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RESEARCH**

APPLICATION NUMBER:

761343Orig1s000

LABELING

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

SELARSDI™ (ustekinumab-aekn) injection, for subcutaneous use
Initial U.S. Approval: 2024

SELARSDI (ustekinumab-aekn) is biosimilar* to STELARA® (ustekinumab)

INDICATIONS AND USAGE
SELARSDI is a human interleukin-12 and -23 antagonist indicated for the treatment of:

- Adult patients with:
- moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy. (1.1)
 - active psoriatic arthritis (PsA). (1.2)

- Pediatric patients 6 years and older with:
- moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy. (1.1)
 - active psoriatic arthritis (PsA). (1.2)

DOSAGE AND ADMINISTRATION
Psoriasis Adult Subcutaneous Recommended Dosage (2.1):

Weight Range (kilograms)	Dosage Regimen
less than or equal to 100 kg	45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks
greater than 100 kg	90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks

Psoriasis Pediatric Patients (6 to 17 years old) Subcutaneous Recommended Dosage (2.1): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	Dose
60 kg to 100 kg	45 mg
greater than 100 kg	90 mg

- Psoriatic Arthritis Adult Subcutaneous Recommended Dosage (2.2):
- The recommended dosage is 45 mg administered subcutaneously initially and 4 weeks later, followed by 45 mg administered subcutaneously every 12 weeks.
 - For patients with co-existent moderate-to-severe plaque psoriasis weighing greater than 100 kg, the recommended dosage is 90 mg administered subcutaneously initially and 4 weeks later, followed by 90 mg administered subcutaneously every 12 weeks.

Psoriatic Arthritis Pediatric (6 to 17 years old) Subcutaneous Recommended Dosage (2.2): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	Dose
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg

DOSAGE FORMS AND STRENGTHS
Subcutaneous injection (3)
Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe

CONTRAINDICATIONS
Clinically significant hypersensitivity to ustekinumab products or to any of the excipients in SELARSDI. (4)

- WARNINGS AND PRECAUTIONS**
- **Infections:** Serious infections have occurred. Avoid starting SELARSDI during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue SELARSDI 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. Consider diagnostic tests for these infections as dictated by clinical circumstances. (5.2)
 - **Tuberculosis (TB):** Evaluate patients for TB prior to initiating treatment with SELARSDI. Initiate treatment of latent TB before administering SELARSDI. (5.3)
 - **Malignancies:** Ustekinumab products may increase risk of malignancy. The safety of ustekinumab products in patients with a history of or a known malignancy has not been evaluated. (5.4)
 - **Hypersensitivity Reactions:** If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue SELARSDI. (5.5)
 - **Posterior Reversible Encephalopathy Syndrome (PRES):** If PRES is suspected, treat promptly, and discontinue SELARSDI. (5.6)
 - **Immunizations:** Avoid use of live vaccines in patients during treatment with SELARSDI. (5.7)
 - **Noninfectious Pneumonia:** Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of ustekinumab products. If diagnosis is confirmed, discontinue SELARSDI and institute appropriate treatment. (5.8)

ADVERSE REACTIONS
Most common adverse reactions are:

- Psoriasis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of SELARSDI has been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Issued: 4/2024

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE**

- 1.1 Plaque Psoriasis (PsO)
- 1.2 Psoriatic Arthritis (PsA)

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage in Plaque Psoriasis
- 2.2 Recommended Dosage in Psoriatic Arthritis
- 2.3 General Considerations for Administration
- 2.4 Instructions for Administration of SELARSDI Prefilled Syringes
 - Equipped with Passive Safety Device

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Infections
- 5.2 Theoretical Risk for Vulnerability to Particular Infections
- 5.3 Pre-treatment Evaluation for Tuberculosis
- 5.4 Malignancies
- 5.5 Hypersensitivity Reactions
- 5.6 Posterior Reversible Encephalopathy Syndrome (PRES)
- 5.7 Immunizations
- 5.8 Noninfectious Pneumonia

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Immunogenicity
- 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Concomitant Therapies
- 7.2 CYP450 Substrates
- 7.3 Allergen Immunotherapy

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 Adult Plaque Psoriasis
- 14.2 Pediatric Plaque Psoriasis
- 14.3 Psoriatic Arthritis

15 REFERENCES**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis (PsO)

SELARSDI™ is indicated for the treatment of adults and pediatric patients 6 years of age and older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

SELARSDI is indicated for the treatment of adults and pediatric patients 6 years of age and older with active psoriatic arthritis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Plaque Psoriasis

Subcutaneous Adult Dosage Regimen

- For patients weighing 100 kg or less, the recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

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

Subcutaneous Pediatric Dosage Regimen

Administer SELARSDI subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of SELARSDI for pediatric patients (6 to 17 years old) with plaque psoriasis based on body weight is shown below (Table 1).

Table 1: Recommended Dose of SELARSDI for Subcutaneous Injection in Pediatric Patients (6 to 17 years old) with Plaque Psoriasis

Body Weight of Patient at the Time of Dosing	Recommended Dose
60 kg to 100 kg	45 mg
more than 100 kg	90 mg

There is no dosage form for SELARSDI that allows weight-based dosing for pediatric patients below 60 kg.

2.2 Recommended Dosage in Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing more than 100 kg, the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Subcutaneous Pediatric Dosage Regimen

Administer SELARSDI subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of SELARSDI for pediatric patients (6 to 17 years old) with psoriatic arthritis, based on body weight, is shown below (Table 2).

Table 2: Recommended Dose of SELARSDI for Subcutaneous Injection in Pediatric Patients (6 to 17 years old) with Psoriatic Arthritis

Body Weight of Patient at the Time of Dosing	Recommended Dose
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg

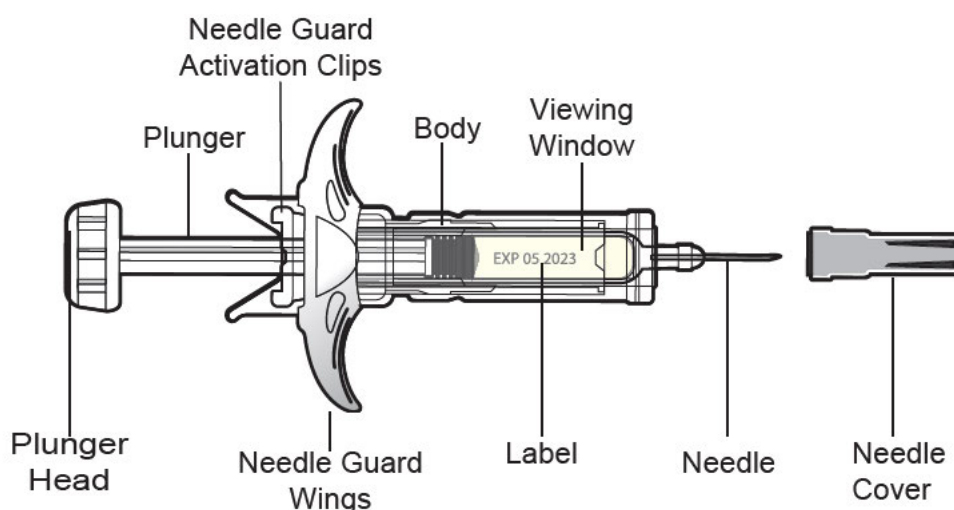
There is no dosage form for SELARSDI that allows weight-based dosing for pediatric patients below 60 kg.

2.3 General Considerations for Administration

- SELARSDI is intended for use under the guidance and supervision of a healthcare provider. SELARSDI should only be administered to patients who will be closely monitored and have regular follow-up visits with a healthcare provider. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In pediatric patients, it is recommended that SELARSDI be administered by a healthcare provider. If a healthcare provider determines that it is appropriate, a patient may self-inject or a caregiver may inject SELARSDI after proper training in subcutaneous injection technique. Instruct patients to follow the directions provided in the Medication Guide [see *Medication Guide*].
- Not made with natural rubber 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.
- Prior to administration, visually inspect SELARSDI for particulate matter and discoloration. SELARSDI is a clear and colorless to slightly yellow solution and free of visible particles. Do not use SELARSDI if it is discolored or cloudy, or if other particulate matter is present. SELARSDI does not contain preservatives; therefore, discard any unused product remaining in the syringe.

2.4 Instructions for Administration of SELARSDI Prefilled Syringes Equipped with Passive Safety Device

Refer to the diagram below for the provided instructions.



- Hold the SYRINGE 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 SELARSDI subcutaneously as recommended [see *Dosage and Administration (2.1, 2.2, 2.3)*].

- Inject all of the medication by pushing in the PLUNGER HEAD all the way in until the plunger head is completely between the needle guard activation clips. **Injection of the entire prefilled syringe contents is necessary to activate the passive safety device 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. The PLUNGER will move up with your thumb and retract the needle into the needle guard, as shown by the illustration below:



- Used syringes should be placed in a puncture-resistant container.

3 DOSAGE FORMS AND STRENGTHS

SELARSDI (ustekinumab-aekn) injection is a clear and colorless to slightly yellow solution and free of visible particles.

- Injection: 45 mg/0.5 mL or 90 mg/mL solution in a single-dose prefilled syringe

4 CONTRAINDICATIONS

SELARSDI is contraindicated in patients with clinically significant hypersensitivity to ustekinumab products or to any of the excipients in SELARSDI [see *Warnings and Precautions (5.5)*].

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Ustekinumab products may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving ustekinumab products [see *Adverse Reactions* (6.1, 6.3)].

Serious infections requiring hospitalization, or otherwise clinically significant infections, reported in clinical trials included the following:

- *Plaque Psoriasis*: diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis, and urinary tract infections.
- *Psoriatic arthritis*: cholecystitis.

Avoid initiating treatment with SELARSDI in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of SELARSDI in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur while on treatment with SELARSDI and discontinue SELARSDI for serious or clinically significant infections until the infection resolves or is adequately treated.

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 non typhi 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 ustekinumab products may be susceptible to these types of infections. Consider appropriate diagnostic testing, (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 SELARSDI.

Avoid administering SELARSDI to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering SELARSDI. Consider anti-tuberculosis therapy prior to initiation of SELARSDI in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving SELARSDI for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

Ustekinumab products are immunosuppressants and may increase the risk of malignancy. Malignancies were reported among subjects who received ustekinumab in clinical trials [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 ustekinumab products has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving ustekinumab products who had pre-existing risk factors for developing non-melanoma skin cancer. Monitor all patients receiving SELARSDI should be monitored for the appearance of non-melanoma skin cancer. Closely follow patients greater than 60 years of age, those with a medical history of

prolonged immunosuppressant therapy and those with a history of PUVA treatment [see *Adverse Reactions* (6.1)].

5.5 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with ustekinumab products [see *Adverse Reactions* (6.1, 6.3)]. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue SELARSDI.

5.6 Posterior Reversible Encephalopathy Syndrome (PRES)

Two cases of posterior reversible encephalopathy syndrome (PRES), also known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS), were reported in clinical trials. Cases have also been reported in postmarketing experience in patients with psoriasis and psoriatic arthritis. Clinical presentation included headaches, seizures, confusion, visual disturbances, and imaging changes consistent with PRES a few days to several months after ustekinumab product initiation. A few cases reported latency of a year or longer. Patients recovered with supportive care following withdrawal of ustekinumab products.

Monitor all patients treated with SELARSDI for signs and symptoms of PRES. If PRES is suspected, promptly administer appropriate treatment and discontinue SELARSDI.

5.7 Immunizations

Prior to initiating therapy with SELARSDI, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with SELARSDI should avoid receiving live vaccines. Avoid administering BCG vaccines during treatment with SELARSDI 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 SELARSDI because of the potential risk for shedding from the household contact and transmission to patient.

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

5.8 Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of ustekinumab products. Clinical presentations included cough, dyspnea, and interstitial infiltrates following one to three doses. Serious outcomes have included respiratory failure and prolonged hospitalization. Patients improved with discontinuation of therapy and in certain cases administration of corticosteroids. If diagnosis is confirmed, discontinue SELARSDI and institute appropriate treatment [see *Postmarketing Experience* (6.3)].

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)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.5)]
- Posterior Reversible Encephalopathy Syndrome (PRES) [see *Warnings and Precautions* (5.6)]
- Noninfectious Pneumonia [see *Warnings and Precautions* (5.8)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the

clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult Subjects with Plaque Psoriasis

The safety data reflect exposure to ustekinumab in 3117 adult subjects with plaque psoriasis, including 2414 exposed for at least 6 months, 1855 exposed for at least one year, 1653 exposed for at least two years, 1569 exposed for at least three years, 1482 exposed for at least four years and 838 exposed for at least five years.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% with higher rates in the ustekinumab groups during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 [see *Clinical Studies (14)*].

Table 3: Adverse Reactions Reported by $\geq 1\%$ of Subjects with Plaque Psoriasis and at Higher Rates in the ustekinumab groups through Week 12 in Ps STUDY 1 and Ps STUDY 2

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

One case of PRES occurred during adult plaque psoriasis clinical trials [see *Warnings and Precautions (5.6)*].

Infections

In the placebo-controlled period of clinical trials of subjects with plaque psoriasis (average follow-up of 12.6 weeks for placebo-treated subjects and 13.4 weeks for ustekinumab-treated subjects), 27% of ustekinumab-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 ustekinumab-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 plaque psoriasis clinical trials (median follow-up of 3.2 years), representing 8998 subject-years of exposure, 72.3% of ustekinumab-treated subjects reported infections (0.87 per subject-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per subject-years of follow-up).

Malignancies

In the controlled and non-controlled portions of plaque psoriasis clinical trials (median follow-up of 3.2 years, representing 8998 subject-years of exposure), 1.7% of ustekinumab-treated subjects reported malignancies excluding non-melanoma skin cancers (0.60 per hundred subject-years of follow-up). Non-melanoma skin cancer was reported in 1.5% of ustekinumab-treated subjects (0.52 per hundred subject-years of follow-up) [see

Warnings and Precautions (5.4)]. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical trials were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in ustekinumab-treated patients during the controlled and uncontrolled portions of trials were similar in type and number to what would be expected in the general U.S. population according to the SEER database (adjusted for age, gender and race).¹

Pediatric Subjects with Plaque Psoriasis

The safety of ustekinumab was assessed in two trials of pediatric subjects with moderate to severe plaque psoriasis. Ps STUDY 3 evaluated safety for up to 60 weeks in 110 pediatric subjects 12 to 17 years old. Ps STUDY 4 evaluated safety for up to 56 weeks in 44 pediatric subjects 6 to 11 years old. The safety profile in pediatric subjects was similar to the safety profile from trials in adults with plaque psoriasis.

Psoriatic Arthritis

The safety of ustekinumab was assessed in 927 subjects in two randomized, double-blind, placebo-controlled trials in adults with active psoriatic arthritis (PsA). The overall safety profile of ustekinumab in subjects with PsA was consistent with the safety profile seen in adult psoriasis clinical trials. A higher incidence of arthralgia, nausea, and dental infections was observed in ustekinumab-treated subjects when compared with placebo-treated subjects (3% vs. 1% for arthralgia and 3% vs. 1% for nausea; 1% vs. 0.6% for dental infections) in the placebo-controlled portions of the PsA clinical trials.

6.2 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ustekinumab or of other ustekinumab products.

Approximately 6 to 12.4% of subjects treated with ustekinumab in plaque psoriasis and psoriatic arthritis clinical trials developed antibodies to ustekinumab, which were generally low-titer. In plaque psoriasis clinical trials, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In plaque psoriasis trials, the majority of subjects who were positive for antibodies to ustekinumab had neutralizing antibodies.

6.3 Postmarketing Experience

The following adverse reactions have been reported during post-approval of ustekinumab products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to ustekinumab products exposure.

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

Infections and infestations: Lower respiratory tract infection (including opportunistic fungal infections and tuberculosis).

Neurological disorders: Posterior Reversible Encephalopathy Syndrome (PRES).

Respiratory, thoracic, and mediastinal disorders: Interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia.

Skin reactions: Pustular psoriasis, erythrodermic psoriasis, hypersensitivity vasculitis.

7 DRUG INTERACTIONS

7.1 Concomitant Therapies

In plaque psoriasis trials the safety of ustekinumab products in combination with immunosuppressive agents or phototherapy has not been evaluated. In psoriatic arthritis trials, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. Use of these concomitant therapies did not appear to influence the overall safety or efficacy of ustekinumab.

7.2 CYP450 Substrates

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF α , IFN) during chronic inflammation. Thus, ustekinumab products, antagonists of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of SELARSDI in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and adjust the individual dose of the drug as needed [see *Clinical Pharmacology* (12.3)].

7.3 Allergen Immunotherapy

Ustekinumab products have not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab products may decrease the protective effect of allergen immunotherapy (decrease tolerance) which 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 allergen immunotherapy, particularly for anaphylaxis.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited data from observational studies, published case reports, and postmarketing surveillance on the use of ustekinumab products during pregnancy are insufficient to inform a drug associated risk of major birth defects, miscarriage, and other adverse maternal or fetal outcomes. Transport of human IgG antibody across the placenta increases as pregnancy progresses and peaks during the third trimester; therefore, SELARSDI may be transferred to the developing fetus (see *Clinical Considerations*). In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed in offspring after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the maximum recommended human dose (MRHD).

The background risk of major birth defects and miscarriage for the indicated population(s) are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage of clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Because ustekinumab products may theoretically interfere with immune response to infections, consider risks and benefits prior to administering live vaccines to infants exposed to SELARSDI in utero. There are insufficient data regarding exposed infant serum levels of ustekinumab products at birth and the duration of persistence of ustekinumab products in infant serum after birth. Although a specific timeframe to delay administration of live attenuated vaccines in infants exposed in utero is unknown, consider the risks and benefits of delaying a minimum of 6 months after birth because of the clearance of the product.

Data

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were

administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

In a combined embryo-fetal development and pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of ustekinumab twice weekly at exposures greater than 100 times the MRHD from the beginning of organogenesis to Day 33 after delivery. Neonatal deaths occurred in the offspring of one monkey administered ustekinumab at 22.5 mg/kg and one monkey dosed at 45 mg/kg. No ustekinumab-related-effects on functional, morphological, or immunological development were observed in the neonates from birth through six months of age.

8.2 Lactation

Risk Summary

Limited data from published literature suggests that ustekinumab products are present in human breast milk. There are no available data on the effects of ustekinumab products on milk production. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to ustekinumab products are unknown. No adverse effects on the breastfed infant causally related to ustekinumab products have been identified in the published literature or postmarketing experience.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SELARSDI and any potential adverse effects on the breastfed child from SELARSDI or from the underlying maternal condition.

8.4 Pediatric Use

Plaque Psoriasis

The safety and effectiveness of SELARSDI have been established for the treatment of moderate to severe plaque psoriasis in pediatric patients 6 to 17 years of age who are candidates for phototherapy or systemic therapy.

Use of SELARSDI in pediatric patients 12 to less than 17 years of age is supported by evidence from a multicenter, randomized, 60week trial (Ps STUDY 3) of ustekinumab that included a 12week, double-blind, placebo-controlled, parallel group portion, in 110 pediatric subjects 12 years of age and older [*see Adverse Reactions (6.1), Clinical Studies (14.2)*].

Use of SELARSDI in pediatric patients 6 to 11 years of age is supported by evidence from an open-label, single-arm, efficacy, safety, and pharmacokinetics trial (Ps STUDY 4) of ustekinumab in 44 subjects [*see Adverse Reactions (6.1), Pharmacokinetics (12.3)*].

The safety and effectiveness of SELARSDI have not been established in pediatric patients less than 6 years of age with plaque psoriasis.

Psoriatic Arthritis

The safety and effectiveness of SELARSDI have been established for treatment of psoriatic arthritis in pediatric patients 6 to 17 years old.

Use of SELARSDI in these age groups is supported by evidence from adequate and well controlled trials of ustekinumab in adults with psoriasis and PsA, pharmacokinetic data from adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and safety data of ustekinumab from two clinical trials in 44 pediatric patients 6 to 11 years old with psoriasis and 110 pediatric patients 12 to 17 years old with psoriasis. The observed pre-dose (trough) concentrations are generally comparable between adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and the PK exposure is expected to be comparable

between adult and pediatric patients with PsA [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), and *Clinical Studies* (14.1, 14.2, 14.3)].

The safety and effectiveness of SELARSDI have not been established in pediatric patients less than 6 years old with psoriatic arthritis.

8.5 Geriatric Use

Of the 6709 patients exposed to ustekinumab, a total of 340 were 65 years of age or older (183 patients with plaque psoriasis, 65 patients with psoriatic arthritis, 58 patients with one indication, and 34 patients with another indication), and 40 patients were 75 years of age or older. Clinical trials of ustekinumab did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

10 OVERDOSAGE

Single doses up to 6 mg/kg intravenously have been administered in clinical trials without dose-limiting toxicity. In case of overdosage, monitor the patient for any signs or symptoms of adverse reactions or effects and institute appropriate symptomatic treatment immediately. Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Ustekinumab-aekn, a human IgG1κ monoclonal antibody, is a human interleukin-12 and -23 antagonist. Using DNA recombinant technology, ustekinumab-aekn is produced in a murine cell line (Sp2/0). The manufacturing process contains steps for the clearance of viruses. Ustekinumab-aekn is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148,079 to 149,690 Daltons.

SELARSDI (ustekinumab-aekn) injection is a sterile, preservative-free, clear and colorless to slightly yellow solution free of visible particles with pH of 5.7 to 6.3.

Available as 45 mg of ustekinumab-aekn in 0.5 mL and 90 mg of ustekinumab-aekn in 1 mL, for subcutaneous use supplied as a sterile solution in a single-dose prefilled syringe with a 29 gauge fixed ½ inch needle. Not made with natural rubber latex.

Each 0.5 mL prefilled syringe delivers 45 mg ustekinumab-aekn, histidine (0.122 mg), L-histidine monohydrochloride monohydrate (0.507 mg), polysorbate 80 (0.02 mg), sucrose (38 mg) and water for injection (q.s).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab-aekn, histidine (0.243 mg), L-histidine monohydrochloride monohydrate (1.013 mg), polysorbate 80 (0.04 mg), sucrose (76 mg) and water for injection (q.s).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab products are human IgG1κ monoclonal antibodies that bind with specificity to the p40 protein subunit used by both the 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 products were 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-12Rβ1.

12.2 Pharmacodynamics

Plaque Psoriasis

In a small exploratory trial, 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 subjects with plaque psoriasis.

12.3 Pharmacokinetics

Absorption

In adult subjects with plaque psoriasis, 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 subjects with plaque psoriasis.

Following multiple subcutaneous doses of ustekinumab in adult subjects with plaque psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean ($\pm$ SD) steady-state trough serum ustekinumab concentrations were 0.69 ± 0.69 mcg/mL for patients less than or equal to 100 kg receiving a 45 mg dose and 0.74 ± 0.78 mcg/mL for patients greater than 100 kg receiving a 90 mg dose. There was no apparent accumulation in serum ustekinumab concentration over time when given subcutaneously every 12 weeks.

Distribution

Population pharmacokinetic analyses showed that the volume of distribution of ustekinumab in the central compartment was 2.7 L (95% CI: 2.69, 2.78) in patients with one indication and 3.0 L (95% CI: 2.96, 3.07) in patients with another indication. The total volume of distribution at steady-state was 4.6 L in patients with one indication and 4.4 L in patients with another indication.

Elimination

The mean ($\pm$ SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all plaque psoriasis trials following subcutaneous administration.

Metabolism

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

Specific Populations

Weight

When given the same dose, subjects with plaque psoriasis or psoriatic arthritis weighing more than 100 kg had lower median serum ustekinumab concentrations compared with those subjects weighing 100 kg or less. The median trough serum concentrations of ustekinumab in subjects of higher weight (greater than 100 kg) in the 90 mg group were comparable to those in subjects of lower weight (100 kg or less) in the 45 mg group.

Age: Geriatric Population

A population pharmacokinetic analysis (N=106/1937 patients with plaque psoriasis 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.

Age: Pediatric Population

Following multiple recommended doses of ustekinumab in pediatric subjects 6 to 17 years of age with plaque psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean $\pm$ SD steady-state trough serum ustekinumab concentrations were 0.36 ± 0.26 mcg/mL and 0.54 ± 0.43 mcg/mL,

respectively, in pediatric subjects 6 to 11 years of age and pediatric subjects 12 to 17 years of age.

Overall, the observed steady-state ustekinumab trough concentrations in pediatric patients with plaque psoriasis were within the range of those observed for adult patients with plaque psoriasis and adult patients with PsA after administration of ustekinumab.

Drug Interaction Studies

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)].

No *in vivo* drug interaction studies have been conducted with ustekinumab products.

Population pharmacokinetic analyses indicated that the clearance of ustekinumab was not impacted by concomitant MTX, NSAIDs, and oral corticosteroids, or prior exposure to a TNF blocker in patients with psoriatic arthritis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of ustekinumab products. 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.

No effects on fertility were observed in male cynomolgus monkeys that were administered ustekinumab at subcutaneous doses up to 45 mg/kg twice weekly (45 times the MRHD on a mg/kg basis) prior to and during the mating period. However, fertility and pregnancy outcomes were not evaluated in mated females.

No effects on fertility were observed in female mice that were administered an analogous IL-12/IL-23p40 antibody by subcutaneous administration at doses up to 50 mg/kg, twice weekly, prior to and during early pregnancy.

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

14.1 Adult Plaque Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled trials (Ps STUDY 1 and Ps 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 trials.

Ps STUDY 1 enrolled 766 subjects and Ps STUDY 2 enrolled 1230 subjects. The trials had the same design through Week 28. In both trials, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of ustekinumab. Subjects randomized to ustekinumab 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 ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16.

In both trials, 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 Ps STUDY 1 and 40% of subjects in Ps 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 subjects had a history of psoriatic arthritis.

In both trials, 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.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 4 below.

Table 4: Clinical Outcomes at Week 12 in Adults with Plaque Psoriasis in Ps STUDY 1 and Ps STUDY 2

	Ps STUDY 1			Ps STUDY 2		
	Ustekinumab			Ustekinumab		
	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 ustekinumab among these subgroups.

In subjects who weighed 100 kg or less, response rates were comparable with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 5 below).

Table 5: Clinical Outcomes by Weight Ps STUDY 1 and Ps STUDY 2

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

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

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

Week 28 dose). The median time to loss of PASI 75 response among the subjects randomized to treatment withdrawal was 16 weeks.

14.2 Pediatric Plaque Psoriasis

A multicenter, randomized, double blind, placebo-controlled trial (Ps STUDY 3) enrolled 110 pediatric subjects 12 to 17 years of age with a minimum BSA involvement of 10%, a PASI score greater than or equal to 12, and a PGA score greater than or equal to 3, who were candidates for phototherapy or systemic therapy and whose disease was inadequately controlled by topical therapy.

Subjects were randomized to receive placebo (n = 37), the recommended dose of ustekinumab (n = 36), or one-half the recommended dose of ustekinumab (n = 37) by subcutaneous injection at Weeks 0 and 4 followed by dosing every 12 weeks (q12w). The recommended dose of ustekinumab was 0.75 mg/kg for subjects weighing less than 60 kg, 45 mg for subjects weighing 60 kg to 100 kg, and 90 mg for subjects weighing greater than 100 kg. At Week 12, subjects who received placebo were crossed over to receive ustekinumab at the recommended dose or one-half the recommended dose.

Of the pediatric subjects, approximately 63% had prior exposure to phototherapy or conventional systemic therapy and approximately 11% had prior exposure to biologics.

The endpoints were the proportion of subjects who achieved a PGA score of cleared (0) or minimal (1), PASI 75, and PASI 90 at Week 12. Subjects were followed for up to 60 weeks following first administration of trial agent.

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 6.

Table 6: Efficacy Results at Week 12 in the Pediatric Subjects 12 to 17 years with Plaque Psoriasis in Ps Study 3		
	Ps STUDY 3	
	Placebo n (%)	Ustekinumab* n (%)
N	37	36
PGA		
PGA of cleared (0) or minimal (1)	2 (5.4%)	25 (69.4%)
PASI		
PASI 75 responders	4 (10.8%)	29 (80.6%)
PASI 90 responders	2 (5.4%)	22 (61.1%)

* Using the weight-based dosage regimen specified in Table 1.

14.3 Psoriatic Arthritis

The safety and efficacy of ustekinumab was assessed in 927 patients (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled trials in adult patients 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite non-steroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Patients in these trials had a diagnosis of PsA for at least 6 months. Patients with each subtype of PsA were enrolled, including polyarticular arthritis with the absence of rheumatoid nodules (39%), spondylitis with peripheral arthritis (28%), asymmetric peripheral arthritis (21%), distal interphalangeal involvement (12%) and arthritis mutilans (0.5%). Over 70% and 40% of the patients, respectively, had enthesitis and dactylitis at baseline.

Patients were randomized to receive treatment with ustekinumab 45 mg, 90 mg, or placebo subcutaneously at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing. Approximately 50% of patients continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of patients achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the patients, respectively, had been previously treated with DMARDs. In PsA STUDY 1, previous treatment with anti-tumor necrosis factor (TNF)- α agent was not allowed. In PsA STUDY 2, 58% (n=180) of the patients had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both trials, a greater proportion of patients achieved ACR 20, ACR 50 and PASI 75 response in the ustekinumab 45 mg and 90 mg groups compared to placebo at Week 24 (see Table 7). ACR 70 responses were also higher in the ustekinumab 45 mg and 90 mg groups, although the difference was only numerical (p=NS) in STUDY 2. Responses were consistent in patients treated with ustekinumab alone or in combination with methotrexate. Responses were similar in patients regardless of prior TNF α exposure.

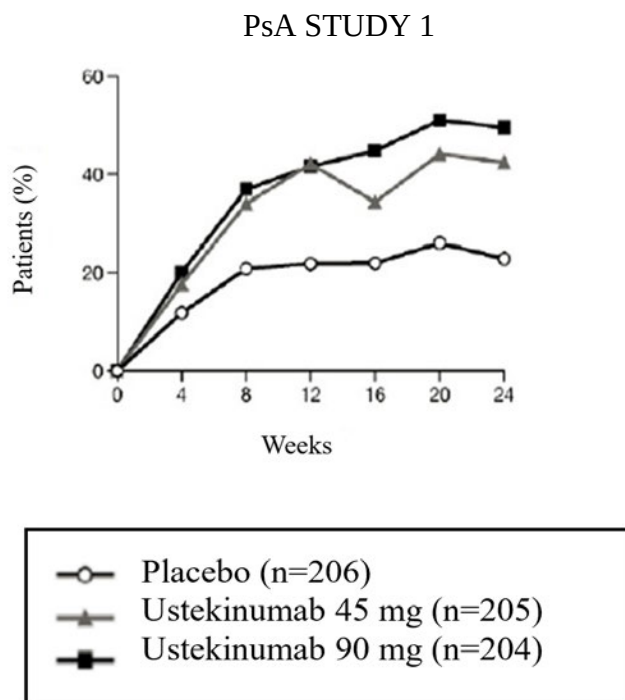
Table 7: ACR 20, ACR 50, ACR 70 and PASI 75 responses in PsA STUDY 1 and PsA STUDY 2 at Week 24

	PsA STUDY 1			PsA STUDY 2		
	Placebo	Ustekinumab 45 mg	90 mg	Placebo	Ustekinumab 45 mg	90 mg
Number of patients randomized	206	205	204	104	103	105
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)	7 (7%)	18 (17%)	24 (23%)
ACR 70 response, N (%)	5 (2%)	25 (12%)	29 (14%)	3 (3%)	7 (7%)	9 (9%)
Number of patients with $\geq 3\%$ BSA^a	146	145	149	80	80	81
PASI 75 response, N (%)	16 (11%)	83 (57%)	93 (62%)	4 (5%)	41 (51%)	45 (56%)

^a Number of patients with $\geq 3\%$ BSA psoriasis skin involvement at baseline

The percent of patients achieving ACR 20 responses by visit is shown in Figure 1.

Figure 1: Percent of patients achieving ACR 20 response through Week 24



The results of the components of the ACR response criteria are shown in Table 8.

Table 8: Mean change from baseline in ACR components at Week 24

	PsA STUDY 1		
	Placebo (N = 206)	Ustekinumab 45 mg (N = 205)	90 mg (N = 204)
Number of swollen joints ^a			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints ^b			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Patient's assessment of pain ^c			
Baseline	6.1	6.2	6.6
Mean Change at Week 24	-0.5	-2.0	-2.6
Patient global assessment ^c			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment ^c			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ) ^d			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL) ^e			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

^a Number of swollen joints counted (0-66)

^b Number of tender joints counted (0-68)

^c Visual analogue scale; 0= best, 10=worst.

^d Disability Index of the Health Assessment Questionnaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

^e CRP: (Normal Range 0.0-1.0 mg/dL)

An improvement in enthesitis and dactylitis scores was observed in each ustekinumab group compared with placebo at Week 24.

Physical Function

Ustekinumab-treated patients showed improvement in physical function compared to patients treated with placebo as assessed by HAQ-DI at Week 24. In both trials, the proportion of HAQ-DI responders (≥ 0.3 improvement in HAQ-DI score) was greater in the ustekinumab 45 mg and 90 mg groups compared to placebo at Week 24.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

SELARSDI (ustekinumab-aekn) injection, is a sterile, preservative-free, clear and colorless to slightly yellow solution and free of visible particles for subcutaneous use. It is supplied as individually packaged, single-dose prefilled syringes.

Single-Dose Prefilled Syringes

- 45 mg/0.5 mL NDC 51759-505-32

- 90 mg/mL NDC 51759-**607**-32

Each prefilled syringe is equipped with a 29 gauge fixed ½ inch needle equipped with a passive safety device and a needle cover. Not made with natural rubber latex.

Storage and Stability

SELARSDI prefilled syringes must be refrigerated at 2°C to 8°C (36°F to 46°F). Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, do not return to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use SELARSDI after the expiration date on the carton or on the prefilled syringe.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that SELARSDI may lower the ability of their immune system to fight infections and to contact their healthcare provider immediately if they develop any signs or symptoms of infection [*see Warnings and Precautions (5.1)*].

Malignancies

Inform patients of the risk of developing malignancies while receiving SELARSDI [*see Warnings and Precautions (5.4)*].

Hypersensitivity Reactions

Advise patients to seek immediate medical attention if they experience any signs or symptoms of serious hypersensitivity reactions and discontinue SELARSDI [*see Warnings and Precautions (5.5)*].

Posterior Reversible Encephalopathy Syndrome (PRES)

Inform patients to immediately contact their healthcare provider if they experience signs and symptoms of PRES (which may include headache, seizures, confusion, or visual disturbances) [*see Warnings and Precautions (5.6)*].

Immunizations

Inform patients that SELARSDI can interfere with the usual response to immunizations and that they should avoid live vaccines [*see Warnings and Precautions (5.7)*].

Administration

Instruct patients to follow sharps disposal recommendations, as described in the Instructions for Use.

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Parsippany, NJ 07054

MEDICATION GUIDE
SELARSDI™ (seh-LARS-dee)
(ustekinumab-aekn)
injection, for subcutaneous use

What is the most important information I should know about SELARSDI?

SELARSDI is a medicine that affects your immune system. SELARSDI can increase your risk of having serious side effects, including:

Serious infections. SELARSDI may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections while taking ustekinumab products, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.

- Your doctor should check you for TB before starting SELARSDI.
- If your doctor feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with SELARSDI and during treatment with SELARSDI.
- Your doctor should watch you closely for signs and symptoms of TB while you are being treated with SELARSDI.

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

Before starting SELARSDI, tell your doctor if you:

- think you have an infection or have symptoms of an infection such as:
 - fever, sweat, or chills
 - muscle aches
 - cough
 - shortness of breath
 - blood in phlegm
 - weight loss
 - warm, red, or painful skin or sores on your body
 - diarrhea or stomach pain
 - burning when you urinate or urinate more often than normal
 - feel very tired
- are being treated for an infection or have any open cuts.
- get a lot of infections or have infections that keep coming back.
- have TB, or have been in close contact with someone with TB.

After starting SELARSDI, call your doctor right away if you have any symptoms of an infection (see above). These may be signs of infections such as chest infections, or skin infections or shingles that could have serious complications. SELARSDI can make you more likely to get infections or make an infection that you have worse.

People who have a genetic problem where the body does not make any of the proteins interleukin 12 (IL-12) and interleukin 23 (IL-23) are at a higher risk for certain serious infections. These infections can spread throughout the body and cause death. People who take SELARSDI may also be more likely to get these infections.

Cancers. SELARSDI may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your doctor if you have ever had any type of cancer. Some people who are receiving ustekinumab products and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with SELARSDI, tell your doctor if you develop any new skin growths.

Posterior Reversible Encephalopathy Syndrome (PRES). PRES is a rare condition that affects the brain and can cause death. The cause of PRES is not known. If PRES is found early and treated, most people recover. Tell your doctor right away if you have any new or worsening medical problems including:

- headache
- seizures
- confusion
- vision problems

What is SELARSDI?

SELARSDI is a prescription medicine used to treat:

- adults and children 6 years and older with moderate or severe psoriasis who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or with pills).
- adults and children 6 years and older with active psoriatic arthritis.

It is not known if SELARSDI is safe and effective in children less than 6 years of age.

Do not take SELARSDI if you are allergic to ustekinumab products or any of the ingredients in SELARSDI. See the end of this Medication Guide for a complete list of ingredients in SELARSDI.

Before you receive SELARSDI, tell your doctor about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **“What is the most important information I should know about SELARSDI?”**
- ever had an allergic reaction to ustekinumab products. Ask your doctor if you are not sure.
- have recently received or are scheduled to receive an immunization (vaccine). People who take SELARSDI should not receive live vaccines. Tell your doctor if anyone in your house needs a live vaccine. The viruses used in some types of live vaccines can spread to people with a weakened immune system, and can cause serious problems. **You should not receive the BCG vaccine during the one year before receiving SELARSDI or one year after you stop receiving SELARSDI.**
- have any new or changing lesions within psoriasis areas or on normal skin.
- are receiving or have received allergy shots, especially for serious allergic reactions. Allergy shots may not work as well for you during treatment with SELARSDI. SELARSDI may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- are pregnant or plan to become pregnant. It is not known if SELARSDI can harm your unborn baby. You and your doctor should decide if you will receive SELARSDI. See **“What should I avoid while using SELARSDI?”**
- received SELARSDI while you were pregnant. It is important that you tell your baby’s healthcare provider before any vaccinations are given to your baby.
- are breastfeeding or plan to breastfeed. SELARSDI can pass into your breast milk.
- Talk to your doctor about the best way to feed your baby if you receive SELARSDI.

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

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I use SELARSDI?

- Use SELARSDI exactly as your doctor tells you to.
- Adults with psoriasis or psoriatic arthritis, and children 6 years and older with psoriasis or psoriatic arthritis will receive SELARSDI as an injection under the skin (subcutaneous injection) as described below.
- **Injecting SELARSDI under your skin**
 - SELARSDI is intended for use under the guidance and supervision of your doctor. In children 6 years and older, it is recommended that SELARSDI be administered by a healthcare provider. If your doctor decides that you or a caregiver may give your injections of SELARSDI at home, you should receive training on the right way to prepare and inject SELARSDI. Your doctor will determine the right dose of SELARSDI for you, the amount for each injection, and how often you should receive it. Do not try to inject SELARSDI yourself until you or your caregiver have been shown how to inject SELARSDI by your doctor or nurse.
 - Inject SELARSDI under the skin (subcutaneous injection) in your upper arms, buttocks, upper legs (thighs) or stomach area (abdomen).
 - Do not give an injection in an area of the skin that is tender, bruised, red or hard.
 - Use a different injection site each time you use SELARSDI.
 - If you inject more SELARSDI than prescribed, call your doctor right away.
 - Be sure to keep all of your scheduled follow-up appointments.

Read the detailed Instructions for Use at the end of this Medication Guide for instructions about how to prepare and inject a dose of SELARSDI, and how to properly throw away (dispose of) used needles and prefilled syringes. The needle and prefilled syringe must never be re-used. SELARSDI can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused portion of SELARSDI.

What should I avoid while using SELARSDI?

You should not receive a live vaccine while taking SELARSDI. See **“Before you receive SELARSDI, tell your doctor about all of your medical conditions, including if you:”**

What are the possible side effects of SELARSDI?

SELARSDI may cause serious side effects, including:

- See **“What is the most important information I should know about SELARSDI?”**
- **Serious allergic reactions.** Serious allergic reactions can occur with SELARSDI. Stop using SELARSDI and get medical help right away if you have any of the following symptoms of a serious allergic reaction:
 - feeling faint
 - chest tightness
 - swelling of your face, eyelids, tongue, or throat
 - skin rash

• **Lung inflammation.** Cases of lung inflammation have happened in some people who receive ustekinumab products and may be serious. These lung problems may need to be treated in a hospital. Tell your doctor right away if you develop shortness of breath or a cough that doesn't go away during treatment with SELARSDI.

Common side effects of SELARSDI include:

• nasal congestion, sore throat, and runny nose	• headache
• upper respiratory infections	• tiredness

These are not all of the possible side effects of SELARSDI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Teva Pharmaceuticals at 1-888-483-8279.

How should I store SELARSDI?

- Store SELARSDI prefilled syringes in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Store SELARSDI in the original carton to protect it from light until time to use it.
- Do not freeze SELARSDI.
- Do not shake SELARSDI.

If needed, individual SELARSDI prefilled syringes may also be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use SELARSDI after the expiration date on the carton or on the prefilled syringe.

Keep SELARSDI and all medicines out of the reach of children.

General information about the safe and effective use of SELARSDI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SELARSDI for a condition for which it was not prescribed. Do not give SELARSDI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about SELARSDI that was written for health professionals.

What are the ingredients in SELARSDI?

Active ingredient: ustekinumab-aekn

Inactive ingredients: histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, sucrose and water for injection.

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Product of Iceland
Marketed By: **Teva Pharmaceuticals**, Parsippany, NJ 07054
For more information, go to www.SELARSDI.com or call 1-888-483-8279.

INSTRUCTIONS FOR USE
SELARSDI™ [seh-LARS-dee]
(ustekinumab-aekn)
injection, for subcutaneous use

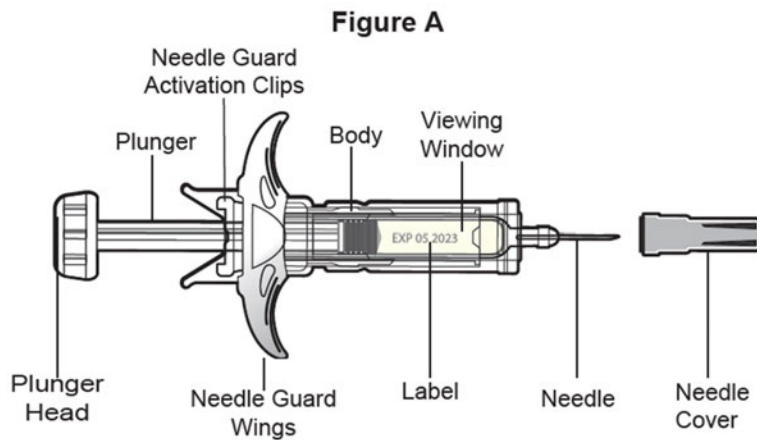
This Instructions for Use contains information on how to inject SELARSDI.

Read this Instructions for Use before you start using SELARSDI. Your doctor or nurse should show you how to prepare and give your injection of SELARSDI the right way.

If you cannot give yourself the injection:

- ask your doctor or nurse to help you, or
- ask someone who has been trained by a doctor or nurse to give your injections.

Do not try to inject SELARSDI yourself until you have been shown how to inject SELARSDI by your doctor, nurse or health professional.



Important Information You Need to Know Before Injecting SELARSDI

- **For subcutaneous injection only (inject directly under the skin).**
- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by your doctor.
 - If your dose is 45 mg, you will receive one 45 mg prefilled syringe.
 - If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. **If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself two injections, one right after the other.**
- Children 12 years of age and older with psoriasis who weigh 132 pounds or more may use a prefilled syringe.
- Check the expiration date on the prefilled syringe and carton. If the expiration date has passed or if the prefilled syringe has been kept at room temperature up to 30°C (86°F) for longer than a maximum single period of 30 days or if the prefilled syringe has been stored above 30°C (86°F), do not use it. If the expiration date has passed or if the prefilled syringe has been stored above 30°C (86°F), call your doctor or pharmacist, or call 1-888-483-8279 for help.
- Make sure the prefilled syringe is not damaged.
- Check your prefilled syringe for any particles or discoloration. Your prefilled syringe should look clear and colorless to slightly yellow solution and should not have any particles.
- **Do not** use if it is frozen, discolored, cloudy, or has particles. Get a new prefilled syringe.
- **Do not shake the prefilled syringe at any time.** Shaking your prefilled syringe may damage your SELARSDI medicine. If your prefilled syringe has been shaken, do not use it. Get a new prefilled syringe.
- To reduce the risk of accidental needle sticks, each prefilled syringe has a needle guard that is automatically activated to cover the needle after you have given your injection. Do not pull back on the plunger at any time.

Storing SELARSDI

- Store SELARSDI in a refrigerator between 36°F to 46°F (2°C to 8°C).
- Store SELARSDI in the original carton to protect it from light until time to use it.
- Do not freeze SELARSDI.
- Do not shake SELARSDI.

If needed, individual prefilled syringes may be stored at room temperature up to 30°C (86°F) for a maximum single period of up to 30 days in the original carton to protect from light. Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided. Once a syringe has been stored at room temperature, it should not be returned to the refrigerator. Discard the syringe if not used within 30 days at room temperature storage. Do not use SELARSDI after the expiration date on the carton or on the prefilled syringe.

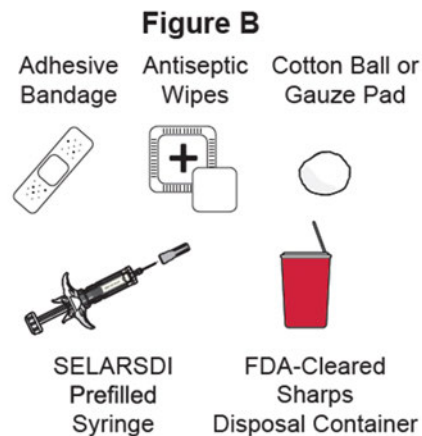
Keep SELARSDI and all medicines out of the reach of children.

Preparing to inject SELARSDI

STEP 1: Gather Supplies

Gather the supplies you will need to prepare and to give your injection. (See Figure B)

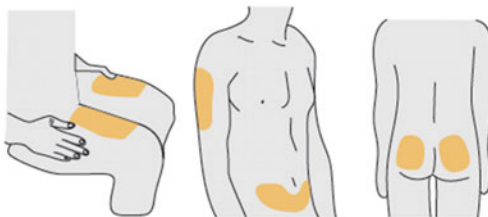
- You will need:
 - antiseptic wipes
 - cotton balls or gauze pads
 - adhesive bandage
 - your prescribed dose of SELARSDI (See Figure A)
 - FDA-cleared sharps disposal container. See “STEP 9: Dispose of the used prefilled syringe.”



STEP 2: Prepare Your Injection Site

- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.
- Choose an injection site around your stomach area (abdomen), buttocks, or upper legs (thighs). If a caregiver is giving you the injection, the outer area of the upper arms may also be used. (See Figure C)
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give your injection.
- **Do not** touch this area again before giving the injection. Let your skin dry before injecting.
- **Do not** fan or blow on the clean area.
- **Do not** inject through clothes.

Figure C
Areas in yellow are recommended
injection sites.

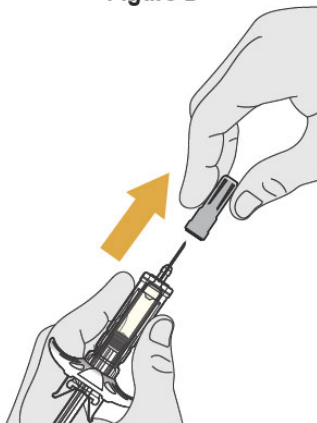


Injecting SELARSDI

STEP 3: Remove Needle Cover

- Remove the needle cover when you are ready to inject your SELARSDI.
- **Do not** touch the plunger or plunger head while removing the needle cover.
- Hold the body of the prefilled syringe with one hand, and pull the needle cover straight off. (See Figure D)
- Put the needle cover in the trash. **Do not** recap.
- You may also see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle or let it touch anything.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place. Call your doctor, nurse or health professional for instructions.

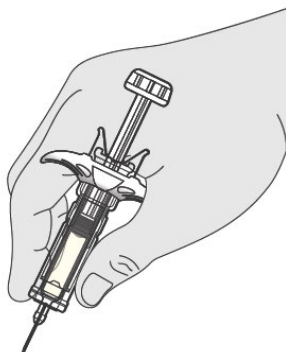
Figure D



STEP 4: Grasp the Syringe

- Hold the body of the prefilled syringe in one hand between the thumb and index fingers. (See Figure E)
- **Do not** pull back on the plunger at any time.

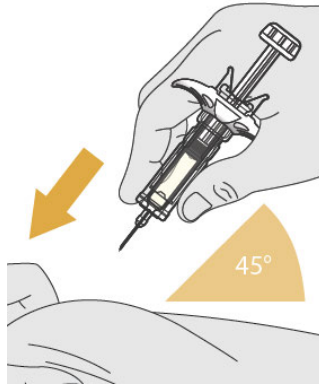
Figure E



STEP 5: Pinch the Skin and Insert Needle

- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure F)**

Figure F



STEP 6: Inject the Drug

- Inject all of the liquid by using your thumb to push in the plunger head all the way in until the plunger head is completely between the needle guard activation clips. **(See Figure G)**

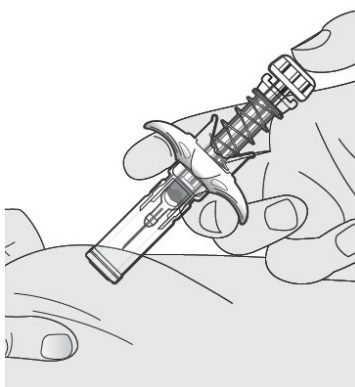
Figure G



STEP 7: Allow Needle to Retract

- 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 H)**

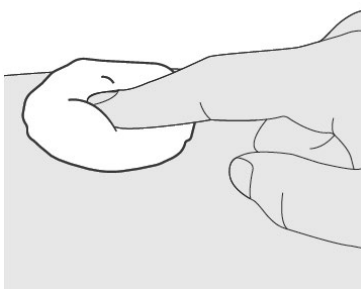
Figure H



STEP 8: Treat Injection Site

- When the needle is pulled out of your skin, there may be a little bleeding at the injection site. This is normal.
- You can press a cotton ball or gauze pad on the skin of the injection site, if needed (**See Figure I**). Do not rub the injection site.
- Cover the injection site with a small adhesive bandage, if necessary.

Figure I



If your dose is 90 mg, you will receive either one 90 mg prefilled syringe or two 45 mg prefilled syringes. If you receive two 45 mg prefilled syringes for a 90 mg dose, you will need to give yourself a second injection right after the first. Repeat Steps 1 to 8 for the second injection using a new syringe.

Choose a different site for the second injection.

Disposing of SELARSDI

STEP 9: Dispose of the used prefilled syringe

- Put the syringe in a FDA-cleared sharps disposal container right away after use (See Figure J). **Do not throw away (dispose of) loose syringes in your household trash.**

Figure J



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
 - made of heavy-duty plastic,
 - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
 - upright and stable during use,
 - leak-resistant, and
 - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this.
- Do not recycle your sharps disposal container.
- If you have any questions, talk to your doctor or pharmacist.

Keep SELARSDI and all medicines out of the reach of children.

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Product of Iceland

Marketed By:
Teva Pharmaceuticals
Parsippany, NJ 07054

For additional information, call Teva Pharmaceuticals at 1-888-483-8279.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Approved: 04/2024





NDC 51759-505-32

 Selarsdi™
(ustekinumab-aekn)
Injection
45 mg/0.5 mL

For Subcutaneous Use

Contains one 45 mg/0.5 mL syringe

Dosage: See Prescribing Information.

Contains no preservative.

Store in a refrigerator at 36°F to 46°F (2°C to 8°C).

Keep in carton to protect from light.

Do not shake. Do not freeze.

Keep out of reach of children.

Single-Dose Prefilled Syringe

Discard Unused Portion

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Product of Iceland

Rx only

Marketed By:

Teva Pharmaceuticals

Parsippany, NJ 07054



LOT: 0000000

EXP: YYYY/MM/DD

Iss. 2/2024

719517

NDC 51759-607-32

 Selarsdi™
(ustekinumab-aekn)
Injection
90 mg/mL

For Subcutaneous Use

Contains one 90 mg/mL syringe

Dosage: See Prescribing Information.

Contains no preservative.

Store in a refrigerator at 36°F to 46°F (2°C to 8°C).

Keep in carton to protect from light.

Do not shake. Do not freeze.

Keep out of reach of children.

Single-Dose Prefilled Syringe

Discard Unused Portion

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Teva Pharmaceuticals

Parsippany, NJ 07054



LOT: 0000000

EXP: YYYY/MM/DD

Iss. 2/2024

719518

NDC 51759-505-32
Selarsdi
(ustekinumab-aekn)
Injection
45 mg/0.5 mL
For Subcutaneous Use
Store at 36°F to 46°F (2°C to 8°C).
Protect from light.
Do not shake. Do not freeze.
Mfd By: Amgen USA Inc.
U.S. License No. 2225
Single-Dose Prefilled Syringe
Discard Unused Portion

LOT: 0000000
EXP: YYYY/MM/DD
Iss. 3/2024 Rx only
719515

NDC 51759-607-32
Selarsdi
(ustekinumab-aekn)
Injection
90 mg/mL
For Subcutaneous Use
Store at 36°F to 46°F (2°C to 8°C).
Protect from light.
Do not shake. Do not freeze.
Mfd By: Amgen USA Inc.
U.S. License No. 2225
Single-Dose Prefilled Syringe
Discard Unused Portion

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