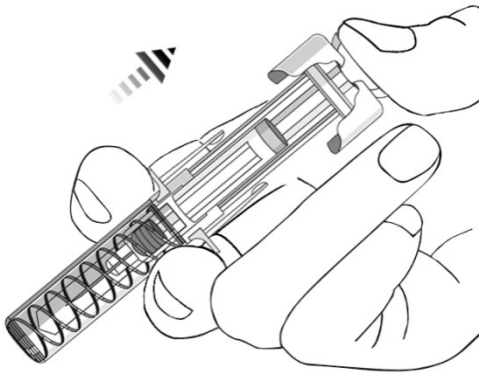


- Hold the BODY and remove the NEEDLE COVER. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE COVER or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE COVER in place.**

- Inject STELARA® subcutaneously as recommended *[see Dosage and Administration (2.2)]*.

- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the needle guard wings. **Injection of the entire prefilled syringe contents is necessary to activate the needle guard.**

- After injection, maintain the pressure on the PLUNGER HEAD and remove the needle from the skin. Slowly take your thumb off the PLUNGER HEAD to allow the empty syringe to move up until the entire needle is covered by the needle guard, as shown by the illustration below:



- 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.

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

4 CONTRAINDICATIONS

None.

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

5.4 Malignancies

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

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

5.5 Hypersensitivity Reactions

Serious allergic reactions, including angioedema and possible anaphylaxis, have been reported post-marketing. If an anaphylactic or other serious allergic reaction occurs, discontinue STELARA® and institute appropriate therapy *[see Adverse Reactions (6.2)]*.

5.6 Reversible Posterior Leukoencephalopathy Syndrome

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

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

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

5.7 Immunizations

Prior to initiating therapy with STELARA®, patients should receive all immunizations appropriate for age as recommended by current immunization guidelines. Patients being treated with STELARA®

should not receive live vaccines. BCG vaccines should not be given during treatment with STELARA® or for one year prior to initiating treatment or one year following discontinuation of treatment. Caution is advised when administering live vaccines to household contacts of patients receiving STELARA® because of the potential risk for shedding from the household contact and transmission to patient.

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

5.8 Concomitant Therapies

The safety of STELARA® in combination with other immunosuppressive agents or phototherapy has not been evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone *[see Nonclinical Toxicology (13)]*.

5.9 Theoretical Risk of Immunotherapy

STELARA® has not been evaluated in patients who have undergone allergy immunotherapy. STELARA® may decrease the protective effect of allergy immunotherapy and may increase the risk of an allergic reaction to a dose of allergen immunotherapy. Therefore, caution should be exercised in patients receiving or who have received allergy immunotherapy, particularly for anaphylaxis.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Studies Experience

The safety data reflect exposure to STELARA® in 2266 psoriasis subjects, including 1970 exposed for at least 6 months, 1285 exposed for at least one year, and 373 exposed for at least 18 months.

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

Table 1 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the STELARA® groups than the placebo group during the placebo-controlled period of STUDY 1 and STUDY 2.

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

	Placebo	STELARA® 45 mg	STELARA® 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%)

Adverse drug reactions that occurred at rates less than 1% included: cellulitis and certain injection site reactions (pain, swelling, pruritus, induration, hemorrhage, bruising, and irritation). One case of RPLS occurred during clinical trials *[see Warnings and Precautions (5.6)]*.

Infections

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

In the controlled and non-controlled portions of psoriasis clinical trials, 61% of STELARA®-treated subjects reported infections (1.24 per subject-year of follow-up). Serious infections were reported in 0.9% of subjects (0.01 per subject-year of follow-up).

Malignancies

In the controlled and non-controlled portions of psoriasis clinical trials, 0.4% of STELARA®-treated subjects reported malignancies excluding non-melanoma skin cancers (0.36 per 100 subject-years of follow-up). Non-melanoma skin cancer was reported in 0.8% of STELARA®-treated subjects (0.80 per 100 subject-years of follow-up) *[see Warnings and Precautions (5.4)]*.

Serious malignancies included breast, colon, head and neck, kidney, prostate, and thyroid cancers.

Immunogenicity

The presence of ustekinumab in the serum can interfere with the detection of anti-ustekinumab antibodies resulting in inconclusive results due to assay interference. In STUDIES 1 and 2, antibody testing was done at time points when ustekinumab may have been present in the serum. Table 2 summarizes the antibody results from STUDIES 1 and 2. In STUDY 1 the last ustekinumab injection was between Weeks 28 and 48 and the last test for anti-ustekinumab antibodies was at Week 52. In STUDY 2 the last ustekinumab injection was at Week 16 and the last test for anti-ustekinumab antibodies was at Week 24.

Table 2

Antibody Results	STUDY 1 (N=743)	STUDY 2 (N=1198)
Positive	38 (5%)	33 (3%)
Negative	351 (47%)	90 (8%)
Inconclusive	354 (48%)	1075 (90%)

The data reflect the percentage of subjects whose test results were positive for antibodies to ustekinumab in a bridging immunoassay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ustekinumab with the incidence of antibodies to other products may be misleading.

6.2 Post-marketing Experience

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

Immune system disorders: Serious allergic reactions (including angioedema, dyspnea and hypotension), hypersensitivity reactions (including rash and urticaria).

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with STELARA®.

7.1 Live Vaccines

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

7.2 Concomitant Therapies

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

7.3 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Thus, STELARA, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of STELARA in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index,

monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) should be considered and the individual dose of the drug adjusted as needed *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 2266 psoriasis subjects exposed to STELARA®, a total of 131 were 65 years or older, and 14 subjects were 75 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

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

11 DESCRIPTION

STELARA® is a human IgG1κ monoclonal antibody against the p40 subunit of the IL-12 and IL-23 cytokines. Using DNA recombinant technology, STELARA® is produced in a well characterized recombinant cell line and is purified using standard bio-processing technology. The manufacturing process contains steps for the clearance of viruses. STELARA® is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

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

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

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

Absorption

In psoriasis subjects, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in psoriasis subjects. Following multiple subcutaneous doses of STELARA®, the steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean (±SD) steady-state trough serum concentration ranged from 0.31 ± 0.33 mcg/mL (45 mg) to 0.64 ± 0.64 mcg/mL (90 mg). There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Distribution

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

Metabolism

The metabolic pathway of ustekinumab has not been characterized. As a human IgG1κ monoclonal antibody ustekinumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

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

Weight

When given the same dose, subjects weighing >100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing ≤100 kg.

Hepatic and Renal Impairment

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

Elderly

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

Drug-Drug Interactions

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

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.

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

Clinical Response

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

Table 3. Clinical Outcomes STUDY 1 and STUDY 2

Week 12	STUDY 1			STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
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%)

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

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

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

	STUDY 1			STUDY 2		
		STELARA®			STELARA®	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Subjects randomized	255	255	256	410	409	411
Week 12						
PASI 75 response						
≤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						
≤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

Subjects in STUDY 1 were evaluated through Week 52. At Week 40, those who were PASI 75 responders at both Weeks 28 and 40 were re-randomized to either continued dosing of STELARA® (STELARA® at Week 40) or to withdrawal of therapy (placebo at Week 40). At Week 52, 89% (144/162) of subjects re-randomized to STELARA® treatment were PASI 75 responders compared with 63% (100/159) of subjects re-randomized to placebo (treatment withdrawal after Week 28 dose).

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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

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

Storage and Stability

STELARA® vials and prefilled syringes must be refrigerated at 2ºC to 8ºC (36ºF to 46ºF). Store STELARA® vials upright. Keep the product in the original carton to protect from light until the time

of use. Do not freeze. Do not shake. STELARA® does not contain a preservative; discard any unused portion.

17 PATIENT COUNSELING INFORMATION

Instruct patients to read the Medication Guide before starting STELARA® therapy and to reread the Medication Guide each time the prescription is renewed.

Infections

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

Malignancies

Patients should be counseled about the risk of malignancies while receiving STELARA®.

Allergic Reactions

Advise patients to seek immediate medical attention if they experience any symptoms of serious allergic reactions.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403

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