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

WEZLANA™ (ustekinumab-auub) injection, for subcutaneous or intravenous use
Initial U.S. Approval: 2023

WEZLANA™ (ustekinumab-auub) is biosimilar* to STELARA® (ustekinumab).

----------INDICATIONS AND USAGE----------
WEZLANA is a human interleukin -12 and -23 antagonist indicated for the treatment of:
Adult patients with:
- *moderate to severe plaque psoriasis (Ps)* who are candidates for phototherapy or systemic therapy. (1.1)
- *active psoriatic arthritis (PsA)*. (1.2)
- *moderately to severely active Crohn's disease (CD)*. (1.3)
- *moderately to severely active ulcerative colitis.* (1.4)

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) 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)	Dosage Regimen
less than 60 kg	0.75 mg/kg
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 RecommendedDosage (2.2): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	Dosage Regimen
less than 60 kg	0.75 mg/kg
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severeplaque psoriasis	90 mg

Crohn's Disease and Ulcerative Colitis Initial Adult Intravenous Recommended Dosage (2.3):
A single intravenous infusion using weight-based dosing:

Weight Range (kilograms)	Recommended Dosage
up to 55 kg	260 mg (2 vials)
greater than 55 kg to 85 kg	390 mg (3 vials)
greater than 85 kg	520 mg (4 vials)

Crohn's Disease and Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage (2.3):
A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

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

Intravenous Infusion (3)
- Injection: 130 mg/26 mL (5 mg/mL) solution in a single-dose vial (3)

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

----------WARNINGS AND PRECAUTIONS---------
- Infections: Serious infections have occurred. Do not start WEZLANA during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing WEZLANA until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported

in patients genetically deficient in IL-12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with WEZLANA. Initiate treatment of latent TB before administering WEZLANA. (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: Anaphylaxis or other clinically significant hypersensitivity reactions may occur. (5.5)
- Posterior Reversible Encephalopathy Syndrome (PRES): If PRES is suspected, treat promptly and discontinue WEZLANA. (5.6)
- 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 WEZLANA and institute appropriate treatment. (5.9)

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

Most common adverse reactions are:
- Psoriasis (≥ 3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease, induction (≥ 3%): vomiting. (6.1)
- Crohn's Disease, maintenance (≥ 3%): nasopharyngitis, injection site erythema, vulvovaginal candidiasis/mycotic infection, bronchitis, pruritus, urinary tract infection, and sinusitis. (6.1)
- Ulcerative colitis, induction (≥ 3%): nasopharyngitis. (6.1)
- Ulcerative colitis, maintenance (≥ 3%): nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Issued: x/202x

***** 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 WEZLANA 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.

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Psoriasis (Ps)

WEZLANA is indicated for the treatment of patients 6 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

1.2 Psoriatic Arthritis (PsA)

WEZLANA is indicated for the treatment of patients 6 years or older with active psoriatic arthritis.

1.3 Crohn's Disease (CD)

WEZLANA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease.

1.4 Ulcerative Colitis

WEZLANA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 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 WEZLANA subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.
The recommended dose of WEZLANA for pediatric patients (6–17 years old) based on body weight is shown below (Table 1).

Table 1. Recommended Dose of WEZLANA for Subcutaneous Injection in Pediatric Patients (6–17 years old) With Psoriasis

Body Weight of Patient at the Time of Dosing	Recommended Dose
less than 60 kg	0.75 mg/kg
60 kg to 100 kg	45 mg
more than 100 kg	90 mg

For pediatric patients weighing less than 60 kg, the administration volume for the recommended dose (0.75 mg/kg) is shown in Table 2; withdraw the appropriate volume from the single-dose vial.

Table 2. Injection Volumes of WEZLANA 45 mg/0.5 mL Single Dose Vials for Pediatric Patients (6–17 years old) With Psoriasis and Pediatric Patients (6-17 years old) With Psoriatic Arthritis* Weighing Less Than 60 kg

Body Weight (kg) at the time of dosing	Dose (mg)	Volume of injection (mL)
15	11.3	0.12
16	12.0	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15.0	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18.0	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21.0	0.23
29	21.8	0.24
30	22.5	0.25
31	23.3	0.26
32	24	0.27
33	24.8	0.27
34	25.5	0.28
35	26.3	0.29
36	27	0.3
37	27.8	0.31
38	28.5	0.32
39	29.3	0.32
40	30	0.33
41	30.8	0.34
42	31.5	0.35
43	32.3	0.36
44	33	0.37
45	33.8	0.37
46	34.5	0.38
47	35.3	0.39
48	36	0.4

Body Weight (kg) at the time of dosing	Dose (mg)	Volume of injection (mL)
49	36.8	0.41
50	37.5	0.42
51	38.3	0.42
52	39	0.43
53	39.8	0.44
54	40.5	0.45
55	41.3	0.46
56	42	0.46
57	42.8	0.47
58	43.5	0.48
59	44.3	0.49

* Refer to 2.2 Psoriatic Arthritis; Subcutaneous Pediatric Dosage Regimen.

2.2 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 WEZLANA subcutaneously at Weeks 0 and 4, then every 12 weeks thereafter.

The recommended dose of WEZLANA for pediatric patients (6 to 17 years old) with psoriatic arthritis, based on body weight, is shown below (Table 3).

Table 3. Recommended Dose of WEZLANA 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
less than 60 kg*	0.75 mg/kg
60 kg or more	45 mg
greater than 100 kg with co-existent moderate-to-severe plaque psoriasis	90 mg

* For pediatric patients weighing less than 60 kg, the administration volume for the recommended dose (0.75 mg/kg) is shown in Table 2; withdraw the appropriate volume from the single-dose vial.

2.3 Crohn's Disease and Ulcerative Colitis

Intravenous Induction Adult Dosage Regimen

A single intravenous infusion dose of WEZLANA using the weight-based dosage regimen specified in Table 4 *[see Instructions for dilution of WEZLANA 130 mg vial for intravenous infusion (2.6)]*.

Table 4. Initial Intravenous Dosage of WEZLANA

Body Weight of Patient at the time of dosing	Dose	Number of 130 mg/26 mL (5 mg/mL) WEZLANA vials
55 kg or less	260 mg	2
more than 55 kg to 85 kg	390 mg	3
more than 85 kg	520 mg	4

Subcutaneous Maintenance Adult Dosage Regimen

The recommended maintenance dosage is a subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

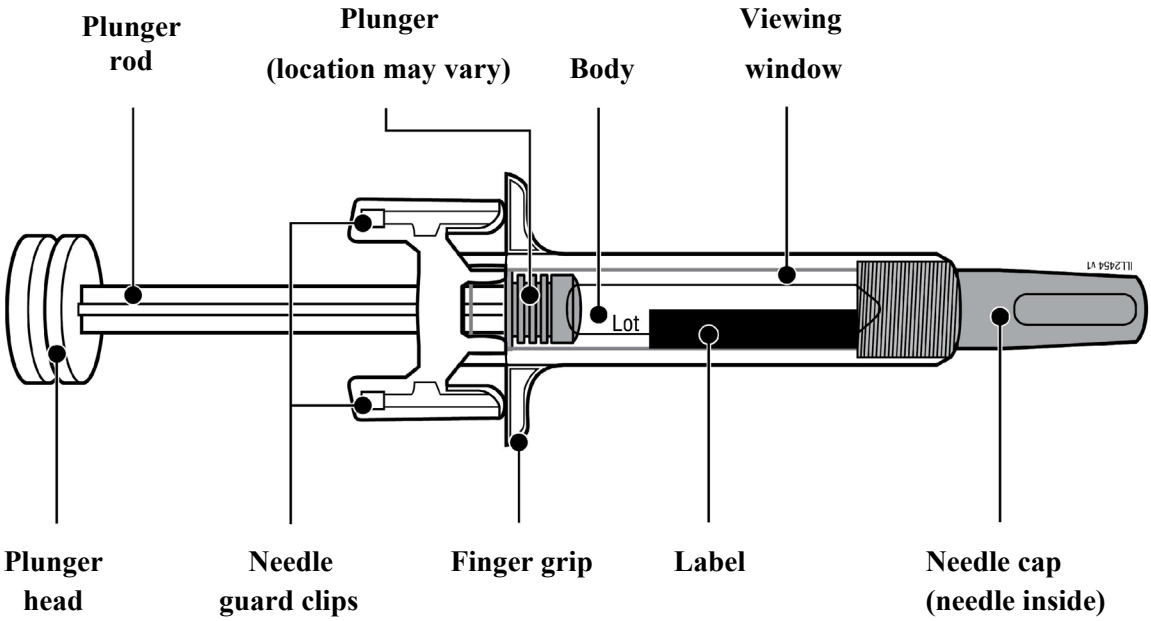
2.4 General Considerations for Administration

- WEZLANA is intended for use under the guidance and supervision of a physician. WEZLANA should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician. 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 WEZLANA be administered by a healthcare provider. If a physician determines that it is appropriate, a patient may self-inject, or a caregiver may inject WEZLANA after proper training in subcutaneous injection technique. Patients should be instructed to follow the directions provided in the Medication Guide *[see Medication Guide]*.
- The needle cap on the prefilled syringe does not contain dry natural rubber (a derivative of 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-dose vial, a 1 mL syringe with a 27 gauge, ½ inch needle is recommended.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. WEZLANA is a clear to opalescent and colorless to light yellow solution. Do not use WEZLANA if it is discolored or cloudy, or if other particulate matter is present. WEZLANA does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

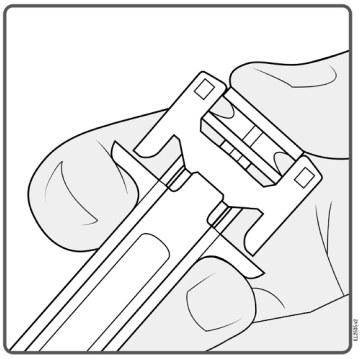
2.5 Instructions for Administration of WEZLANA Prefilled Syringes Equipped with Needle Safety Guard

Refer to the diagram below for the provided instructions.

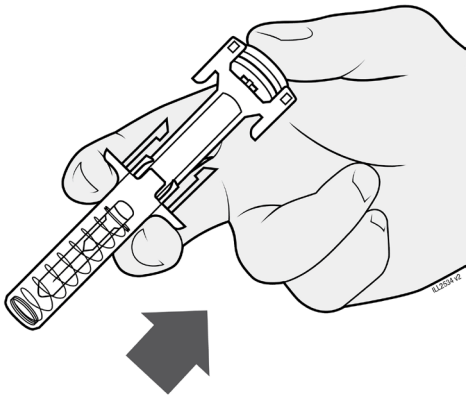
To prevent premature activation of the needle safety guard, do not touch the NEEDLE GUARD CLIPS at any time during use.



- Hold the BODY and remove the NEEDLE CAP. **Do not hold the PLUNGER or PLUNGER HEAD while removing the NEEDLE CAP or the PLUNGER may move. Do not use the prefilled syringe if it is dropped without the NEEDLE CAP in place**.
  Inject WEZLANA subcutaneously as recommended *[see Dosage and Administration (2.1, 2.2, 2.3)]*.
- Inject all of the medication by pushing in the PLUNGER until the PLUNGER HEAD is completely between the finger grip. **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.

2.6 Preparation and Administration of WEZLANA 130 mg/26 mL (5 mg/mL) Vial for Intravenous Infusion (Crohn's Disease and Ulcerative Colitis)

WEZLANA solution for intravenous infusion must be diluted, prepared and infused by a healthcare professional using aseptic technique.

1. Calculate the dose and the number of WEZLANA vials needed based on patient weight (Table 4). Each 26 mL vial of WEZLANA contains 130 mg of ustekinumab-auub.
2. Withdraw, and then discard a volume of the 0.9% Sodium Chloride Injection, USP from the 250 mL infusion bag equal to the volume of WEZLANA to be added (discard 26 mL sodium chloride for each vial of WEZLANA needed, for 2 vials- discard 52 mL, for 3 vials- discard 78 mL, 4 vials- discard 104 mL). Alternatively, a 250 mL infusion bag containing 0.45% Sodium Chloride Injection, USP may be used.
3. Withdraw 26 mL of WEZLANA from each vial needed and add it to the 250 mL infusion bag. The final volume in the infusion bag should be 250 mL. Gently mix.
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
5. Infuse the diluted solution over a period of at least one hour. Once diluted, the infusion should be completely administered within eight hours of the dilution in the infusion bag.
6. Use only an infusion set with an in-line, sterile, non-pyrogenic, low protein -binding filter (pore size 0.2 micrometer).
7. Do not infuse WEZLANA concomitantly in the same intravenous line with other agents.
8. WEZLANA does not contain preservatives. Each vial is for one-time use in only one patient. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.

Storage

If necessary, the diluted infusion solution may be kept at room temperature up to 25°C (77°F) for up to 7 hours. Storage time at room temperature begins once the diluted solution has been prepared. The infusion should be completed within 8 hours after the dilution in the infusion bag (cumulative time after preparation including the storage and the infusion period). Do not freeze. Discard any unused portion of the infusion solution.

3 DOSAGE FORMS AND STRENGTHS

WEZLANA (ustekinumab-auub) is a clear to opalescent and colorless to light yellow solution.

Subcutaneous Injection

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

- Injection: 45 mg/0.5 mL solution in a single -dose vial

Intravenous Infusion

- Injection: 130 mg/26 mL (5 mg/mL) solution in a single -dose vial

4 CONTRAINDICATIONS

WEZLANA is contraindicated in patients with clinically significant hypersensitivity to ustekinumab products or to any of the excipients *[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 studies included the following:

- *Psoriasis*: diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections.
- *Psoriatic arthritis*: cholecystitis.
- *Crohn's disease*: anal abscess, gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeria meningitis.
- *Ulcerative colitis*: gastroenteritis, ophthalmic herpes zoster, pneumonia, and listeriosis.

Treatment with WEZLANA should not be initiated 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 WEZLANA 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 WEZLANA and consider discontinuing WEZLANA 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 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 ustekinumab products may 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 WEZLANA.

Do not administer WEZLANA to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior

to administering WEZLANA. Consider anti-tuberculosis therapy prior to initiation of WEZLANA 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 WEZLANA 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 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 ustekinumab products has not been evaluated in patients who have a history of malignancy or who have a known malignancy.

There have been postmarketing 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. All patients receiving WEZLANA should be monitored for the appearance of non-melanoma skin cancer. Patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely *[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 WEZLANA.

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, psoriatic arthritis and Crohn's disease. 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 WEZLANA for signs and symptoms of PRES. If PRES is suspected, promptly administer appropriate treatment, and discontinue WEZLANA.

5.7 Immunizations

Prior to initiating therapy with WEZLANA, patients should receive all age-appropriate immunizations as recommended by current immunization guidelines. Patients being treated with WEZLANA should not receive live vaccines. BCG vaccines should not be given during treatment with WEZLANA 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 WEZLANA because of the potential risk for shedding from the household contact and transmission to patient.

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

5.8 Concomitant Therapies

In clinical studies of psoriasis, the safety of ustekinumab products in combination with other biologic immunosuppressive agents or phototherapy was not 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 Concomitant Therapies (7.1),*

Nonclinical Toxicology (13.1)].

5.9 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 WEZLANA 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)]*

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 psoriasis subjects, 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 5 summarizes the adverse reactions that occurred at a rate of at least 1% and at a higher rate in the ustekinumab groups than the placebo group during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14)]*.

Table 5. Adverse Reactions Reported by ≥ 1% of Subjects Through Week 12 in Ps STUDY 1 and Ps STUDY 2

		Ustekinumab	
Subjects treated	**Placebo 665**	**45 mg 664**	**90 mg 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 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 studies *[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 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 psoriasis clinical studies (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 psoriasis clinical studies (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 studies were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in ustekinumab-treated patients during the controlled and uncontrolled portions of studies 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 studies of pediatric subjects with moderate to severe plaque psoriasis. Ps STUDY 3 evaluated safety for up to 60 weeks in 110 adolescents (12 to 17 years old). Ps STUDY 4 evaluated safety for up to 56 weeks in 44 children (6 to 11years old). The safety profile in pediatric subjects was similar to the safety profile from studies in adults with plaque psoriasis.

Psoriatic Arthritis

The safety of ustekinumab was assessed in 927 subjects in two randomized, double-blind, placebo-controlled studies 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 studies. 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 studies.

Crohn's Disease

The safety of ustekinumab was assessed in 1407 subjects with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450) in three randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. These 1407 subjects included 40 subjects who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In Studies CD-1 and CD-2 there were 470 subjects who received ustekinumab 6 mg/kg as a weight-based single intravenous induction dose and 466 who received placebo *[see Dosage and Administration (2.3)]*. Subjects who were responders in either Study CD-1 or CD-2 were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, or placebo for 44 weeks in Study CD-3. Subjects in these 3 studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents [azathioprine (AZA), 6-mercaptopurine (6-MP), methotrexate (MTX)], oral corticosteroids (prednisone or budesonide), and/or antibiotics for their Crohn's disease *[see Clinical Studies (14.4)]*.

The overall safety profile of ustekinumab was consistent with the safety profile seen in the adult psoriasis and psoriatic arthritis clinical studies. Common adverse reactions in Studies CD-1 and CD-2 and in Study CD-3 are listed in Tables 6 and 7, respectively.

Table 6. Common Adverse Reactions Through Week 8 in Studies CD-1 and CD-2 Occurring in ≥ 3% of Ustekinumab-Treated Subjects and Higher Than Placebo

	Placebo N = 466	**Ustekinumab 6 mg/kg single intravenous induction dose N = 470**
Vomiting	3%	4%

Other less common adverse reactions reported in subjects in Studies CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 7. Common Adverse Reactions Through Week 44 in Study CD-3 Occurring in ≥ 3% of Ustekinumab-Treated Subjects and Higher Than Placebo

	Placebo N = 133	Ustekinumab 90 mg subcutaneous maintenance dose every 8 weeks N = 131
Nasopharyngitis	8%	11%
Injection site erythema	0	5%
Vulvovaginal candidiasis/mycotic infection	1%	5%
Bronchitis	3%	5%
Pruritus	2%	4%
Urinary tract infection	2%	4%
Sinusitis	2%	3%

Infections

In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, and pneumonia. In addition, listeria meningitis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the Crohn's disease clinical studies, 0.2% of ustekinumab-treated subjects (0.36 events per hundred patient-years) and 0.2% of placebo-treated subjects (0.58 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.2% of ustekinumab-treated subjects (0.27 events per hundred patient-years) and in none of the placebo-treated subjects.

Hypersensitivity Reactions Including Anaphylaxis

In CD studies, two patients reported hypersensitivity reactions following ustekinumab administration. One patient experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single subcutaneous administration (0.1% of patients receiving subcutaneous ustekinumab). In addition, one patient experienced signs and symptoms consistent with or related to a hypersensitivity reaction (chest discomfort, flushing, urticaria, and increased body temperature) after the initial intravenous ustekinumab dose (0.08% of patients receiving intravenous ustekinumab). These patients were treated with oral antihistamines or corticosteroids and in both cases, symptoms resolved within an hour.

Ulcerative Colitis

The safety of ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical studies (UC-1 [IV induction] and UC-2 [SC maintenance]) in 960 adult subjects with moderately to severely active ulcerative colitis *[see Clinical Studies (14.5)]*. The overall safety profile of ustekinumab in patients with ulcerative colitis was consistent with the safety profile seen across all approved indications. Adverse reactions reported in at least 3% of ustekinumab-treated subjects and at a higher rate than placebo were:

- Induction (UC-1): nasopharyngitis (7% vs 4%).
- Maintenance (UC-2): nasopharyngitis (24% vs 20%), headache (10% vs 4%), abdominal pain (7% vs 3%), influenza (6% vs 5%), fever (5% vs 4%), diarrhea (4% vs 1%), sinusitis (4% vs 1%), fatigue (4% vs 2%), and nausea (3% vs 2%).

Infections

In patients with ulcerative colitis, serious or other clinically significant infections included gastroenteritis and pneumonia. In addition, listeriosis and ophthalmic herpes zoster were reported in one patient each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the ulcerative colitis clinical studies, 0.4% of ustekinumab-treated subjects (0.48 events per hundred patient-years) and 0.0% of placebo-treated subjects (0.00 events per hundred patient-years) developed non-melanoma skin cancer. Malignancies other than non-melanoma skin cancers occurred in 0.5% of ustekinumab-treated subjects (0.64 events per hundred patient-years) and 0.2% of placebo-treated subjects (0.40 events per hundred patient-years).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ustekinumab products may be misleading.

Approximately 6 to 12.4% of subjects treated with ustekinumab in psoriasis and psoriatic arthritis clinical studies developed antibodies to ustekinumab, which were generally low-titer. In psoriasis clinical studies, antibodies to ustekinumab were associated with reduced or undetectable serum ustekinumab concentrations and reduced efficacy. In psoriasis studies, the majority of subjects who were positive for antibodies to ustekinumab had neutralizing antibodies. In Crohn's disease and ulcerative colitis clinical studies, 2.9% and 4.6% of subjects, respectively, developed antibodies to ustekinumab when treated with ustekinumab for approximately one year. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was seen.

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 product exposure.

Immune system disorders: Serious hypersensitivity reactions (including anaphylaxis and angioedema), other hypersensitivity reactions (including rash and urticaria) *[see Warnings and Precautions (5.5)]*.

Infections and infestations: Lower respiratory tract infection (including opportunistic fungal infections and tuberculosis) *[see Warnings and Precautions (5.1)]*.

Neurological disorders: Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.6)].*

Respiratory, thoracic and mediastinal disorders: Interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia *[see Warnings and Precautions (5.9)].*

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

7 DRUG INTERACTIONS

7.1 Concomitant Therapies

In psoriasis studies the safety of ustekinumab products in combination with immunosuppressive agents or phototherapy has not been evaluated *[see Warnings and Precautions (5.8)]*. In psoriatic arthritis studies, concomitant MTX use did not appear to influence the safety or efficacy of ustekinumab. In Crohn's disease and ulcerative colitis induction studies, immunomodulators (6-MP, AZA, MTX) were used concomitantly in approximately 30% of subjects and corticosteroids were used concomitantly in approximately 40% and 50% of Crohn's disease and ulcerative colitis subjects, respectively. 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, TNFα, IFN) during chronic inflammation. Thus, ustekinumab products, an antagonist of IL-12 and IL-23, could normalize the formation of CYP450 enzymes. Upon initiation of WEZLANA 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)]*.

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 on the use of ustekinumab products in pregnant women are insufficient to inform a drug associated risk *[see Data]*. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the human exposure at the maximum recommended human subcutaneous 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.

Data

Human Data

Limited data on use of ustekinumab products in pregnant women from observational studies, published case reports and postmarketing surveillance are insufficient to inform a drug associated risk.

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 human subcutaneous exposure 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

There are no data on the presence of ustekinumab products in human milk, the effects on the breastfed infant, or the effects on milk production. Ustekinumab was present in the milk of lactating monkeys administered ustekinumab. Due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk. Maternal IgG is known to be present in human milk. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because ustekinumab is a large molecule and is degraded in the gastrointestinal tract. However, if ustekinumab products are transferred into human milk the effects of local exposure in the gastrointestinal tract are unknown.

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

8.4 Pediatric Use

Plaque Psoriasis

The safety and effectiveness of WEZLANA have been established for the treatment of moderate to severe plaque psoriasis in pediatric patients 6 to 17 years old. Use of WEZLANA in patients 12 to less than 17 years old is supported by WEZLANA's approval as a biosimilar to ustekinumab and evidence from a multicenter, randomized, 60-week trial (Ps STUDY 3) of ustekinumab that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older *[see Adverse Reactions (6.1), Clinical Studies (14.2)]*.

Use of WEZLANA in patients 6 to 11 years is supported by WEZLANA's approval as a biosimilar to ustekinumab and evidence from an open-label, single-arm, efficacy, safety, and pharmacokinetics study (Ps STUDY 4) of ustekinumab in 44 subjects *[see Adverse Reactions (6.1), Pharmacokinetics (12.3)]*.

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

Psoriatic Arthritis

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

Use of WEZLANA in these age groups is supported by WEZLANA's approval as a biosimilar to ustekinumab and evidence from adequate and well controlled studies 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 studies 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 WEZLANA have not been established in pediatric patients less than 6 years old with psoriatic arthritis.

Crohn's Disease and Ulcerative Colitis

The safety and effectiveness of WEZLANA have not been established in pediatric patients with Crohn's disease or ulcerative colitis.

8.5 Geriatric Use

Of the 6709 patients exposed to ustekinumab, a total of 340 were 65 years or older (183 patients with psoriasis, 65 patients with psoriatic arthritis, 58 patients with Crohn's disease and 34 patients with ulcerative colitis), and 40 patients were 75 years or older. Although no overall differences in safety or efficacy were observed between older and younger patients, the number of patients aged 65 and over is not sufficient to determine whether they respond differently from younger patients.

10 OVERDOSAGE

Single doses up to 6 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

Ustekinumab-auub, a human IgG1κ monoclonal antibody, is a human interleukin -12 and -23 antagonist. Using DNA recombinant technology, ustekinumab-auub is produced in a mammalian cell line (Chinese Hamster Ovary). The manufacturing process contains steps for the clearance of viruses. Ustekinumab-auub is comprised of 1326 amino acids and has an estimated molecular mass that ranges from 148 to 150 kDa.

WEZLANA (ustekinumab-auub) injection is a sterile, preservative-free, clear to opalescent and colorless to light yellow solution with a pH of 6.0.

WEZLANA for Subcutaneous Use

Available as 45 mg of ustekinumab-auub in 0.5 mL and 90 mg of ustekinumab-auub in 1 mL, supplied as a sterile solution in a single-dose prefilled syringe with a 27 gauge fixed ½ inch needle and as 45 mg of ustekinumab-auub in 0.5 mL in a single-dose Type I glass vial with a coated stopper. The syringe is fitted with a passive needle guard and a needle cap that does not contain dry natural rubber (a derivative of latex).

Each 0.5 mL prefilled syringe or vial delivers 45 mg ustekinumab-auub, histidine (0.23 mg) and histidine hydrochloride monohydrate (0.36 mg), Polysorbate 80 (0.02 mg), and sucrose (38 mg).

Each 1 mL prefilled syringe delivers 90 mg ustekinumab-auub, histidine (0.46 mg) and histidine hydrochloride monohydrate (0.72 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

WEZLANA for Intravenous Infusion

Available as 130 mg of ustekinumab-auub in 26 mL, supplied as a single-dose Type I glass vial with a coated stopper.

Each 26 mL vial delivers 130 mg ustekinumab-auub, edetate disodium (0.47 mg), histidine (20 mg), histidine hydrochloride monohydrate (27 mg), methionine (10.4 mg), Polysorbate 80 (10.4 mg) and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab products are human IgG1κ monoclonal antibody that binds 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. The cytokines IL-12 and IL-23 have been implicated as important contributors to the chronic inflammation that is a hallmark of Crohn's disease and ulcerative colitis. In animal models of colitis, genetic absence or antibody blockade of the p40 subunit of IL-12 and IL-23, the target of ustekinumab products, was shown to be protective.

12.2 Pharmacodynamics

Psoriasis

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 subjects with psoriasis.

Ulcerative Colitis

In both study UC-1 (induction) and study UC-2 (maintenance), a positive relationship was observed between exposure and rates of clinical remission, clinical response, and endoscopic improvement. The response rate approached a plateau at the ustekinumab exposures associated with the recommended dosing regimen for maintenance treatment *[see Clinical Studies (14.5)]*.

12.3 Pharmacokinetics

Absorption

In adult subjects with 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 psoriasis.

Following multiple subcutaneous doses of ustekinumab in adult subjects with psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. The mean (±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.

Following the recommended intravenous induction dose, mean ±SD peak serum ustekinumab concentration was 125.2 ± 33.6 mcg/mL in patients with Crohn's disease, and 129.1 ± 27.6 mcg/mL in patients with ulcerative colitis. Starting at Week 8, the recommended subcutaneous maintenance dosing of 90 mg ustekinumab was administered every 8 weeks. Steady state ustekinumab concentration was achieved by the start of the second maintenance dose. There was no apparent accumulation in ustekinumab concentration over time when given subcutaneously every 8 weeks. Mean ±SD steady-state trough concentration was 2.5 ± 2.1 mcg/mL in patients with Crohn's disease, and 3.3 ± 2.3 mcg/mL in patients with ulcerative colitis for 90 mg ustekinumab administered every 8 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 Crohn's disease and 3.0 L (95% CI: 2.96, 3.07) in patients with ulcerative colitis. The total volume of distribution at steady state was 4.6 L in patients with Crohn's disease and 4.4 L in patients with ulcerative colitis.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all psoriasis studies following subcutaneous administration. Population pharmacokinetic analyses showed that the clearance of ustekinumab was 0.19 L/day (95% CI: 0.185, 0.197) in patients with Crohn's disease and 0.19 L/day (95% CI: 0.179, 0.192) in patients with ulcerative colitis with an estimated median terminal half-life of approximately 19 days for both IBD (Crohn's disease and ulcerative colitis) populations.

These results indicate the pharmacokinetics of ustekinumab were similar between patients with Crohn's disease and ulcerative colitis.

Metabolism

The metabolic pathway of ustekinumab products have not been characterized. As a human IgG1κ 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 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 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 psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week 28. At Week 28, the mean ±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 adolescent subjects 12 to 17 years of age.

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

In patients with Crohn's disease and ulcerative colitis, population pharmacokinetic analyses did not indicate changes in ustekinumab clearance with concomitant use of corticosteroids or immunomodulators (AZA, 6-MP, or MTX); and serum ustekinumab concentrations were not impacted by concomitant use of these medications.

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 Psoriasis

Two multicenter, randomized, double-blind, placebo-controlled studies (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 studies.

Ps STUDY 1 enrolled 766 subjects and Ps 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 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 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 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.

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 8 below.

Table 8. Clinical Outcomes Ps STUDY 1 and Ps STUDY 2

Week 12	**Ps STUDY 1**			**Ps STUDY 2**		
	Placebo	**ustekinumab**		**Placebo**	**ustekinumab**	
		45 mg	**90 mg**		**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 similar 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 9 below).

Table 9. 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 at Week 12*						
≤ 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 at Week 12*						
≤ 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 study 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 Adolescent Subjects with Plaque Psoriasis

A multicenter, randomized, double blind, placebo-controlled study (Ps STUDY 3) enrolled 110 adolescent 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 adolescent 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 patients 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 study agent.

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 10.

Table 10. Summary of Efficacy Endpoints in the Adolescent Psoriasis Study at Week 12

	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 and Table 2.

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 studies 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 studies 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 studies, 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 11). 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 TNFα exposure.

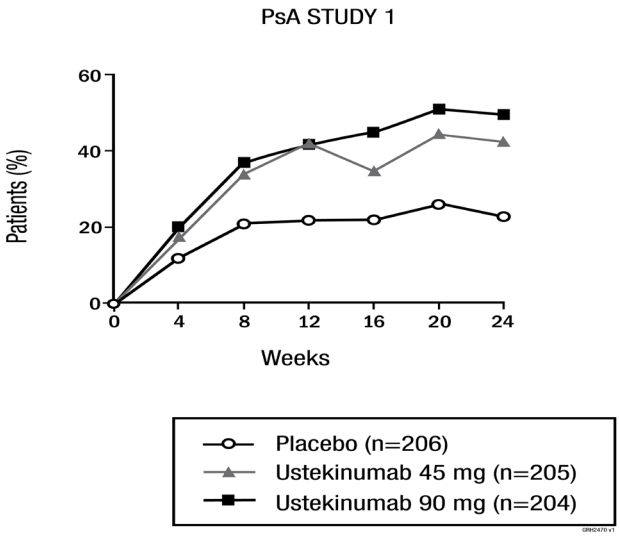
Table 11. ACR 20, ACR 50, ACR 70 and PASI 75 responses in Ps A STUDY 1 and Ps A STUDY 2 at Week 24

	PsA STUDY 1 ustekinumab			PsA STUDY 2 ustekinumab		
	Placebo	**45 mg**	**90 mg**	**Placebo**	**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 ≥ 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 ≥ 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 12.

Table 12. Mean change from baseline in ACR components at Week 24

	Placebo	Ps A STUDY 1 ustekinumab	
		45 mg	90 mg
	(N = 206)	(N = 205)	(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 studies, 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.

14.4 Crohn's Disease

Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical studies in adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450). There were two 8-week intravenous induction studies (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance study (CD-3) representing 52 weeks of therapy. Patients in CD-1 had failed or were intolerant to treatment

with one or more TNF blockers, while patients in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker.

Studies CD-1 and CD-2

In studies CD-1 and CD-2, 1409 patients were randomized, of whom 1368 (CD-1, n = 741; CD-2, n = 627) were included in the final efficacy analysis. Induction of clinical response (defined as a reduction in CDAI score of greater than or equal to 100 points or CDAI score of less than 150) at Week 6 and clinical remission (defined as a CDAI score of less than 150) at Week 8 were evaluated. In both studies, patients were randomized to receive a single intravenous administration of ustekinumab at either approximately 6 mg/kg, placebo (see Table 4), or 130 mg (a lower dose than recommended).

In Study CD-1, patients had failed or were intolerant to prior treatment with a TNF blocker: 29% patients had an inadequate initial response (primary non-responders), 69% responded but subsequently lost response (secondary non-responders) and 36% were intolerant to a TNF blocker. Of these patients, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the study, approximately 46% of the patients were receiving corticosteroids and 31% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 319 in the ustekinumab approximately 6 mg/kg group and 313 in the placebo group.

In Study CD-2, patients had failed or were intolerant to prior treatment with corticosteroids (81% of patients), at least one immunomodulator (6-MP, AZA, MTX; 68% of patients), or both (49% of patients). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the study, approximately 39% of the patients were receiving corticosteroids and 35% of the patients were receiving immunomodulators (AZA, 6-MP, MTX). The median baseline CDAI score was 286 in the ustekinumab and 290 in the placebo group.

In these induction studies, a greater proportion of patients treated with ustekinumab (at the recommended dose of approximately 6 mg/kg dose) achieved clinical response at Week 6 and clinical remission at Week 8 compared to placebo (see Table 13 for clinical response and remission rates).

Clinical response and remission were significant as early as Week 3 in ustekinumab-treated patients and continued to improve through Week 8.

Table 13. Induction of Clinical Response and Remission in CD-1[*] and CD-2[†]

	CD-1 n = 741			CD-2 n = 627		
	Placebo N = 247	**Ustekinumab[‡] N = 249**	**Treatment difference and 95% CI**	**Placebo N = 209**	**Ustekinumab[‡] N = 209**	**Treatment difference and 95% CI**
Clinical Response (100 point), Week 6	53 (21%)	84 (34%)[§]	12% (4%, 20%)	60 (29%)	116 (56%)[¶]	27% (18%, 36%)
Clinical Remission, Week 8	18 (7%)	52 (21%)[¶]	14% (8%, 20%)	41 (20%)	84 (40%)[¶]	21% (12%, 29%)
Clinical Response (100 point), Week 8	50 (20%)	94 (38%)[¶]	18% (10%, 25%)	67 (32%)	121 (58%)[¶]	26% (17%, 35%)
70 Point Response, Week 6	75 (30%)	109 (44%)[§]	13% (5%, 22%)	81 (39%)	135 (65%)[¶]	26% (17%, 35%)
70 Point Response, Week 3	67 (27%)	101 (41%)[§]	13% (5%, 22%)	66 (32%)	106 (51%)[¶]	19% (10%, 28%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI score by at least 100 points or being in clinical remission: 70 point response is defined as reduction in CDAI score by at least 70 points

* Patient population consisted of patients who failed or were intolerant to TNF blocker therapy.
† Patient population consisted of patients who failed or were intolerant to corticosteroids or immunomodulators (e.g., 6-MP, AZA, MTX) and previously received but not failed a TNF blocker or were never treated with a TNF blocker.
‡ Infusion dose of ustekinumab using the weight-based dosage regimen specified in Table 4.
§ $0.001 \leq p < 0.01$.
¶ $p < 0.001$.

Study CD-3

The maintenance study (CD-3) evaluated 388 patients who achieved clinical response (≥ 100 points reduction in CDAI score) at Week 8 with either induction dose of ustekinumab in studies CD-1 or CD-2. Patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks or placebo for 44 weeks (see Table 14).

Table 14. Clinical Response and Remission in CD-3 (Week 44; 52 weeks from initiation of the induction dose)

	Placebo* N = 131†	**90 mg ustekinumab every 8 weeks N = 128†**	**Treatment difference and 95% CI**
Clinical Remission	47 (36%)	68 (53%)‡	17% (5%,29%)
Clinical Response	58 (44%)	76 (59%)§	15% (3%,27%)
Clinical Remission in patients in remission at the start of maintenance therapy ¶	36/79 (46%)	52/78 (67%)‡	21% (6%, 36%)

Clinical remission is defined as CDAI score < 150; Clinical response is defined as reduction in CDAI of at least 100 points or being in clinical remission
* The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.
† Patients who achieved clinical response to ustekinumab at the end of the induction study.
‡ $p < 0.01$.
§ $0.01 \leq p < 0.05$.
¶ Patients in remission at the end of maintenance therapy who were in remission at the start of maintenance therapy. This does not account for any other time point during maintenance therapy.

At Week 44, 47% of patients who received ustekinumab were corticosteroid -free and in clinical remission, compared to 30% of patients in the placebo group.

At Week 0 of Study CD-3, 34/56 (61%) ustekinumab-treated patients who previously failed or were intolerant to TNF blocker therapies were in clinical remission and 23/56 (41%) of these patients were in clinical remission at Week 44. In the placebo arm, 27/61 (44%) patients were in clinical remission at Week 0 while 16/61 (26%) of these patients were in remission at Week 44.

At Week 0 of Study CD-3, 46/72 (64%) ustekinumab-treated patients who had previously failed immunomodulator therapy or corticosteroids (but not TNF blockers) were in clinical remission and 45/72 (63%) of these patients were in clinical remission at Week 44. In the placebo arm, 50/70 (71%) of these patients were in clinical remission at Week 0 while 31/70 (44%) were in remission at Week 44. In the subset of these patients who were also naïve to TNF blockers, 34/52 (65%) of ustekinumab-treated patients were in clinical remission at Week 44 as compared to 25/51 (49%) in the placebo arm.

Patients who were not in clinical response 8 weeks after ustekinumab induction were not included in the primary efficacy

analyses for Study CD-3; however, these patients were eligible to receive a 90 mg subcutaneous injection of ustekinumab upon entry into Study CD-3. Of these patients, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the study.

14.5 Ulcerative Colitis

Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical studies [UC-1 and UC-2 (NCT02407236)] in adult patients with moderately to severely active ulcerative colitis who had an inadequate response to or failed to tolerate a biologic (i.e., TNF blocker and/or vedolizumab), corticosteroids, and/or 6-MP or AZA therapy. The 8-week intravenous induction study (UC-1) was followed by the 44-week subcutaneous randomized withdrawal maintenance study (UC-2) for a total of 52 weeks of therapy.

Disease assessment was based on the Mayo score, which ranged from 0 to 12 and has four subscores that were each scored from 0 (normal) to 3 (most severe): stool frequency, rectal bleeding, findings on centrally- reviewed endoscopy, and physician global assessment. Moderately to severely active ulcerative colitis was defined at baseline (Week 0) as Mayo score of 6 to 12, including a Mayo endoscopy subscore ≥ 2. An endoscopy score of 2 was defined by marked erythema, absent vascular pattern, friability, erosions; and a score of 3 was defined by spontaneous bleeding, ulceration. At baseline, patients had a median Mayo score of 9, with 84% of patients having moderate disease (Mayo score 6–10) and 15% having severe disease (Mayo score 11–12).

Patients in these studies may have received other concomitant therapies including aminosalicylates, immunomodulatory agents (AZA, 6-MP, or MTX), and oral corticosteroids (prednisone).

Study UC-1

In UC-1, 961 patients were randomized at Week 0 to a single intravenous administration of ustekinumab of approximately 6 mg/kg, 130 mg (a lower dose than recommended), or placebo. Patients enrolled in UC-1 had to have failed therapy with corticosteroids, immunomodulators or at least one biologic. A total of 51% had failed at least one biologic and 17% had failed both a TNF blocker and an integrin receptor blocker. Of the total population, 46% had failed corticosteroids or immunomodulators but were biologic-naïve and an additional 3% had previously received but had not failed a biologic. At induction baseline and throughout the study, approximately 52% patients were receiving oral corticosteroids, 28% patients were receiving immunomodulators (AZA, 6-MP, or MTX) and 69% patients were receiving aminosalicylates.

The primary endpoint was clinical remission at Week 8. Clinical remission with a definition of: Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0 (no rectal bleeding), and Mayo endoscopy subscore of 0 or 1 (Mayo endoscopy subscore of 0 defined as normal or inactive disease and Mayo subscore of 1 defined as presence of erythema, decreased vascular pattern and no friability) is provided in Table 15.

The secondary endpoints were clinical response, endoscopic improvement, and histologic-endoscopic mucosal improvement. Clinical response with a definition of (≥ 2 points and ≥ 30% decrease in modified Mayo score, defined as 3-component Mayo score without the Physician's Global Assessment, with either a decrease from baseline in the rectal bleeding subscore ≥ 1 or a rectal bleeding subscore of 0 or 1), endoscopic improvement with a definition of Mayo endoscopy subscore of 0 or 1, and histologic-endoscopic mucosal improvement with a definition of combined endoscopic improvement and histologic improvement of the colon tissue [neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue]) are provided in Table 15.

In UC-1, a significantly greater proportion of patients treated with ustekinumab (at the recommended dose of approximately 6 mg/kg dose) were in clinical remission and response and achieved endoscopic improvement and histologic-endoscopic mucosal improvement compared to placebo (see Table 15).

Table 15. Proportion of Patients Meeting Efficacy Endpoints at Week 8 in UC-1

Endpoint	Placebo N = 319		Ustekinumab* N = 322		Treatment difference and 97.5% CI †
	N	%	N	%	
Clinical Remission‡	**22**	**7%**	**62**	**19%**	12% (7%, 18%) §
Bio-naïve¶	14/151	9%	36/147	24%	
Prior biologic failure	7/161	4%	24/166	14%	
Endoscopic Improvement#	**40**	**13%**	**80**	**25%**	12% (6%, 19%) §
Bio-naïve¶	28/151	19%	43/147	29%	
Prior biologic failure	11/161	7%	34/166	20%	
Clinical Responseᵖ	**99**	**31%**	**186**	**58%**	27% (18%, 35%) §
Bio-naïve¶	55/151	36%	94/147	64%	
Prior biologic failure	42/161	26%	86/166	52%	
Histologic-Endoscopic Mucosal Improvement	**26**	**8%**	**54**	**17%**	9% (3%, 14%) §
Bio-naïve¶	19/151	13%	30/147	20%	
Prior biologic failure	6/161	4%	21/166	13%	

‡ Histologic-endoscopic mucosal improvement was defined as combined endoscopic improvement (Mayo endoscopy subscore of 0 or 1) and histologic improvement of the colon tissue (neutrophil infiltration in < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue).

* Infusion dose of ustekinumab using the weight- based dosage regimen specified in Table 3.

† Adjusted treatment difference (97.5% CI).

‡ Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

§ $p < 0.001$.

¶ An additional 7 patients on placebo and 9 patients on ustekinumab (6 mg/kg) had been exposed to, but had not failed, biologics.

Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

ᵖ Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥ 30% and ≥ 2 points, with either a decrease from baseline in the rectal bleeding subscore ≥ 1 or a rectal bleeding subscore of 0 or 1.

The relationship of histologic-endoscopic mucosal improvement, as defined in UC-1, at Week 8 to disease progression and long-term outcomes was not evaluated during UC-1.

Rectal Bleeding and Stool Frequency Subscores

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in ustekinumab-treated patients.

Study UC-2

The maintenance study (UC-2) evaluated 523 patients who achieved clinical response 8 weeks following the intravenous administration of either induction dose of ustekinumab in UC-1. These patients were randomized to receive a subcutaneous maintenance regimen of either 90 mg ustekinumab every 8 weeks, or every 12 weeks (a lower dose than recommended), or placebo for 44 weeks.

The primary endpoint was the proportion of patients in clinical remission at Week 44. The secondary endpoints included the proportion of patients maintaining clinical response at Week 44, the proportion of patients with endoscopic

improvement at Week 44, the proportion of patients with corticosteroid -free clinical remission at Week 44, and the proportion of patients maintaining clinical remission at Week 44 among patients who achieved clinical remission 8 weeks after induction.

Results of the primary and secondary endpoints at Week 44 in patients treated with ustekinumab at the recommended dosage (90 mg every 8 weeks) compared to the placebo are shown in Table 16.

Table 16. Efficacy Endpoints of Maintenance at Week 44 in UC-2 (52 Weeks from Initiation of the Induction Dose)

Endpoint	**Placebo* N = 175†**		**90 mg ustekinumab every 8 weeks N = 176**		**Treatment difference and 95% CI**
	N	**%**	**N**	**%**	
Clinical Remission‡	**46**	**26%**	**79**	**45%**	19% (9%, 28%) §
Bio-naïve¶	30/84	36%	39/79	49%	
Prior biologic failure	16/88	18%	37/91	41%	
Maintenance of Clinical Response at Week 44†	**84**	**48%**	**130**	**74%**	26% (16%, 36%) §
Bio-naïve¶	49/84	58%	62/79	78%	
Prior biologic failure	35/88	40%	64/91	70%	
Endoscopic Improvement#	**47**	**27%**	**83**	**47%**	20% (11%, 30%) §
Bio-naïve¶	29/84	35%	42/79	53%	
Prior biologic failure	18/88	20%	38/91	42%	
Corticosteroid-free Clinical Remissionᵖ	**45**	**26%**	**76**	**43%**	17% (8%, 27%) §
Bio-naïve¶	30/84	36%	38/79	48%	
Prior biologic failure	15/88	17%	35/91	38%	
Maintenance of Clinical Remission at Week 44 in patients who achieved clinical remission 8 weeks after induction	**18/50**	**36%**	**27/41**	**66%**	31% (12%, 50%) ß
Bio-naïve¶	12/27	44%	14/20	70%	
Prior biologic failure	6/23	26%	12/18	67%	

* The placebo group consisted of patients who were in response to ustekinumab and were randomized to receive placebo at the start of maintenance therapy.

† Clinical response was defined as a decrease from baseline in the modified Mayo score by ≥30% and ≥2 points, with either a decrease from baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore of 0 or 1.

‡ Clinical remission was defined as Mayo stool frequency subscore of 0 or 1, Mayo rectal bleeding subscore of 0, and Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

§ p = < 0.001.

¶ An additional 3 patients on placebo and 6 patients on ustekinumab had been exposed to, but had not failed, biologics.

Endoscopic improvement was defined as Mayo endoscopy subscore of 0 or 1 (modified so that 1 does not include friability).

Þ Corticosteroid-free clinical remission was defined as patients in clinical remission and not receiving corticosteroids at Week 44.

ß p=0.004.

Other Endpoints

Week 16 Responders to Ustekinumab Induction

Patients who were not in clinical response 8 weeks after induction with ustekinumab in UC-1 were not included in the primary efficacy analyses for Study UC-2; however, these patients were eligible to receive a 90 mg subcutaneous injection of ustekinumab at Week 8. Of these patients, 55/101 (54%) achieved clinical response eight weeks later (Week 16) and received ustekinumab 90 mg subcutaneously every 8 weeks during the UC-2 trial. At Week 44, there were 97/157 (62%) patients who maintained clinical response and there were 51/157 (32%) who achieved clinical remission.

Histologic-Endoscopic Mucosal Improvement at Week 44

The proportion of patients achieving histologic-endoscopic mucosal improvement during maintenance treatment in UC-2 was 75/172 (44%) among patients on ustekinumab and 40/172 (23%) in patients on placebo at Week 44. The relationship of histologic-endoscopic mucosal improvement, as defined in UC-2, at Week 44 to progression of disease or long-term outcomes was not evaluated in UC-2.

Endoscopic Normalization

Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0. At Week 8 in UC-1, endoscopic normalization was achieved in 25/322 (8%) of patients treated with ustekinumab and 12/319 (4%) of patients in the placebo group. At Week 44 of UC-2, endoscopic normalization was achieved in 51/176 (29%) of patients treated with ustekinumab and in 32/175 (18%) of patients in placebo group.

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

WEZLANA (ustekinumab-auub) injection is a sterile, preservative-free, clear to opalescent and colorless to light yellow solution. It is supplied as individually packaged, single-dose prefilled syringes or single-dose vials.

For Subcutaneous Use

Prefilled Syringes
- 45 mg/0.5 mL (NDC 55513-076-01, NDC 72511-076-01)
- 90 mg/mL (NDC 55513-089-01, NDC 72511-089-01)

Each prefilled syringe is equipped with a 27 gauge fixed ½ inch needle, a needle safety guard, and a needle cover that does not contain dry natural rubber.

Single-dose Vial
- 45 mg/0.5 mL (NDC 55513-055-01, NDC 72511-055-01)

For Intravenous Infusion

Single-dose Vial
- 130 mg/26 mL (5 mg/mL) (NDC 55513-066-01)

Storage and Stability

WEZLANA vials and 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 syringe and 45 mg vial 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 or the 45 mg vial is first removed from the refrigerator on the carton in the space provided. Once the prefilled syringe or the 45 mg vial has been stored at room temperature, it should not be returned to the refrigerator.

Discard the prefilled syringe or the 45 mg vial if not used within 30 days at room temperature storage. Do not use WEZLANA after the expiration date on the carton or on the prefilled syringe or on the 45 mg vial.

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 WEZLANA 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 WEZLANA *[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 WEZLANA *[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 WEZLANA 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.

Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

U.S. License Number 1080

1xxxxxx-vx

MEDICATION GUIDE

WEZLANA™ (wez-LAH-nah)

(ustekinumab-auub)

injection, for subcutaneous or intravenous use

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

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

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

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

Before starting WEZLANA, 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 WEZLANA, 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. WEZLANA 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 WEZLANA may also be more likely to get these infections.

Cancers. WEZLANA 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 WEZLANA, 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 WEZLANA?

WEZLANA 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
- adults 18 years and older with moderately to severely active Crohn’s disease.
- adults 18 years and older with moderately to severely active ulcerative colitis.

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

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

Before you receive WEZLANA, 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 WEZLANA?"**
- 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 WEZLANA 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 WEZLANA or one year after you stop receiving WEZLANA.**
- 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 WEZLANA. WEZLANA 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 WEZLANA can harm your unborn baby. You and your doctor should decide if you will receive WEZLANA.
- are breastfeeding or plan to breastfeed. It is thought that WEZLANA passes into your breast milk in small amounts.
- Talk to your doctor about the best way to feed your baby if you receive WEZLANA.

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 WEZLANA?

- Use WEZLANA exactly as your doctor tells you to.
- **The needle cover on the WEZLANA prefilled syringe does not contain latex.**
- Adults with Crohn's disease and ulcerative colitis will receive the first dose of WEZLANA through a vein in the arm (intravenous infusion) in a healthcare facility by a healthcare provider. It takes at least 1 hour to receive the full dose of medicine. You will then receive WEZLANA as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of WEZLANA, as described below.
- Adults with psoriasis or psoriatic arthritis and children 6 years and older with psoriasis or psoriatic arthritis will receive WEZLANA as an injection under the skin (subcutaneous injection) as described below.
- **Injecting WEZLANA under your skin**
  - WEZLANA is intended for use under the guidance and supervision of your doctor. In children 6 years and older, it is recommended that WEZLANA be administered by a healthcare provider. If your doctor decides that you or a caregiver may give your injections of WEZLANA at home, you should receive training on the right way to prepare and inject WEZLANA. Your doctor will determine the right dose of WEZLANA for you, the amount for each injection, and how often you should receive it. Do not try to inject WEZLANA yourself until you or your caregiver have been shown how to inject WEZLANA by your doctor or nurse.
  - Inject WEZLANA 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 WEZLANA.
  - If you inject more WEZLANA 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 WEZLANA, and how to properly throw away (dispose of) used needles and syringes. The syringe, needle and vial must never be re-used. After the rubber stopper is punctured, WEZLANA can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused portion of WEZLANA.

What should I avoid while using WEZLANA?

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

What are the possible side effects of WEZLANA?

WEZLANA may cause serious side effects, including:

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

Common side effects of WEZLANA include:

- nasal congestion, sore throat, and runny nose
- upper respiratory infections
- fever
- headache
- tiredness
- itching
- nausea and vomiting
- redness at the injection site
- vaginal yeast infections
- urinary tract infections
- sinus infection
- bronchitis
- diarrhea
- stomach pain

These are not all of the possible side effects of WEZLANA. 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 1-800-77-AMGEN (1-800-772-6436)

How should I store WEZLANA?

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

If needed, individual prefilled syringe and 45 mg vial 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 or the 45 mg vial is first removed from the refrigerator on the carton in the space provided. Once the prefilled syringe or the 45 mg vial has been stored at room temperature, it should not be returned to the refrigerator.

Discard the prefilled syringe or the 45 mg vial if not used within 30 days at room temperature storage. Do not use WEZLANA after the expiration date on the carton or on the prefilled syringe or on the 45 mg vial.

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

General information about the safe and effective use of WEZLANA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WEZLANA for a condition for which it was not prescribed. Do not give WEZLANA 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 WEZLANA that was written for health professionals.

What are the ingredients in WEZLANA?

Active ingredient: ustekinumab-auub

Inactive ingredients: Single-dose prefilled syringe for subcutaneous use contains histidine, histidine hydrochloride monohydrate, Polysorbate 80, and sucrose. **Single-dose vial for subcutaneous use** contains histidine, histidine hydrochloride monohydrate, Polysorbate 80 and sucrose. **Single-dose vial for intravenous infusion** contains edetate disodium, histidine, histidine hydrochloride monohydrate, methionine, Polysorbate 80, and sucrose.

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799 USA

US License Number 1080

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This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 10/2023

INSTRUCTIONS FOR USE

WEZLANA™ (wez-LAH-nah)

(ustekinumab-auub)

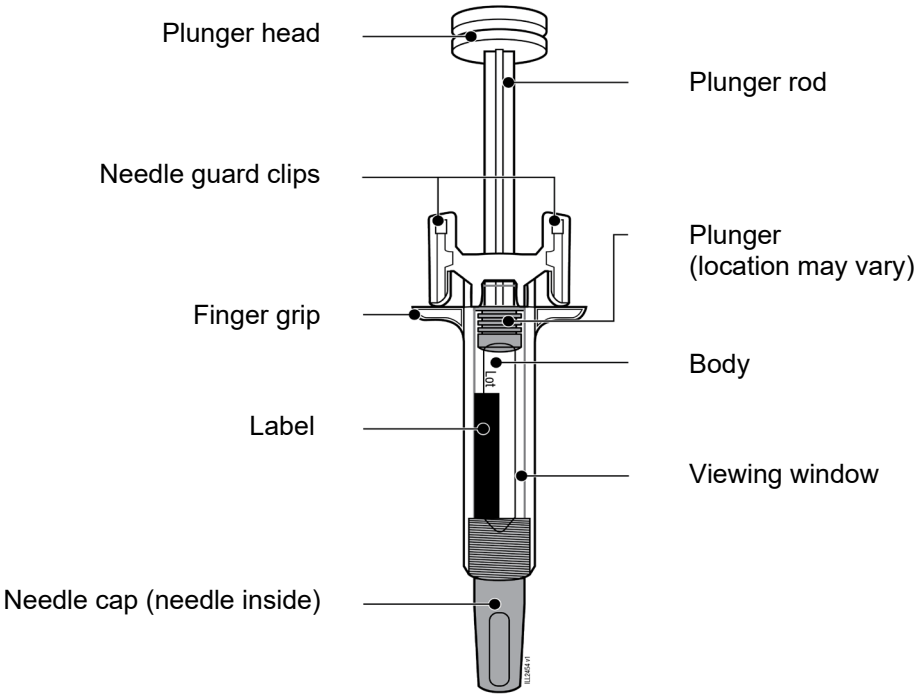
injection, for subcutaneous use

single-dose prefilled syringe

This Instructions for Use contains information on how to inject WEZLANA with a prefilled syringe.

The medicine in the WEZLANA prefilled syringe is for injection under-the-skin (subcutaneous injection). See the WEZLANA Medication Guide for more information about WEZLANA.

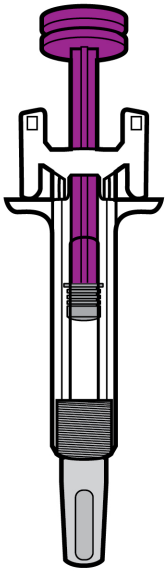
Getting to Know Your Prefilled Syringe



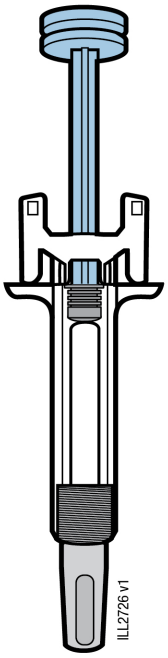
Step 1. Important Information You Need to Know Before Injecting WEZLANA

Dosing:

- WEZLANA comes in two different doses: 45 mg and 90 mg. Check your prescription to make sure you have the correct dose.
- 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, you will need to give yourself two injections, one right after the other.
- The look of the prefilled syringe will be different for each dose. The amount of medicine in the syringe will also be different for each dose.
- The 45 mg dose will have a smaller amount of medicine and the 90 mg dose will have a larger amount of medicine. Check the figures below to see what your dose looks like in the syringe.



45 mg/0.5 mL



90 mg/mL

Using your WEZLANA prefilled syringe:

- It is important that you do not try to give the injection until you have fully read and understood this Instructions for Use.
- If your doctor decides that you or a caregiver can give your WEZLANA injection at home, you should receive training on the right way to prepare and inject WEZLANA. **Do not** try to inject WEZLANA yourself until you have been shown the right way to give the injections by your doctor or nurse.
- Children 12 years of age and older with psoriasis who weigh 132 pounds or more may use a prefilled syringe under supervision of a parent or caregiver.
- **Do not** use the syringe if the carton is damaged or seal is broken.
- **Do not** use the syringe after the expiration date on the label.
- **Do not** shake the syringe.
- **Do not** remove the needle cap from the syringe until you are ready to inject.
- **Do not** use the syringe if it has been frozen.
- **Do not** use the syringe if it has been dropped on a hard surface. Part of the syringe may be broken even if you cannot see the break. Use a new syringe and call 1-800-77-AMGEN (1-800-772-6436).
- The syringe is not made with natural rubber latex.

Important: Keep the syringe and sharps disposal container out of the sight and reach of children.

Frequently asked questions:

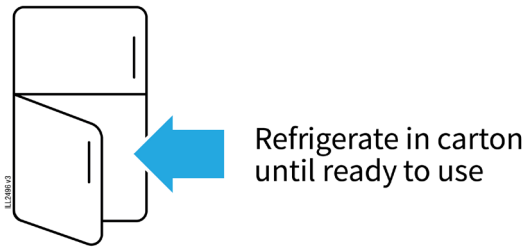
For additional information and answers to frequently asked questions, visit **www.WEZLANA.com**.

Where to get help:

If you want more information or help using WEZLANA:

- Contact your doctor or nurse
- Visit **www.WEZLANA.com, or**
- Call 1-800-77-AMGEN (1-800-772-6436).

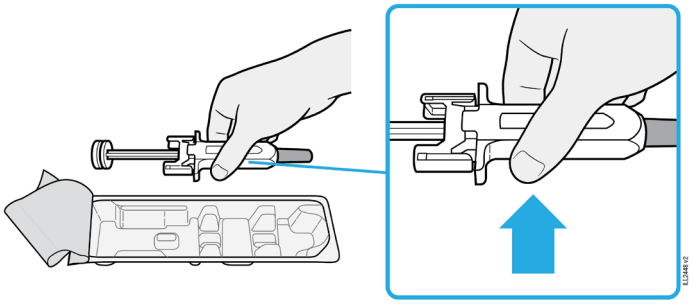
Step 2. Storing and Preparing to Inject WEZLANA



2a Refrigerate the syringe carton until you are ready to use it.

- Keep the syringe in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Keep the syringe in the original carton to protect it from light or physical damage until you are ready to use it.
- **Do not** freeze the syringe.
- **Do not** store the syringe in extreme heat or cold. For example, avoid storing in your vehicle`s glove box or trunk.

Important: Keep the syringe out of the sight and reach of children.



2b Grasp the syringe by the body and remove it from the carton. To prevent early activation of the needle safety guard, do not touch the NEEDLE GUARD CLIPS at any time during use.

- **Do not** grab the plunger rod, finger grip or the needle cap.
- **Do not** grab the needle guard clips.
- Remove the number of syringes you need for your injection.
- Put any unused syringes back into refrigerator.

2c Wait 30 minutes for the syringe to reach room temperature.

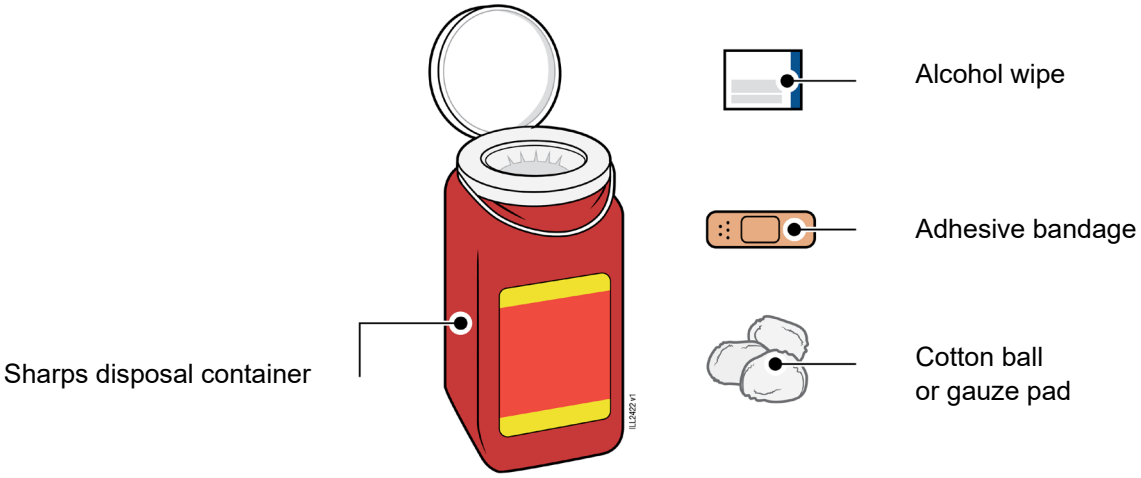
- Let the syringe warm up naturally.

- **Do not** heat with hot water, a microwave, or direct sunlight.
- **Do not** shake the syringe at any time.
- Using the syringe at room temperature allows for a more comfortable injection.

2d You may also keep WEZLANA at room temperature for up to 30 days, if needed.

- Keep it at room temperature between 68°F to 77°F (20°C to 25°C).
- **Do not** use WEZLANA if the syringe has been stored above 86ºF (30ºC).
- **Do not** put WEZLANA back in refrigerator after it has been stored at room temperature.
- Record the date you removed WEZLANA from the refrigerator and use within **30** days.

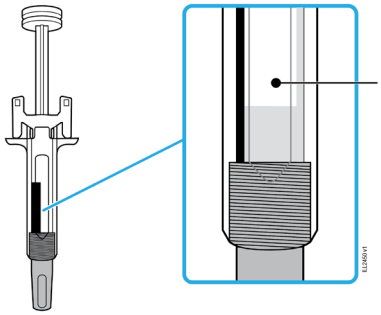
Important: Place the syringe in a sharps disposal container if it has reached room temperature and has not been used within **30** days.



2e Gather and place the following items for your injection on a clean, flat, and well-lit surface:

- WEZLANA syringe (room temperature)
- Sharps disposal container (see Step 5. Disposing of WEZLANA and Checking the Injection Site)
- Alcohol wipe
- Adhesive bandage
- Cotton ball or gauze pad

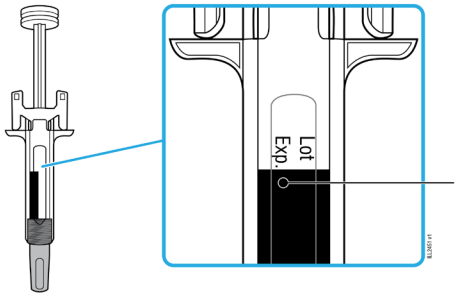
Step 3. Getting Ready for Your Injection



3a Inspect the medicine through the viewing window. It should be clear to white like an opal and colorless to light yellow.

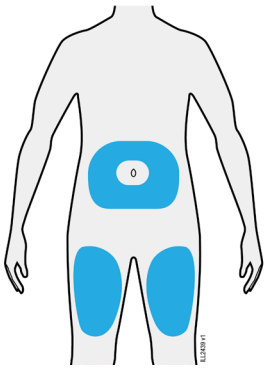
- It is okay to see air bubbles.
- **Do not** use WEZLANA if the medicine is frozen, cloudy, discolored, or has large particles.

Important: If the medicine is cloudy, discolored or has flakes or if the syringe is damaged or expired, call 1-800-77-AMGEN (1-800-772-6436).



3b Check the expiration (Exp.) date and inspect the syringe for damage.

- **Do not** use if the expiration date has passed.
- **Do not** use the syringe if:
  - the needle cap is missing or loose
  - it has cracks or broken parts
  - it has been dropped on a hard surface or dropped without the needle cap in place
- Make sure you have the right medicine and dose.



3c Choose 1 of these injection locations.

- Choose an injection site around your stomach area (abdomen) or upper legs (thighs).
- If a caregiver is giving you the injection, the outer upper area of the upper arms, or the buttocks may also be used.
- Choose a different location (site) for each injection.
- The areas in blue are the recommended injection locations.

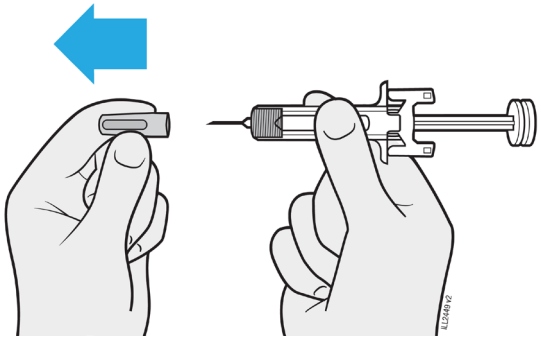
Important: Avoid areas where the skin is tender, bruised, red, or hard.

3d Wash your hands thoroughly with soap and water.

3e Clean the injection site with alcohol wipe.
- Let your skin dry on its own.
- **Do not** touch the clean area again before injecting.

Step 4. Injecting WEZLANA

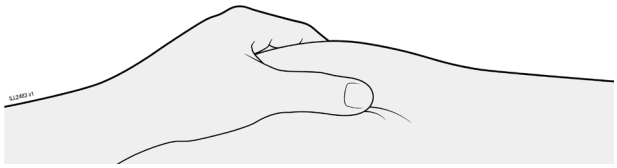
Important: Only remove the needle cap when you can inject WEZLANA right away (within 5 minutes) because the medicine can dry out.



4a Pull the needle cap straight off while holding the syringe body.

- **Do not** hold the plunger or plunger head while removing the needle cap.
- **Do not** twist or bend the needle cap.
- **Never** put the needle cap back on. It may damage the needle.
- **Do not** let anything touch the needle after the cap is removed.
- **Do not** place the syringe on any surface after the cap is removed.
- **Do not** try to push air bubbles out. It is okay to see air bubbles.
- A drop of medicine at the needle tip is normal.

PINCH

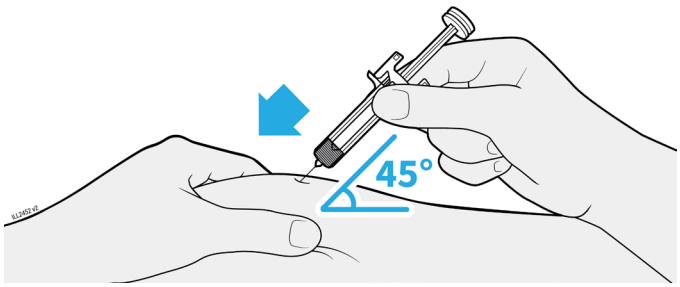


4b Pinch the skin around injection site before injection.

- Gently pinch the skin with one hand between the thumb and index finger to create a bump for the injection.
- If possible, the bump should be about 2 inches wide.

Important: Continue to pinch the skin until the injection is complete.

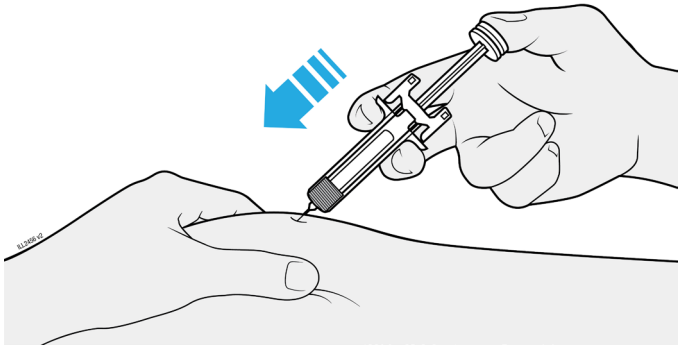
INSERT



4c Insert the needle into the pinched skin.

- Insert the needle into the pinched skin at about a 45-degree angle.
- **Do not** place your finger on the plunger rod while inserting the needle, as this may result in lost medicine.

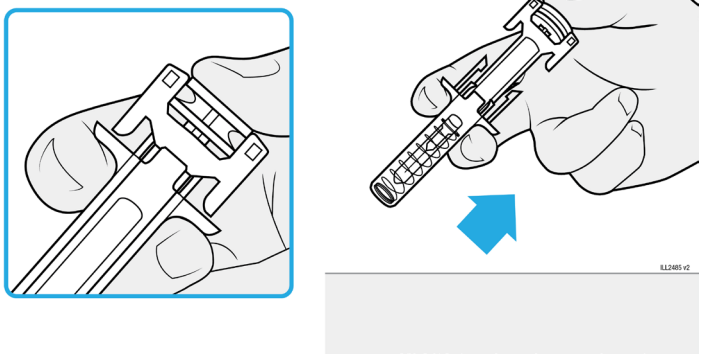
INJECT



4d Slowly press the plunger head all the way down with your thumb until it is completely between the needle guard clips. Hold the finger grips with your fingers as shown in the figure.

- **Do not** pull back on the plunger rod at any time.
- **Do not** remove the syringe until all medicine has been injected.

LIFT



4e Keep pressure on the plunger head with your thumb and remove the needle from your skin.

- Let go of the skin after the needle is removed.
- Slowly take your thumb off the plunger head. This will let the empty syringe move up until the entire needle is automatically covered by the needle guard.

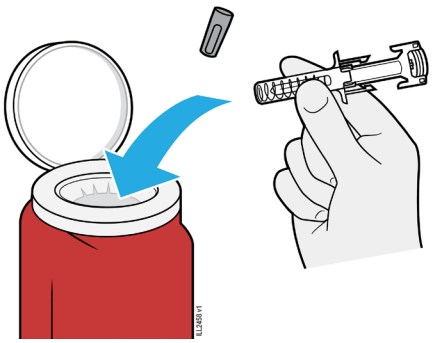
If a second injection is required:

4f Repeat steps 2a-4e if a second injection is required.

- Check your prescription for your dose.
- 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 injection.
    - Repeat Steps 2a–4e for the second injection using a new WEZLANA syringe.
    - Choose a different site for the second injection.

Step 5. Disposing of WEZLANA and Checking the Injection Site

Important: Never put the needle cap back on the syringe.

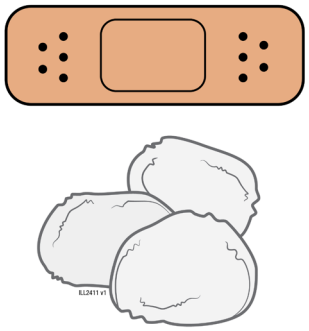


5a Place the used syringe and needle cap in an FDA-cleared sharps disposal container right away after use.

- **Do not** reuse the syringe.

Important: Do not throw away (dispose of) the syringe in your household trash.

5b Check injection site.



- **Do not** rub the injection site.
- If there is blood, press a cotton ball or gauze pad on your injection site.
- Apply an adhesive bandage if necessary.

Additional information about your sharps disposal container

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a 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.

Disposing of sharps containers:

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 state or local laws about how you should throw away used needles and syringes.

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 used sharps disposal container in your household trash unless your community guidelines permit this.
Do not recycle your used sharps disposal container.

For more information or help call 1-800-77-AMGEN (1-800-772-6436).

AMGEN®

Manufactured by:

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
US License Number 1080

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