USTEKINUMAB- ustekinumab injection, solution
USTEKINUMAB- ustekinumab solution
Janssen Biotech, Inc.

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

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

RECENT MAJOR CHANGES

Indications and Usage (1.3)	4/2026
Indications and Usage (1.4)	8/2026
Dosage and Administration (2.4)	4/2026
Dosage and Administration (2.6, 2.8)	8/2026
Warnings and Precautions Infections (5.1)	8/2026
Serious Hypersensitivity Reactions (5.5)	11/2025

INDICATIONS AND USAGE

Ustekinumab is a human interleukin-12 and -23 antagonist indicated for the treatment of:

- Moderate to severe plaque psoriasis in adults and pediatric patients 6 years of age and older who are candidates for phototherapy or systemic therapy. (1.1)
- Active psoriatic arthritis in adults and pediatric patients 6 years of age and older. (1.2)
- Moderately to severely active Crohn's disease in adults and pediatric patients 2 years of age and older. (1.3)
- Moderately to severely active ulcerative colitis in adults and pediatric patients 2 years of age and older. (1.4)

DOSAGE AND ADMINISTRATION

Adult Patients with Plaque Psoriasis Subcutaneous Recommended Dosage (2.1):

Weight Range (kilograms)	Recommended Dosage
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

Pediatric Patients 6 Years of Age and Older with Plaque Psoriasis 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)	Recommended Dose
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 Patients 6 Years of Age and Older Subcutaneous Recommended Dosage (2.2): Weight-based dosing is recommended at the initial dose, 4 weeks later, then every 12 weeks thereafter.

Weight Range (kilograms)	**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

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

Weight Range (kilograms)	**Recommended Dose**
55 kg or less	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Crohn's Disease Maintenance Adult Subcutaneous Recommended Dosage (2.3): A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
Crohn's Disease Initial Pediatric Intravenous Recommended Dose (2.4):

- *For patients weighing 10 kg or more*: A single intravenous infusion using weight-based dosing:

Weight Range (kilograms)	**Recommended Dose**
10 kg to 25 kg	10 mg/kg
greater than 25 kg to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Crohn's Disease Maintenance Pediatric Subcutaneous Recommended Dosage (2.4): The recommended maintenance dosage in pediatric patients using weight-based dosing is:

- *10 kg to 35 kg*: A subcutaneous 2.5 mg/kg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
- *Greater than 35 kg*: A subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

Ulcerative Colitis Initial Adult Intravenous Recommended Dose (2.5): A single intravenous infusion using weight-based dosing:

Weight Range (kilograms)	**Recommended Dose**
up to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Ulcerative Colitis Maintenance Adult Subcutaneous Recommended Dosage (2.5): A subcutaneous 90 mg dose 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
Ulcerative Colitis Initial Pediatric Intravenous Recommended Dosage (2.6):

- *For patients weighing 10 kg or more*: A single intravenous infusion using weight-based dosing:

Weight Range (kilograms)	**Recommended Dose**
10 kg to 25 kg	10 mg/kg
greater than 25 kg to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Ulcerative Colitis Maintenance Pediatric Subcutaneous Recommended Dosage (2.6): The recommended

maintenance dosage in pediatric patients using weight-based dosing is:

- *10 kg to 35 kg*: A subcutaneous 2.5 mg/kg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
- *Greater than 35 kg*: A subcutaneous 90 mg dose administered 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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Infections: Serious infections have occurred. Avoid starting Ustekinumab during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue Ustekinumab until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL-12/IL-23. Consider diagnostic tests for these infections as dictated by clinical circumstances. (5.2)
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with Ustekinumab. Initiate treatment of latent TB before administering Ustekinumab. (5.3)
- Malignancies: Ustekinumab may increase risk of malignancy. The safety of Ustekinumab in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Serious Hypersensitivity Reactions: If a severe or other clinically significant hypersensitivity reaction occurs, discontinue Ustekinumab immediately and initiate appropriate medical treatment. (5.5)
- Posterior Reversible Encephalopathy Syndrome (PRES): If PRES is suspected, treat promptly, and discontinue Ustekinumab. (5.6)
- Immunizations: Avoid use of live vaccines in patients during treatment with Ustekinumab. (5.7)
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of Ustekinumab. If diagnosis is confirmed, discontinue Ustekinumab and institute appropriate treatment. (5.8)

ADVERSE REACTIONS

Most common adverse reactions are:

- Psoriasis and Psoriatic Arthritis (≥3%): nasopharyngitis, upper respiratory tract infection, headache, and fatigue. (6.1)
- Crohn's Disease
  - induction (≥3%): vomiting. (6.1)
  - 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)
  - maintenance (≥3%): nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis (PsO)

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

1.2 Psoriatic Arthritis (PsA)

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

1.3 Crohn's Disease (CD)

Ustekinumab is indicated for the treatment of adults and pediatric patients 2 years of age and older with moderately to severely active Crohn's disease.

1.4 Ulcerative Colitis (UC)

Ustekinumab is indicated for the treatment of adults and pediatric patients 2 years of age and older with moderately to severely active ulcerative colitis.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage in Plaque Psoriasis

Subcutaneous Adult Dosage Regimen

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

(14.1)].

Subcutaneous Pediatric Dosage Regimen

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

The recommended dose of Ustekinumab for pediatric patients 6 years of age and older with plaque psoriasis based on body weight is shown below (Table 1).

Table 1: Recommended Dose of Ustekinumab for Subcutaneous Injection in Pediatric Patients 6 Years of Age and Older With Plaque 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 vial.

Table 2: Injection Volumes of Ustekinumab 45 mg/0.5 mL Vials for Pediatric Patients 6 Years of Age and Older With Plaque Psoriasis and Pediatric Patients 6 Years of Age and Older 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	0.13
17	12.8	0.14
18	13.5	0.15
19	14.3	0.16
20	15	0.17
21	15.8	0.17
22	16.5	0.18
23	17.3	0.19
24	18	0.20
25	18.8	0.21
26	19.5	0.22
27	20.3	0.22
28	21	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
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 Recommended Dosage in Psoriatic Arthritis

Subcutaneous Adult Dosage Regimen

- The recommended dosage 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 dosage is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.

Subcutaneous Pediatric Dosage Regimen

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

The recommended dose of Ustekinumab for pediatric patients 6 years of age and older with psoriatic arthritis, based on body weight, is shown below (Table 3).

Table 3: Recommended Dose of Ustekinumab for Subcutaneous Injection in Pediatric Patients 6 Years of Age

and Older 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 vial.

2.3 Recommended Adult Dosage in Crohn's Disease

Intravenous Induction Adult Dosage Regimen

The recommended induction dosage is a single intravenous infusion using the weight-based dosage regimen specified in Table 4 *[see Dosage and Administration (2.8)]*.

Table 4: Initial Intravenous Dose of Ustekinumab in Adult Patients with Crohn's Disease

Body Weight of Patient at the Time of Dosing	Dose
55 kg or less	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

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 Recommended Pediatric Dosage in Crohn's Disease

Intravenous Induction Pediatric Dosage Regimen

The recommended induction dosage in pediatric patients weighing 10 kg and above is a single intravenous infusion using the weight-based dosage regimen specified in Table 5 *[see Dosage and Administration (2.8)]*.

Table 5: Initial Intravenous Dose of Ustekinumab in Pediatric Patients (Weighing 10 kg or More) with Crohn's Disease

Body Weight of Patient at the Time of Dosing	Dose
10 kg to 25 kg	10 mg/kg
greater than 25 kg to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Subcutaneous Maintenance Pediatric Dosage Regimen

The recommended maintenance dosage in pediatric patients using weight-based dosing is:

- *10 kg to 35 kg*: A subcutaneous 2.5 mg/kg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
- *Greater than 35 kg*: A subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.5 Recommended Adult Dosage in Ulcerative Colitis

Intravenous Induction Adult Dosage Regimen

The recommended induction dosage is a single intravenous infusion using the weight-based dosage regimen specified in Table 6 *[see Dosage and Administration (2.8)]*.

Table 6: Initial Intravenous Dosage of Ustekinumab in Adult Patients with Ulcerative Colitis

Body Weight of Patient at the Time of Dosing	Dose
55 kg or less	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

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.

2.6 Recommended Pediatric Dosage in Ulcerative Colitis

Intravenous Induction Pediatric Dosage Regimen

The recommended induction dosage in pediatric patients weighing 10 kg and above is a single intravenous infusion using the weight-based dosage regimen specified in Table 7 *[see Dosage and Administration (2.8)].*

Table 7: Initial Intravenous Dosage of Ustekinumab in Pediatric Patients with Ulcerative Colitis Weighing 10 kg or More

Body Weight of Patient at the Time of Dosing	Dose
10 kg to 25 kg	10 mg/kg
greater than 25 kg to 55 kg	260 mg
greater than 55 kg to 85 kg	390 mg
greater than 85 kg	520 mg

Subcutaneous Maintenance Pediatric Dosage Regimen

The recommended maintenance dosage in pediatric patients using weight-based dosing

is:

- *10 kg to 35 kg*: A subcutaneous 2.5 mg/kg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.
- *Greater than 35 kg*: A subcutaneous 90 mg dose administered 8 weeks after the initial intravenous dose, then every 8 weeks thereafter.

2.7 General Considerations for Administration

- Ustekinumab is intended for use under the guidance and supervision of a healthcare provider. Ustekinumab should only be administered to patients who will be closely monitored and have regular follow-up visits with a healthcare provider. The appropriate dose should be determined by a healthcare provider using the patient's current weight at the time of dosing. In pediatric patients, it is recommended that Ustekinumab be administered by a healthcare provider. If a healthcare provider determines that it is appropriate, a patient may self-inject or a caregiver may inject Ustekinumab after proper training in subcutaneous injection technique. Instruct patients to follow the directions provided in the Instructions for Use *[see Instructions for Use]*.
- The needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex). The needle cover should not be handled by persons sensitive to latex.
- It is recommended that each injection be administered at a different anatomic location (such as upper arms, gluteal regions, thighs, or any quadrant of abdomen) than the previous injection, and not into areas where the skin is tender, bruised, erythematous, or indurated. When using the vial, a 1 mL syringe with a 27 gauge, ½ inch needle is recommended.
- Prior to administration, visually inspect Ustekinumab for particulate matter and discoloration. Ustekinumab is a colorless to light yellow solution and may contain a few small translucent or white particles. Do not use Ustekinumab if it is discolored or cloudy, or if other particulate matter is present. Ustekinumab does not contain preservatives; therefore, discard any unused product remaining in the vial and/or syringe.

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

Ustekinumab 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 Ustekinumab vials needed based on patient weight (see Table 4, Table 5, Table 6, and Table 7 above).
2. Obtain the appropriate infusion solution (Table 8). Withdraw and discard a volume of the infusion solution equal to the volume of Ustekinumab solution to be added:

Table 8: Appropriate Infusion Solution and Final Infusion Volumes for Intravenous Infusion of Ustekinumab Solution

Patient Population	Body Weight of Patient at the Time of Dosing	Infusion Solution	Final Volume in the Infusion Bag

Pediatric	10 kg to 25 kg	0.9% Sodium Chloride Injection	100 mL*
	Greater than 25 kg	0.9% Sodium Chloride Injection	250 mL*
Adult	All weights	0.45% or 0.9% Sodium Chloride Injection	250 mL*

* Remove a volume of infusion solution equal to the volume of Ustekinumab solution to be added to obtain the final volume.

3. Add the volume of Ustekinumab solution equal to the calculated dose of Ustekinumab to the infusion solution and gently mix.
4. Visually inspect the diluted solution before infusion. 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 the storage time *(see Storage below)*.
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 Ustekinumab concomitantly in the same intravenous line with other agents.
8. Ustekinumab does not contain preservatives. Each vial is for a one-time use in only one patient. Discard any remaining solution. Dispose any unused medicinal product in accordance with local requirements.
9. Discard any unused portion of the infusion solution.

Storage

Do not freeze.

Storage time at room temperature begins once the diluted solution has been prepared.

100 mL infusion bag:

- If necessary, the diluted infusion solution may be kept at room temperature up to 25 °C (77 °F) for **up to 3 hours.**
- The infusion should be completed **within 4 hours** after the dilution in the infusion bag (cumulative time after preparation including the storage and the infusion period).

250 mL infusion bag:

- If necessary, the diluted infusion solution may be kept at room temperature up to 25 °C (77 °F) for up to 7 hours.
- 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).

3 DOSAGE FORMS AND STRENGTHS

Ustekinumab (ustekinumab) is a colorless to light yellow solution and may contain a few small translucent or white particles.

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Ustekinumab may increase the risk of infections and reactivation of latent infections. Serious bacterial, mycobacterial, fungal, and viral infections were observed in patients receiving Ustekinumab *[see Adverse Reactions (6.1, 6.2)]*.

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

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

Avoid initiating treatment with Ustekinumab 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 Ustekinumab 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 Ustekinumab and discontinue Ustekinumab 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 may be susceptible to these types of infections. Consider appropriate diagnostic testing, (e.g., tissue culture, stool culture, as dictated by clinical circumstances).

5.3 Pre-treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis infection prior to initiating treatment with Ustekinumab.

Avoid administering Ustekinumab to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering Ustekinumab. Consider anti-tuberculosis therapy prior to initiation of Ustekinumab 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 Ustekinumab for signs and symptoms of active tuberculosis during and after treatment.

5.4 Malignancies

Ustekinumab is an immunosuppressant and may increase the risk of malignancy. Malignancies were reported among subjects who received Ustekinumab in clinical trials *[see Adverse Reactions (6.1)]*. In rodent models, inhibition of IL-12/IL-23p40 increased the risk of malignancy *[see Nonclinical Toxicology (13.1)]*.

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

There have been post-marketing reports of the rapid appearance of multiple cutaneous squamous cell carcinomas in patients receiving Ustekinumab who had pre-existing risk factors for developing non-melanoma skin cancer. Monitor all patients receiving Ustekinumab for the appearance of non-melanoma skin cancer. Closely follow patients greater than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment *[see Adverse Reactions (6.1)]*.

5.5 Serious Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with Ustekinumab in clinical trials and postmarketing. Some serious hypersensitivity reactions have occurred during the first intravenous dose of Ustekinumab *[see Adverse Reactions (6.1, 6.2)].*

If a severe or clinically significant hypersensitivity reaction occurs, discontinue Ustekinumab immediately and initiate appropriate medical treatment *[see Contraindications (4)].*

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 initiation. A few cases reported latency of a year or longer. Patients recovered with supportive care following withdrawal of ustekinumab.

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

5.7 Immunizations

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

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

5.8 Noninfectious Pneumonia

Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of Ustekinumab. 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 Ustekinumab and institute appropriate treatment *[see Adverse Reactions (6.2)]*.

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

6.1 Clinical Trials Experience

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

Adult Subjects with Plaque Psoriasis

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

Table 9 summarizes the adverse reactions that occurred at a rate of at least 1% with higher rates in the Ustekinumab groups during the placebo-controlled period of Ps STUDY 1 and Ps STUDY 2 *[see Clinical Studies (14.1)]*.

Table 9: Adverse Reactions, Reported by ≥1% of Subjects

with Plaque Psoriasis and at Higher Rates in the Ustekinumab Groups through Week 12 in Ps STUDY 1 and Ps STUDY 2

		Ustekinumab	
	Placebo	**45 mg**	**90 mg**
Subjects treated	**665**	**664**	**666**
Nasopharyngitis	51 (8%)	56 (8%)	49 (7%)
Upper respiratory tract infection	30 (5%)	36 (5%)	28 (4%)
Headache	23 (3%)	33 (5%)	32 (5%)
Fatigue	14 (2%)	18 (3%)	17 (3%)
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 clinical trials in adult subjects with plaque psoriasis *[see Warnings and Precautions (5.6)]*.

Infections

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

In the controlled and non-controlled portions of clinical trials in subjects with plaque psoriasis (median follow-up of 3.2 years), representing 8998 patient-years of exposure, 72.3% of Ustekinumab-treated subjects reported infections (0.87 per patient-years of follow-up). Serious infections were reported in 2.8% of subjects (0.01 per patient-years of follow-up).

Malignancies

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

of follow-up) *[see Warnings and Precautions (5.4)]*. The most frequently observed malignancies other than non-melanoma skin cancer during the clinical trials were: prostate, melanoma, colorectal and breast. Malignancies other than non-melanoma skin cancer in Ustekinumab-treated subjects during the controlled and uncontrolled portions of trials were similar in type and number to what would be expected in the general U.S. population according to the 1969–2004 SEER database (adjusted for age, gender and race).

Pediatric Subjects with Plaque Psoriasis

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

Psoriatic Arthritis

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

Adult Subjects with 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 trials. These 1407 subjects included 40 subjects who received a prior investigational intravenous ustekinumab formulation but were not included in the efficacy analyses. In trials 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 trial 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 trial CD-3. Subjects in these 3 trials 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 clinical trials in adult subjects with plaque psoriasis and psoriatic arthritis. Common adverse reactions in trials CD-1 and CD-2 and in trial CD-3 are listed in Tables 10 and 11, respectively.

Table 10: Common Adverse Reactions Through Week 8 in Trials CD-1 and CD-2 occurring in ≥3% of Ustekinumab-Treated Subjects and Higher Than Subjects Receiving 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 trials CD-1 and CD-2 included asthenia (1% vs 0.4%), acne (1% vs 0.4%), and pruritus (2% vs 0.4%).

Table 11: Common Adverse Reactions Through Week 44 in Trial CD-3 occurring in ≥3% of Ustekinumab-Treated Subjects and Higher Than Subjects Receiving 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 subjects 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 subject each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the Crohn's disease clinical trials, 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 *[see Warnings and Precautions (5.4)]*.

Hypersensitivity Reactions Including Anaphylaxis

In CD trials, two subjects reported hypersensitivity reactions following Ustekinumab administration. One subject experienced signs and symptoms consistent with anaphylaxis (tightness of the throat, shortness of breath, and flushing) after a single

subcutaneous administration (0.1% of subjects receiving subcutaneous Ustekinumab). In addition, one subject 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 subjects receiving intravenous Ustekinumab). These subjects were treated with oral antihistamines or corticosteroids and in both cases symptoms resolved within an hour *[see Warnings and Precautions (5.5)]*.

Pediatric Subjects with Crohn's Disease

The safety of Ustekinumab has been studied in 101 pediatric subjects (2 to 17 years of age) with moderately to severely active Crohn's disease and 48 subjects received the recommended maintenance dosage *[see Clinical Studies (14.5)]*. In general, adverse reactions reported in the clinical trial of pediatric subjects with Crohn's disease were similar to those reported in adult subjects with Crohn's disease in Studies CD-1, CD-2, and CD-3 *[see Clinical Studies (14.4)]*. Other adverse reactions reported in at least 10% of pediatric subjects were upper respiratory tract infection (13% during induction and 17% during maintenance), COVID-19 (17% during maintenance), and headache (10% during maintenance).

One pediatric subject discontinued treatment with Ustekinumab after developing anaphylactic shock within the first two minutes of initiation of the first intravenous infusion and was stabilized with medical intervention *[see Warnings and Precautions (5.5)].*

Adult Subjects with Ulcerative Colitis

The safety of Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical trials (UC-1 [IV induction] and UC-2 [SC maintenance]) in 960 adult subjects with moderately to severely active ulcerative colitis *[see Clinical Studies (14.6)]*. The overall safety profile of Ustekinumab in subjects 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 subjects with ulcerative colitis, serious or other clinically significant infections included gastroenteritis and pneumonia. In addition, listeriosis and ophthalmic herpes zoster were reported in one subject each *[see Warnings and Precautions (5.1)]*.

Malignancies

With up to one year of treatment in the ulcerative colitis clinical trials, 0.4% of Ustekinumab-treated subjects (0.48 events per hundred patient-years) and 0.0% of subjects receiving placebo (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 subjects receiving placebo (0.40 events per hundred patient-years) *[see Warnings and Precautions (5.4)]*.

Pediatric Subjects with Ulcerative Colitis

The safety of Ustekinumab was assessed in 112 pediatric subjects (3 to 17 years of age) with moderately to severely active ulcerative colitis and 54 subjects received the recommended maintenance dosage *[see Clinical Studies (14.7)]*. In general, adverse reactions reported in the clinical trial of pediatric subjects with ulcerative colitis were similar to those reported in adult subjects with ulcerative colitis in Studies UC-1 and UC-2 *[see Clinical Studies (14.6)]*. One pediatric subject experienced worsening of preexisting peripheral neuropathy during treatment with Ustekinumab, resulting in hospitalization.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of Ustekinumab. 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 exposure.

Immune system disorders: Hypersensitivity reactions (e.g., anaphylaxis, angioedema, dyspnea, rash, urticaria), including a fatal case that presented with chest tightness and dyspnea during infusion of the first dose. Some cases of serious hypersensitivity reactions have been reported in patients with a history of alpha-gal syndrome, allergy to mammalian meat or meat products, or anti-alpha-gal IgE. In most of these cases the reactions occurred at the time of initial administration.

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

Neurological disorders: Posterior Reversible Encephalopathy Syndrome (PRES).

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

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

7 DRUG INTERACTIONS

7.1 Concomitant Therapies

In trials in subjects with plaque psoriasis the safety of Ustekinumab in combination with immunosuppressive agents or phototherapy has not been evaluated. In trials in subjects with psoriatic arthritis, concomitant MTX use did not appear to influence the safety or efficacy of Ustekinumab. In trials in subjects with Crohn's disease (CD-1 and CD-2) and ulcerative colitis (UC-1), 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 suppressed by increased levels of certain cytokines (e.g., IL-1, IL-6, TNFα, IFN) during chronic inflammation. Thus, use of Ustekinumab, an antagonist of IL-12 and IL-23, could normalize the formation of

CYP450 enzymes. Upon initiation or discontinuation of Ustekinumab in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for therapeutic effect or drug concentration and adjust the individual dosage of the CYP substrate as needed. See the prescribing information of specific CYP substrates.

A CYP-mediated drug interaction effect was not observed in subjects with Crohn's disease *[see Clinical Pharmacology (12.3)]*.

7.3 Allergen Immunotherapy

Ustekinumab has not been evaluated in patients who have undergone allergy immunotherapy. Ustekinumab 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

Available data from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Ustekinumab Pregnancy Registry, published literature and pharmacovigilance in pregnant women have not identified a Ustekinumab-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother and the fetus associated with inflammatory bowel disease (IBD) in pregnancy. In animal reproductive and developmental toxicity studies, no adverse developmental effects were observed in offspring after administration of ustekinumab to pregnant monkeys at exposures greater than 100 times the maximum recommended human dose (MRHD).

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

Clinical Considerations

Disease-associated Maternal and Embryo/Fetal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with IBD is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions

Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. Therefore, Ustekinumab may be present in infants exposed *in utero*. The potential clinical impact of ustekinumab exposure in infants exposed *in utero* should be considered.

Data

Human Data

An observational pregnancy registry conducted by (OTIS)/MotherToBaby in the U.S. and Canada (enrollment between 2013 and 2019) assessed the risk of major birth defects, pattern of major and minor anomalies in live-born infants, miscarriage, and adverse infant outcomes in women with Ustekinumab exposure. In the registry study, there were 101 participants and 107 pregnancies with exposure to Ustekinumab (88 prospective; 19 retrospective). Most participants had a primary indication of CD (65.4%) or psoriasis (30.8%). The pregnancy registry did not identify a Ustekinumab-associated risk of major birth defects, pattern of major or minor anomalies, increased risk of miscarriage or adverse infant outcomes. Methodological limitations of the registry include small sample size, lack of an internal comparison group, a mix of prospective and retrospective reports, and unmeasured confounders. The conclusions from the pregnancy registry were consistent with the published literature and pharmacovigilance.

Animal Data

Ustekinumab was tested in two embryo-fetal development toxicity studies in cynomolgus monkeys. No teratogenic or other adverse developmental effects were observed in fetuses from pregnant monkeys that were administered ustekinumab subcutaneously twice weekly or intravenously weekly during the period of organogenesis. Serum concentrations of ustekinumab in pregnant monkeys were greater than 100 times the serum concentration in patients treated subcutaneously with 90 mg of ustekinumab weekly for 4 weeks.

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

8.2 Lactation

Risk Summary

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

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

8.4 Pediatric Use

Plaque Psoriasis

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

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

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

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

Psoriatic Arthritis

The safety and effectiveness of Ustekinumab have been established for treatment of psoriatic arthritis in pediatric patients 6 years of age and older.

Use of Ustekinumab in these age groups is supported by evidence from adequate and well controlled trials of Ustekinumab in adult subjects with psoriasis and PsA, pharmacokinetic data from adult subjects with psoriasis, adult subjects with PsA and pediatric subjects with psoriasis, and safety data from two clinical trials in 44 pediatric subjects 6 to 11 years old with psoriasis and 110 pediatric subjects 12 years of age and older with psoriasis. The observed pre-dose (trough) concentrations are generally comparable between adult subjects with psoriasis, adult subjects with PsA and pediatric subjects with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric subjects 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 Ustekinumab have not been established in pediatric patients less than 6 years old with psoriatic arthritis.

Crohn's Disease

The safety and effectiveness of Ustekinumab have been established for the treatment of moderately to severely active Crohn's disease in pediatric patients aged 2 years and older. Use of Ustekinumab for this indication is supported by evidence from adequate and well-controlled studies in adults with additional safety, efficacy, and pharmacokinetic data from a 52-week study in 101 pediatric subjects aged 2 to 17 years of age. The adverse reaction profile in these pediatric subjects was similar to adverse reactions reported in the clinical trials of adults with Crohn's disease. Other adverse reactions reported in at least 10% of pediatric subjects were upper respiratory tract infection (13% during induction and 17% during maintenance), COVID-19 (17% during maintenance), and headache (10% during maintenance) *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.4, 14.5)]*.

The safety and effectiveness of Ustekinumab for the treatment of moderately to severely active Crohn's disease have not been established in pediatric patients less than 2 years of age.

Ulcerative Colitis

The safety and effectiveness of Ustekinumab have been established for the treatment of moderately to severely active ulcerative colitis in pediatric patients aged 2 years and older. Use of Ustekinumab for this indication is supported by evidence from adequate and well-controlled studies in adult subjects with ulcerative colitis, pharmacokinetic and safety data from pediatric subjects with Crohn's disease aged 2 to 17 years of age, and additional safety, efficacy, and pharmacokinetic data from a 52-week study in 112 pediatric subjects with ulcerative colitis aged 3 to 17 years of age. The adverse reaction profile in the pediatric subjects with ulcerative colitis was similar to adverse reactions reported in the clinical trials of adults with ulcerative colitis. One pediatric subject experienced worsening of preexisting peripheral neuropathy during treatment with Ustekinumab, resulting in hospitalization *[see Warnings and Precautions (5.1), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6, 14.7)]*.

The safety and effectiveness of Ustekinumab for the treatment of moderately to severely active ulcerative colitis have not been established in pediatric patients less than 2 years of age.

8.5 Geriatric Use

Of the 6709 subjects exposed to Ustekinumab, a total of 340 were 65 years of age or older (183 subjects with plaque psoriasis, 65 subjects with psoriatic arthritis, 58 subjects with Crohn's disease, and 34 subjects with ulcerative colitis), and 40 subjects were 75 years of age or older. Clinical trials of Ustekinumab did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

11 DESCRIPTION

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

Ustekinumab® (ustekinumab) injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles with pH of 5.7–6.3.

Ustekinumab for Subcutaneous Use

Available as 45 mg of ustekinumab in 0.5 mL and 90 mg of ustekinumab 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 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 cover that contains dry natural rubber (a derivative of latex).

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

Each 1 mL prefilled syringe delivers 90 mg ustekinumab, L-histidine and L-histidine monohydrochloride monohydrate (1 mg), Polysorbate 80 (0.04 mg), and sucrose (76 mg).

Ustekinumab for Intravenous Infusion

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

Each 26 mL vial delivers 130 mg ustekinumab, EDTA disodium salt dihydrate (0.52 mg), L-histidine (20 mg), L-histidine hydrochloride monohydrate (27 mg), L-methionine (10.4 mg), Polysorbate 80 (10.4 mg), and sucrose (2210 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ustekinumab is a 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 was shown to disrupt IL-12 and IL-23 mediated signaling and cytokine cascades by disrupting the interaction of these cytokines with a shared cell-surface receptor chain, IL-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, was shown to be protective.

12.2 Pharmacodynamics

Plaque Psoriasis

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

Ulcerative Colitis

In both trial UC-1 (induction) and trial 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 (14.6)]*.

12.3 Pharmacokinetics

Absorption

In adult subjects with plaque psoriasis, the median time to reach the maximum serum concentration (T_{max}) was 13.5 days and 7 days, respectively, after a single subcutaneous administration of 45 mg (N=22) and 90 mg (N=24) of ustekinumab. In healthy subjects (N=30), the median T_{max} value (8.5 days) following a single subcutaneous administration of 90 mg of ustekinumab was comparable to that observed in subjects with plaque psoriasis.

Following multiple subcutaneous doses of Ustekinumab in adult subjects with plaque psoriasis, steady-state serum concentrations of ustekinumab were achieved by Week

28. The mean (±SD) steady-state trough serum ustekinumab concentrations were 0.69 ± 0.69 mcg/mL for subjects less than or equal to 100 kg receiving a 45 mg dose and 0.74 ± 0.78 mcg/mL for subjects 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 subjects with Crohn's disease, and 129.1 ± 27.6 mcg/mL in subjects 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 subjects with Crohn's disease, and 3.3 ± 2.3 mcg/mL in subjects 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 subjects with Crohn's disease and 3.0 L (95% CI: 2.96, 3.07) in subjects with ulcerative colitis. The total volume of distribution at steady-state was 4.6 L in subjects with Crohn's disease and 4.4 L in subjects with ulcerative colitis.

Elimination

The mean (±SD) half-life ranged from 14.9 ± 4.6 to 45.6 ± 80.2 days across all trials in subjects with plaque psoriasis following subcutaneous administration. Population pharmacokinetic analyses showed that the clearance of ustekinumab was 0.19 L/day (95% CI: 0.185, 0.197) in subjects with Crohn's disease and 0.19 L/day (95% CI: 0.179, 0.192) in subjects 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 subjects with Crohn's disease and ulcerative colitis.

Metabolism

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

Specific Populations

Weight

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

Age: Geriatric Population

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

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

Age: Pediatric Population

Following multiple recommended doses of Ustekinumab in pediatric subjects 6 years of age and older with plaque 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 pediatric subjects 12 years of age and older.

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

The pharmacokinetics of ustekinumab were studied in pediatric subjects with Crohn's disease aged 2 to 17 years and weighing 13 to 88 kg. There are no clinically significant differences in serum ustekinumab exposure expected between adult patients and pediatric patients with Crohn's disease who receive the recommended dosage *[see Dosage and Administration (2.4)]*.

The pharmacokinetics of ustekinumab were studied in pediatric subjects with ulcerative colitis aged 3 to 17 years and weighing 14 to 80 kg. There are no clinically significant differences in serum ustekinumab exposures expected between adult patients and pediatric patients aged 2 years and older with ulcerative colitis disease who receive the recommended dosage *[see Dosage and Administration (2.6)]*.

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).

No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with ustekinumab at the approved recommended dosage in subjects with Crohn's disease *[see Drug Interactions (7.2)]*.

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 subjects with psoriatic arthritis.

In subjects 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.

12.6 Immunogenicity

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

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

In clinical trials in adult subjects with Crohn's disease and ulcerative colitis, 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.

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. Published literature showed that administration of murine IL-12 caused an anti-tumor effect in mice that contained transplanted tumors and IL-12/IL-23p40 knockout mice or mice treated with anti-IL-12/IL-23p40 antibody had decreased host defense to tumors. Mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone developed UV-induced skin cancers earlier and more frequently compared to wild-type mice. The relevance of these experimental findings in mouse models for malignancy risk in humans is unknown.

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Adult Subjects with Plaque Psoriasis

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

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

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

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

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

Clinical Response

The results of Ps STUDY 1 and Ps STUDY 2 are presented in Table 12 below.

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

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

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

In subjects who weighed 100 kg or less, response rates were comparable with both the 45 mg and 90 mg doses; however, in subjects who weighed greater than 100 kg, higher response rates were seen with 90 mg dosing compared with 45 mg dosing (Table 13 below).

Table 13: Clinical Outcomes by Weight at Week 12 in Adult Subjects with Plaque Psoriasis in Ps STUDY 1 and Ps STUDY 2

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

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

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

14.2 Pediatric Subjects with Plaque Psoriasis

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

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

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

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

Clinical Response

The efficacy results at Week 12 for Ps STUDY 3 are presented in Table 14.

Table 14: Efficacy Results at Week 12 in Pediatric Subjects 12 Years of Age and Older with Plaque Psoriasis in Ps STUDY 3

	Ps STUDY 3	
	Placebo n (%)	**Ustekinumab* n (%)**
N	**37**	**36**
PGA		
PGA of Cleared (0) or Minimal (1)	2 (5.4%)	25 (69.4%)
PASI		
PASI 75 responders	4 (10.8%)	29 (80.6%)
PASI 90 responders	2 (5.4%)	22 (61.1%)

* Using the weight-based dosage regimen specified in Table 1 and Table 2.

14.3 Psoriatic Arthritis

The safety and efficacy of Ustekinumab was assessed in 927 subjects (PsA STUDY 1, n=615; PsA STUDY 2, n=312), in two randomized, double-blind, placebo-controlled trials in adult subjects 18 years of age and older with active PsA (≥5 swollen joints and ≥5 tender joints) despite nonsteroidal anti-inflammatory (NSAID) or disease modifying antirheumatic (DMARD) therapy. Subjects in these trials had a diagnosis of PsA for at least 6 months. Subjects 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 subjects, respectively, had enthesitis and dactylitis at baseline.

Subjects 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 subjects continued on stable doses of MTX (≤25 mg/week). The primary endpoint was the percentage of subjects achieving ACR 20 response at Week 24.

In PsA STUDY 1 and PsA STUDY 2, 80% and 86% of the subjects, 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 subjects had been previously treated with TNF blocker, of whom over 70% had discontinued their TNF blocker treatment for lack of efficacy or intolerance at any time.

Clinical Response

In both trials, a greater proportion of subjects 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 15). 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 subjects treated with Ustekinumab alone or in combination with methotrexate. Responses were similar in subjects regardless of prior TNFα exposure.

Table 15: ACR 20, ACR 50, ACR 70 and PASI 75 Responses In PsA STUDY 1 And PsA STUDY 2 At Week 24

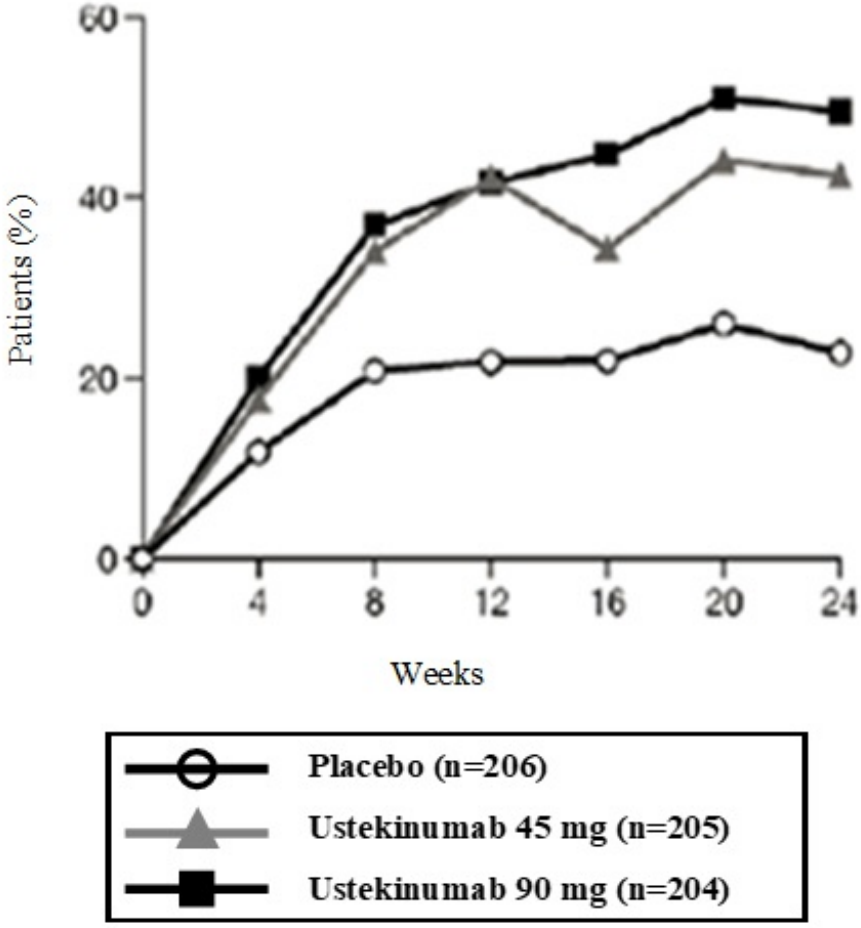
	PsA STUDY 1			PsA STUDY 2		
		Ustekinumab			Ustekinumab	
	Placebo	45 mg	90 mg	Placebo	45 mg	90 mg
Number of subjects randomized	**206**	**205**	**204**	**104**	**103**	**105**
ACR 20 response, N (%)	47 (23%)	87 (42%)	101 (50%)	21 (20%)	45 (44%)	46 (44%)
ACR 50 response, N (%)	18 (9%)	51 (25%)	57 (28%)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

* Number of subjects with ≥ 3% BSA psoriasis skin involvement at baseline

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

Figure 1: Percent of Subjects Achieving ACR 20 Response through Week 24

PsA STUDY 1



The results of the components of the ACR response criteria are shown in Table 16.

Table 16: Mean Change From Baseline In ACR Components At Week 24

	PsA STUDY 1		
		Ustekinumab	
	Placebo (N=206)	45 mg (N=205)	90 mg (N=204)
Number of swollen joints*			
Baseline	15	12	13
Mean Change at Week 24	-3	-5	-6
Number of tender joints†			
Baseline	25	22	23
Mean Change at Week 24	-4	-8	-9
Subject's assessment of pain‡			
Baseline	6.1	6.2	6.6

Mean Change at Week 24	-0.5	-2.0	-2.6
Subject global assessment‡			
Baseline	6.1	6.3	6.4
Mean Change at Week 24	-0.5	-2.0	-2.5
Physician global assessment‡			
Baseline	5.8	5.7	6.1
Mean Change at Week 24	-1.4	-2.6	-3.1
Disability index (HAQ)§			
Baseline	1.2	1.2	1.2
Mean Change at Week 24	-0.1	-0.3	-0.4
CRP (mg/dL)¶			
Baseline	1.6	1.7	1.8
Mean Change at Week 24	0.01	-0.5	-0.8

* Number of swollen joints counted (0–66)
† Number of tender joints counted (0–68)
‡ Visual analog scale; 0= best, 10=worst.
§ 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.
¶ 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 subjects showed improvement in physical function compared to subjects receiving placebo as assessed by HAQ-DI at Week 24. In both trials, the proportion of HAQ-DI responders (≥0.3 improvement in HAQ-DI score) was greater in the Ustekinumab 45 mg and 90 mg groups compared to placebo at Week 24.

14.4 Adult Crohn's Disease

Ustekinumab was evaluated in three randomized, double-blind, placebo-controlled clinical trials in adult subjects 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 trials (CD-1 and CD-2) followed by a 44-week subcutaneous randomized withdrawal maintenance trial (CD-3) representing 52 weeks of therapy. Subjects in CD-1 had failed or were intolerant to treatment with one or more TNF blockers, while subjects in CD-2 had failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a TNF blocker.

Trials CD-1 and CD-2

In trials CD-1 and CD-2, 1409 subjects 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 trials, subjects 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 trial CD-1, subjects had failed or were intolerant to prior treatment with a TNF blocker: 29% subjects 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 subjects, 48% failed or were intolerant to one TNF blocker and 52% had failed 2 or 3 prior TNF blockers. At baseline and throughout the trial, approximately 46% of the subjects were receiving corticosteroids and 31% of the subjects 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 trial CD-2, subjects had failed or were intolerant to prior treatment with corticosteroids (81% of subjects), at least one immunomodulator (6-MP, AZA, MTX; 68% of subjects), or both (49% of subjects). Additionally, 69% never received a TNF blocker and 31% previously received but had not failed a TNF blocker. At baseline, and throughout the trial, approximately 39% of the subjects were receiving corticosteroids and 35% of the subjects 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 trials, a greater proportion of subjects 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 17 for clinical response and remission rates). Clinical response and remission were significant as early as Week 3 in Ustekinumab-treated subjects and continued to improve through Week 8.

Table 17: 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),	50 (20%)	94 (38%)[¶]	18% (10%, 25%)	67 (32%)	121 (58%)[¶]	26% (17%, 35%)

Week 8						
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 subjects who failed or were intolerant to TNF blocker therapy
† Patient population consisted of subjects 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.
§ $0.001 \leq p < 0.01$
¶ $p < 0.001$

Trial CD-3

The maintenance trial (CD-3) evaluated 388 subjects who achieved clinical response (≥100 point reduction in CDAI score) at Week 8 with either induction dose of Ustekinumab in trials CD-1 or CD-2. Subjects were randomized to receive a subcutaneous maintenance regimen of either 90 mg Ustekinumab every 8 weeks or placebo for 44 weeks (see Table 18).

Table 18: Clinical Response and Remission In CD-3 (Week 44; 52 Weeks From Initiation Of 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 Subjects 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 subjects who were in response to Ustekinumab and were randomized to receive placebo at the start of maintenance therapy.
† Subjects who achieved clinical response to Ustekinumab at the end of the induction trial.
‡ $p < 0.01$
§ $0.01 \leq p < 0.05$

¶ Subjects 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 subjects who received Ustekinumab were corticosteroid-free and in clinical remission, compared to 30% of subjects in the placebo group.

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

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

Subjects who were not in clinical response 8 weeks after Ustekinumab induction were not included in the primary efficacy analyses for trial CD-3; however, these subjects were eligible to receive a 90 mg subcutaneous injection of Ustekinumab upon entry into trial CD-3. Of these subjects, 102/219 (47%) achieved clinical response eight weeks later and were followed for the duration of the trial.

14.5 Pediatric Crohn's Disease

The efficacy and safety of Ustekinumab was evaluated in 101 pediatric subjects aged 2 years to 17 years in a multi-center trial consisting of an open-label intravenous 8-week induction phase followed by randomization to one of two subcutaneous dosage regimens in a 44-week double-blind maintenance phase representing 52 weeks of therapy. Efficacy analyses were conducted in 93 subjects with moderately to severely active Crohn's disease (NCT04673357).

Pediatric subjects enrolled in the study had an inadequate response or were intolerant to treatment with oral corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and/or prior biologic therapy (TNF blockers or vedolizumab).

Of the 93 subjects included in the efficacy analyses, the mean age was 14 years (range 5 to 17 years), the median weight was 49 kg, and 39% were female. Additionally, 99% identified as not Hispanic or Latino and 1% as not reported; 89% identified as White, 8% as Asian, 2% as Black or African American, and 1% as not reported. The median Pediatric Crohn's Disease Activity Index (PCDAI) was 40 and the median Simple Endoscopic Score for Crohn's Disease (SES-CD) was 12.

Subjects received induction treatment with a single Ustekinumab intravenous dose, of approximately 6 mg/kg (subjects weighing 40 kg or more) or 250 mg/m^2 (subjects weighing less than 40 kg, based on body surface area [BSA]), followed by a randomized double-blind subcutaneous maintenance regimen of 90 mg Ustekinumab (subjects weighing 40 kg or more) or 60 mg/m^2 Ustekinumab (subjects weighing less than 40 kg,

based on BSA) every 8 weeks or another subcutaneous dosage regimen.

The recommended dosage for pediatric subjects weighing 10 kg to less than 40 kg differs from the BSA-based dosage in this study. There are no anticipated clinically relevant differences in efficacy between the recommended and studied pediatric dosages of Ustekinumab *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

The primary endpoint of the study was clinical remission at Week 52 (from initiation of induction) which was evaluated in the subset of subjects who achieved clinical response at Week 8.

Efficacy Results

At Week 8, the proportion of subjects who achieved clinical remission (defined as PCDAI score of ≤10) was 46% (43/93).

The proportion of subjects in clinical response at Week 8, defined as a reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score ≤30, was 87% (81/93).

Of the 81 subjects who received intravenous induction treatment and achieved clinical response or remission at Week 8, there were 39 subjects who received the subcutaneous maintenance dosage described above every 8 weeks. Efficacy endpoints assessed at Week 52, including clinical response and/or remission (shown in Table 19), were assessed in this subset of subjects.

Table 19: Proportion of Pediatric Subjects with Moderately to Severely Active Crohn's Disease Meeting Efficacy Endpoints at Week 52 (From Initiation of Induction) in a Clinical Trial

Endpoint	90 mg or 60 mg/m^2 Ustekinumab Every 8 Weeks* n/N (%) [95% CI]
Clinical Remission†	20/39 (51%) [36%, 66%]
Clinical Response‡	23/39 (59%) [43%, 73%]
Clinical Remission in Subjects in Clinical Remission at Week 8§	17/21 (81%) [59%, 93%]

* This subcutaneous dosage regimen followed 8 weeks after a single intravenous induction dose of approximately 6 mg/kg (subjects weighing 40 kg or more) or 250 mg/m^2 (subjects weighing less than 40 kg, based on body surface area [BSA]).
† Clinical remission is defined as PCDAI score ≤10.
‡ Clinical response is defined as reduction from baseline in the PCDAI score of >12.5 points with a total PCDAI score ≤30
§ Endpoint was evaluated in subjects 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 52, the proportion of subjects in endoscopic response, defined as a reduction in the SES-CD score of > 50% or SES-CD score ≤ 2, in subjects with a baseline SES-CD score of ≥ 3, was 26% (10/39). The proportion of subjects achieving corticosteroid-free clinical remission defined as PCDAI score of ≤10 points and not receiving corticosteroids

for at least 90 days prior to Week 52, was 49% (19/39).

14.6 Adult Ulcerative Colitis

Ustekinumab was evaluated in two randomized, double-blind, placebo-controlled clinical trials [UC-1 and UC-2 (NCT02407236)] in adult subjects 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 trial (UC-1) was followed by the 44-week subcutaneous randomized withdrawal maintenance trial (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, subjects had a median Mayo score of 9, with 84% of subjects having moderate disease (Mayo score 6–10) and 15% having severe disease (Mayo score 11–12).

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

Trial UC-1

In UC-1, 961 subjects 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. Subjects 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 trial, approximately 52% subjects were receiving oral corticosteroids, 28% subjects were receiving immunomodulators (AZA, 6-MP, or MTX) and 69% subjects 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 20.

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 20.

In UC-1, a significantly greater proportion of subjects 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 20).

Table 20: Proportion of Subjects 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 Improvementß	**26**	**8%**	**54**	**17%**	9% (3%, 14%) §
Bio-naïve¶	19/151	13%	30/147	20%	
Prior biologic failure	6/161	4%	21/166	13%	

* Infusion dose of Ustekinumab using the weight-based dosage regimen specified in Table 6.
† 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 subjects on placebo and 9 subjects 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.
ß 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).

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 subjects.

Trial UC-2

The maintenance trial (UC-2) evaluated 523 subjects who achieved clinical response 8 weeks following the intravenous administration of either induction dose of Ustekinumab in UC-1. These subjects 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 subjects in clinical remission at Week 44. The secondary endpoints included the proportion of subjects maintaining clinical response at Week 44, the proportion of subjects with endoscopic improvement at Week 44, the proportion of subjects with corticosteroid-free clinical remission at Week 44, and the proportion of subjects maintaining clinical remission at Week 44 among subjects who achieved clinical remission 8 weeks after induction.

Results of the primary and secondary endpoints at Week 44 in subjects treated with Ustekinumab at the recommended dosage (90 mg every 8 weeks) compared to the placebo are shown in Table 21.

Table 21: 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					17%

Corticosteroid-free Clinical Remission[Þ]	**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 subjects 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 subjects 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 subjects on placebo and 6 subjects 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 subjects in clinical remission and not receiving corticosteroids at Week 44.
ß p=0.004

Other Endpoints

Week 16 Responders to Ustekinumab Induction

Subjects who were not in clinical response 8 weeks after induction with Ustekinumab in UC-1 were not included in the primary efficacy analyses for trial UC-2; however, these subjects were eligible to receive a 90 mg subcutaneous injection of Ustekinumab at Week 8. Of these subjects, 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%) subjects who maintained clinical response and there were 51/157 (32%) who achieved clinical remission.

Histologic-Endoscopic Mucosal Improvement at Week 44

The proportion of subjects achieving histologic-endoscopic mucosal improvement during maintenance treatment in UC-2 was 75/172 (44%) among subjects on Ustekinumab and 40/172 (23%) in subjects 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 subjects treated with Ustekinumab and 12/319 (4%) of subjects in the placebo group. At Week 44 of UC-2, endoscopic normalization was achieved in 51/176 (29%) of subjects treated with Ustekinumab and in 32/175 (18%) of subjects in placebo

group.

14.7 Pediatric Ulcerative Colitis

The efficacy and safety of Ustekinumab was evaluated in 112 pediatric subjects aged 3 years to 17 years in a multi-center trial consisting of an open-label intravenous 8-week induction phase followed by randomization to one of two subcutaneous dosage regimens in a 44-week double-blind maintenance phase representing 52 weeks of therapy. Efficacy analyses were conducted in 107 subjects with moderately to severely active ulcerative colitis (NCT04630028).

Pediatric subjects enrolled in the study had an inadequate response or were intolerant to treatment with corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, methotrexate), and/or prior biologic therapy (TNF blocker or vedolizumab) therapy.

Of the 107 subjects included in the efficacy analyses, the mean age was 13 years (range 3 to 17 years), the median weight was 46 kg (range 14 to 80 kg), and 54% were female. Additionally, 96% identified as not Hispanic or Latino, 2% as unknown, 1% as Hispanic or Latino, and 1% as not reported; 84% identified as White, 11% as Asian, 2% as Black or African American, 1% as unknown, and 1% as not reported. At baseline, subjects had a median Mayo score of 8; approximately 43% of subjects were receiving corticosteroids and 38% of subjects were receiving immunomodulators.

Subjects received induction treatment with a single Ustekinumab intravenous dose, of approximately 6 mg/kg (subjects weighing 40 kg or more) or 250 mg/m^2 (subjects weighing less than 40 kg, based on BSA), followed by a randomized double-blind subcutaneous maintenance regimen of 90 mg Ustekinumab (subjects weighing 40 kg or more) or 60 mg/m^2 Ustekinumab (subjects weighing less than 40 kg, based on BSA) every 8 weeks or another subcutaneous dosage regimen.

The recommended dosage for pediatric subjects weighing 10 kg to less than 40 kg differs from the BSA-based dosage in this study. There are no anticipated clinically relevant differences in efficacy between the recommended and studied pediatric dosages of Ustekinumab *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*.

The primary endpoint of the study was clinical remission at Week 52 (from initiation of induction) which was evaluated in the subset of subjects who achieved clinical response at Week 8. Clinical remission was defined, based on Mayo subscores, as: a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore had not increased from induction baseline. Clinical response was defined as a ≥2 points and ≥30% decrease from baseline in the Modified Mayo score, defined as 3-component Mayo score without the Physician's Global Assessment, with either a decrease from baseline in rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.

Efficacy Results

At Week 8, the proportion of subjects who achieved clinical remission was 25% (27/107) and the proportion of subjects in clinical response was 69% (74/107).

Of the 74 subjects who received intravenous induction treatment and achieved clinical response at Week 8, there were 38 who received the subcutaneous maintenance

dosage described above every 8 weeks. Efficacy endpoints assessed at Week 52, including clinical remission (shown in Table 22), were assessed in this subset of subjects.

Table 22: Proportion of Pediatric Subjects with Moderately to Severely Active Ulcerative Colitis Meeting Efficacy Endpoints at Week 52 (From Initiation of Induction) in a Clinical Trial

Endpoint	90 mg or 60 mg/m^2 Ustekinumab Every 8 weeks * n/N (%) [95% CI]
Clinical Remission†	20/38 (53%) [37%, 68%]
Corticosteroid-free Clinical Remission‡	20/38 (53%) [37%, 68%]
Maintenance of Clinical Remission at Week 52 in subjects who achieved clinical remission 8 weeks after induction	9/16 (56%) [33%, 77%]
Endoscopic Improvement§	20/38 (53%) [37%, 68%]

* This subcutaneous dosage regimen followed 8 weeks after a single intravenous induction dose of approximately 6 mg/kg (subjects weighing 40 kg or more) or 250 mg/m^2 (subjects weighing less than 40 kg, based on body surface area [BSA]).
† Clinical remission was defined by Mayo subscores as: a stool frequency subscore of 0 or 1, a rectal bleeding subscore of 0, and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy, where the stool frequency subscore has not increased from induction baseline.
‡ Corticosteroid-free clinical remission is defined as subjects in clinical remission and not receiving corticosteroids for at least 90 days prior to maintenance Week 44.
§ Endoscopic improvement is defined as a Mayo endoscopy subscore of 0 or 1 with no friability present on the endoscopy.

At Week 52, the proportion of subjects with histologic-endoscopic mucosal improvement, defined as achieving a combination of histologic improvement (neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations or granulation tissue according to the Geboes grading system) and endoscopic improvement (a Mayo endoscopy subscore of 0 or 1 with no friability present in the endoscopy) was 50% (19/38).

16 HOW SUPPLIED/STORAGE AND HANDLING

Ustekinumab® (ustekinumab) injection is a sterile, preservative-free, colorless to light yellow solution and may contain a few small translucent or white particles. 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 57894-440-01)
- 90 mg/mL (NDC 57894-441-01)

Each prefilled syringe is equipped with a 27-gauge fixed ½ inch needle, a needle safety guard, and a needle cover that contains dry natural rubber.

Single-dose Vial

- 45 mg/0.5 mL (NDC 57894-440-03)

For Intravenous Infusion

Single-dose Vial

- 130 mg/26 mL (5 mg/mL) (NDC 57894-444-01)

Storage and Stability

Store Ustekinumab vials and prefilled syringes refrigerated between 2 ºC to 8 ºC (36 ºF to 46 ºF). Store Ustekinumab vials upright. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake.

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

17 PATIENT COUNSELING INFORMATION

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

Infections

Inform patients that Ustekinumab 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 Ustekinumab *[see Warnings and Precautions (5.4)]*.

Serious Hypersensitivity Reactions

- Inform patients that serious hypersensitivity reactions have been reported with intravenous and subcutaneous administration of Ustekinumab. Instruct patients to discontinue Ustekinumab and seek immediate medical attention if they experience any signs or symptoms of hypersensitivity reactions *[see Warnings and Precautions (5.5)].*
- Inform patients the needle cover on the prefilled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex *[see Dosage and Administration (2.7)]*.
- Inform patients that serious hypersensitivity reactions have been reported with postmarketing use of Ustekinumab in patients with a history of alpha-gal syndrome, allergy to mammalian meat or meat products, or anti-alpha-gal IgE *[see Adverse Reactions (6.2)]*. Instruct patients to inform their healthcare provider if they have a hypersensitivity to alpha-gal or have been diagnosed with alpha-gal syndrome.

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 Ustekinumab 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.

Prefilled Syringe Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

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

For patent information: www.janssenpatents.com

MEDICATION GUIDE
Ustekinumab (yü-stə-kin-ü-mab)
injection, for subcutaneous or intravenous use

What is the most important information I should know about Ustekinumab?
Ustekinumab is a medicine that affects your immune system. Ustekinumab can increase your risk of having serious side effects, including:

- **Serious infections.** Ustekinumab may lower the ability of your immune system to fight infections and may increase your risk of infections. Some people have serious infections during treatment with Ustekinumab, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses. Some people have to be hospitalized for treatment of their infection.
  - Your healthcare provider should check you for TB before starting Ustekinumab.
  - If your healthcare provider feels that you are at risk for TB, you may be treated with medicine for TB before you begin treatment with Ustekinumab and during treatment with Ustekinumab.
  - Your healthcare provider should watch you closely for signs and symptoms of TB while you are being treated with Ustekinumab.

  You should not start Ustekinumab if you have any kind of infection unless your healthcare provider says it is okay.

  Before starting Ustekinumab, tell your healthcare provider if you:
  - think you have an infection or have symptoms of an infection such as:
    - fever, sweat, or chills
    - muscle aches
    - cough
    - shortness of
    - 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

- shortness of breath
- blood in phlegm
- 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 Ustekinumab, call your healthcare provider right away if you get 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. Ustekinumab 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 Ustekinumab may also be more likely to get these infections.
- **Cancers.** Ustekinumab may decrease the activity of your immune system and increase your risk for certain types of cancers. Tell your healthcare provider if you have ever had any type of cancer. Some people who are receiving Ustekinumab and have risk factors for skin cancer have developed certain types of skin cancers. During your treatment with Ustekinumab, tell your healthcare provider if you develop any new skin growths.

What is Ustekinumab?

Ustekinumab is a prescription medicine used to treat:

- adults and children 6 years of age and older with moderate to severe plaque 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 of age and older with active psoriatic arthritis.
- adults and children 2 years of age and older with moderately to severely active Crohn's disease.
- adults and children 2 years of age and older with moderately to severely active ulcerative colitis.

It is not known if Ustekinumab is safe and effective in children less than 2 years of age with Crohn's disease, in children less than 2 years of age with ulcerative colitis or in children less than 6 years of age with plaque psoriasis or psoriatic arthritis.

Who should not use Ustekinumab?

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

Before you use or receive Ustekinumab, tell your healthcare provider 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 Ustekinumab?**"
- ever had an allergic reaction to Ustekinumab. Ask your healthcare provider if you are not sure.
- are allergic to latex. The needle cover on the prefilled syringe contains latex.

- have recently received or are scheduled to receive an immunization (vaccine). People who are being treated with Ustekinumab should avoid receiving live vaccines. Tell your healthcare provider 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 avoid receiving the BCG vaccine during the 1 year before receiving Ustekinumab or 1 year after you stop receiving Ustekinumab.**
- 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 Ustekinumab. Ustekinumab may also increase your risk of having an allergic reaction to an allergy shot.
- receive or have received phototherapy for your psoriasis.
- have an allergy to alpha-gal or have been diagnosed with alpha-gal syndrome (a type of food allergy to certain meats or meat products that may be triggered by some tick bites).
- are pregnant or plan to become pregnant. It is not known if Ustekinumab can harm your unborn baby. You and your healthcare provider should decide if you will receive Ustekinumab.
- are breastfeeding or plan to breastfeed. Ustekinumab can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive Ustekinumab.

Tell your healthcare provider 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 healthcare provider and pharmacist when you get a new medicine.

How should I use Ustekinumab?

- Use Ustekinumab exactly as the healthcare provider tells you to. The healthcare provider will determine the right dose of Ustekinumab, the amount for each injection, and how often it should be given. Be sure to keep all scheduled follow-up appointments.
- **The needle cover on the Ustekinumab prefilled syringe contains latex. Do not handle the needle cover if you are sensitive to latex.**
- Adults and children 2 years of age and older with Crohn’s disease and ulcerative colitis will receive the first dose of Ustekinumab 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. Ustekinumab will then be received as an injection under the skin (subcutaneous injection) 8 weeks after the first dose of Ustekinumab, as described below.
- Adults and children 6 years of age and older with plaque psoriasis or psoriatic arthritis will receive Ustekinumab as an injection under the skin as described below.
- **Injecting Ustekinumab under the skin**
  - Ustekinumab is intended for use under the guidance and supervision of a healthcare provider.
  - In children, it is recommended that Ustekinumab be administered by a healthcare provider. If a healthcare provider decides that you or a caregiver may give the injections of Ustekinumab at home, you or a caregiver should receive training on the right way to prepare and inject Ustekinumab.

- Do not try to inject Ustekinumab until you have been shown how to inject Ustekinumab by a healthcare provider.
- Ustekinumab can be injected under the skin in the 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 Ustekinumab.

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

What should I avoid while using Ustekinumab?

You should avoid receiving a live vaccine during treatment with Ustekinumab. See **"Before you use or receive Ustekinumab, tell your healthcare provider about all of your medical conditions, including if you:"**

What are the possible side effects of Ustekinumab?

Ustekinumab may cause serious side effects, including:

- See "**What is the most important information I should know about Ustekinumab?**"
- **Serious allergic reactions.** Serious allergic reactions including death can occur with Ustekinumab. Stop using Ustekinumab and get medical help right away if you get any of the following symptoms of a serious allergic reaction:

  - feeling faint
  - swelling of your face, eyelids, tongue, or throat
  - chest discomfort
  - trouble breathing
  - skin rash

- **Posterior Reversible Encephalopathy Syndrome (PRES).** PRES is a rare condition that affects the brain and can cause death. Tell your healthcare provider right away if you get any symptoms of PRES during treatment with Ustekinumab, including:

  - headache
  - seizures
  - confusion
  - vision problems

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

The most common side effects of Ustekinumab include:

- nasal congestion, sore throat, and runny nose
- upper respiratory infections
- redness at the injection site
- vaginal yeast infections
- urinary tract infections

- fever
- headache
- tiredness
- itching
- nausea and vomiting
- influenza
- urinary tract infections
- sinus infection
- bronchitis
- diarrhea
- stomach pain
- joint pain

These are not all of the possible side effects of Ustekinumab. 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 Janssen Biotech, Inc. at 1-800-526-7736.

How should I store Ustekinumab?

- Store Ustekinumab vials and prefilled syringes in a refrigerator between 36 °F to 46 °F (2 °C to 8 °C).
- Store Ustekinumab vials standing up straight (upright).
- Store Ustekinumab in the original carton to protect it from light until time to use it.
- Do not freeze Ustekinumab.
- Do not shake Ustekinumab.
- If needed, individual Ustekinumab prefilled syringes may also be stored at room temperature up to 86 °F (30 °C) for a maximum single period of up to 30 days in the original carton to protect from light.
- Record the date when the prefilled syringe is first removed from the refrigerator on the carton in the space provided.
- After a prefilled syringe has been stored at room temperature, do not return it to the refrigerator.
- Throw away (discard) the prefilled syringe if it is not used within 30 days at room temperature storage.
- Do not use Ustekinumab after the expiration date on the carton or on the prefilled syringe.

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

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

What are the ingredients in Ustekinumab?
Active ingredient: ustekinumab
Inactive ingredients: Single-dose prefilled syringe and single-dose vial for subcutaneous use contain L-histidine, L-histidine monohydrochloride monohydrate, Polysorbate 80, and Sucrose. **Single-dose vial for intravenous infusion** contains EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, Polysorbate 80, and Sucrose.
Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License No. 1864
For patent information: www.janssenpatents.com
For more information call 1-800-526-7736.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 08/2026

INSTRUCTIONS FOR USE

Ustekinumab (yü-stə-'kin-ü-mab)
injection, for subcutaneous use

This Instructions for Use contains information on how to inject Ustekinumab using a prefilled syringe.

Read this Instructions for Use before you start using Ustekinumab. A healthcare provider should show you how to prepare and give an injection of Ustekinumab the right way.

If you cannot give the injection:
- ask a healthcare provider to help you, or
- ask someone who has been trained by a healthcare provider to give the injections.

Do not try to inject Ustekinumab until you have been shown how to inject Ustekinumab by a healthcare provider.

Important Information You Need to Know Before Injecting Ustekinumab:
- **For subcutaneous use only** (inject directly under the skin).
- Before you start, check the carton to make sure that it is the right dose. You will have either 45 mg or 90 mg as prescribed by the healthcare provider.
  - If the dose is 45 mg, you will receive one 45 mg prefilled syringe.
  - If the 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 two injections, one right after the other.**
- Check the expiration date on the prefilled syringe and carton. **Do not** use Ustekinumab after the expiration date has passed or if the prefilled syringe has been kept at room temperature up to 86 °F (30 °C) for longer than a maximum single period of 30 days or if the prefilled syringe has been stored above 86 °F (30 °C). Call the healthcare provider or pharmacist, or call 1-800-526-7736 for help.
- Make sure the syringe is not damaged.
- **The needle cover on the prefilled syringe contains latex. Do not handle the needle cover on the Ustekinumab prefilled syringe if you are allergic to latex.**
- Check the prefilled syringe for any particles or discoloration. The liquid in the prefilled syringe should look clear and colorless to light yellow with a few small clear or white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new prefilled syringe.
- **Do not shake the prefilled syringe at any time.** Shaking the prefilled syringe may damage the Ustekinumab medicine. If the prefilled syringe has been shaken, do not use it. Get a new prefilled syringe.
- To reduce the risk of accidental needle sticks, each prefilled syringe has a needle guard that is automatically activated to cover the needle after you have given the injection. Do not pull back on the plunger at any time.

Storing Ustekinumab prefilled syringes

- Store Ustekinumab prefilled syringes in the refrigerator between 36 °F to 46 °F (2 °C to 8 °C).
- Store Ustekinumab prefilled syringes in the original carton to protect from light.
- **Do not** freeze Ustekinumab prefilled syringes.
- If needed, individual Ustekinumab prefilled syringes may be stored at room temperature up to 86 °F (30 °C) for a maximum single period of up to 30 days in the original carton to protect from light.
- Record the date when the prefilled syringe is removed from the refrigerator on the carton in the space provided.
- After a prefilled syringe has been stored at room temperature, do not return it to the refrigerator.
- Throw away (discard) the prefilled syringe if it is not used within 30 days at room temperature storage.

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

Gather the supplies you will need to prepare and to give the injection. (See Figure A) You will need:

- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of Ustekinumab **(See Figure B)**
- FDA-cleared sharps disposal container. **See "Step 4: Disposing of the syringes"**

Figure A

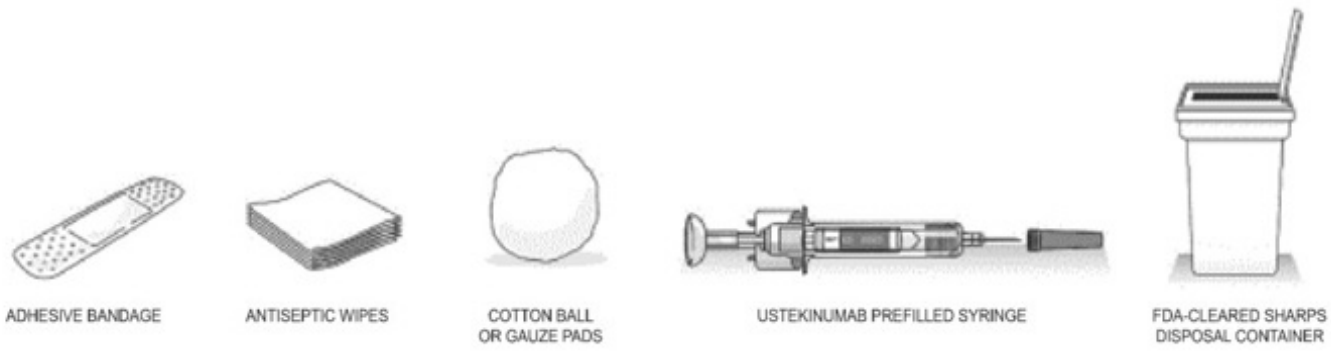
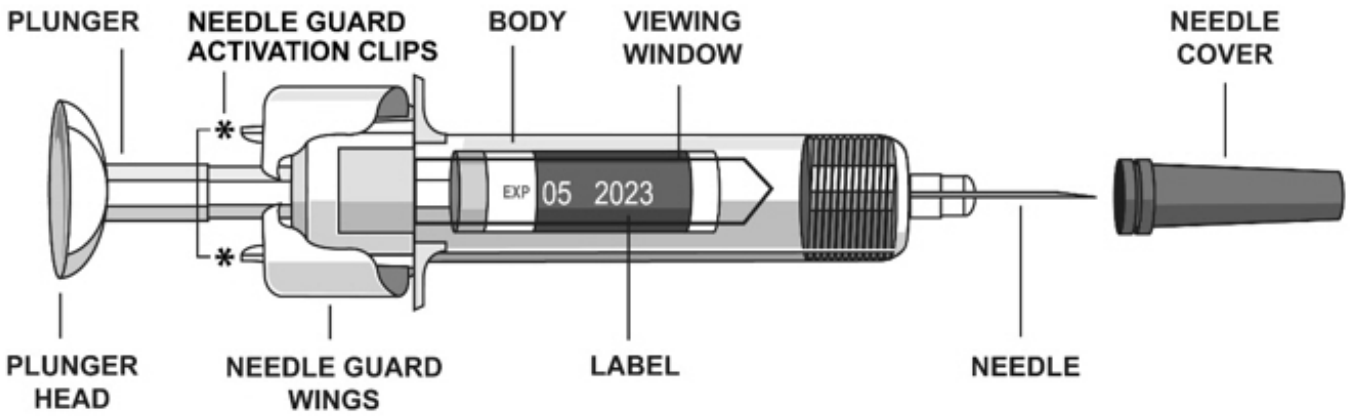


Figure B

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



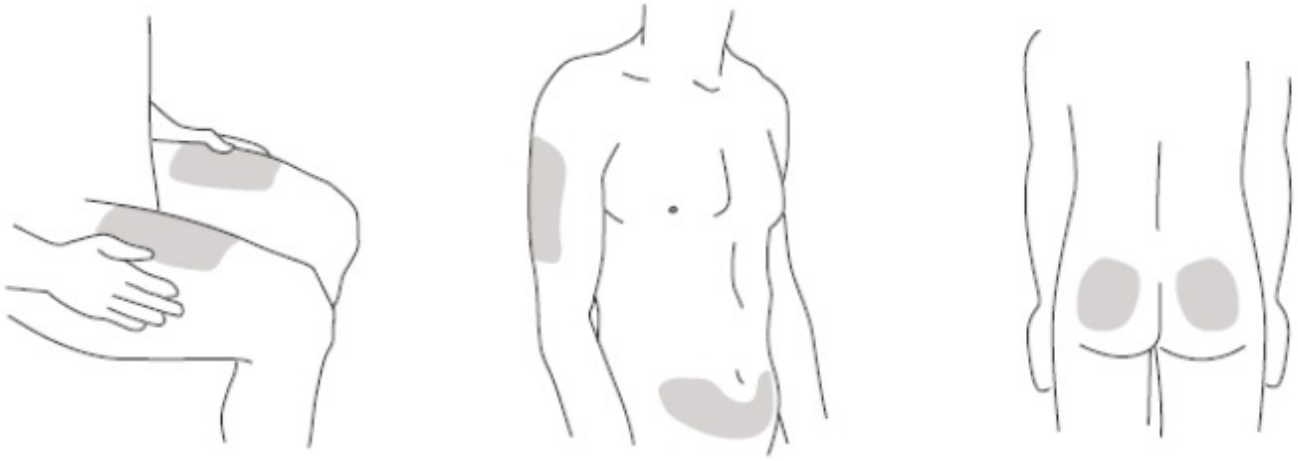
Step 1: Preparing the injection

- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.
- Hold the prefilled syringe with the covered needle pointing upward.

Step 2: Preparing the injection site

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

Figure C



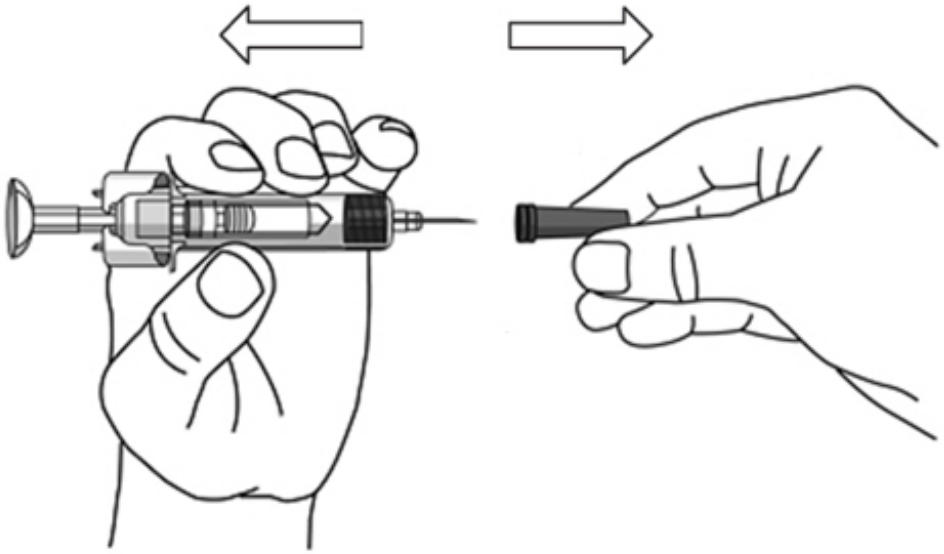
*Areas in gray are recommended injection sites.

Step 3: Injecting Ustekinumab

- Remove the needle cover when you are ready to inject Ustekinumab.
- **Do not** touch the plunger or plunger head while removing the needle cover.

- Hold the body of the prefilled syringe with 1 hand and pull the needle cover straight off. **(See Figure D)**
- Put the needle cover in the trash.
- You may also see a drop of liquid at the end of the needle. This is normal.
- **Do not** touch the needle or let it touch anything.
- **Do not** use the prefilled syringe if it is dropped without the needle cover in place.

Figure D

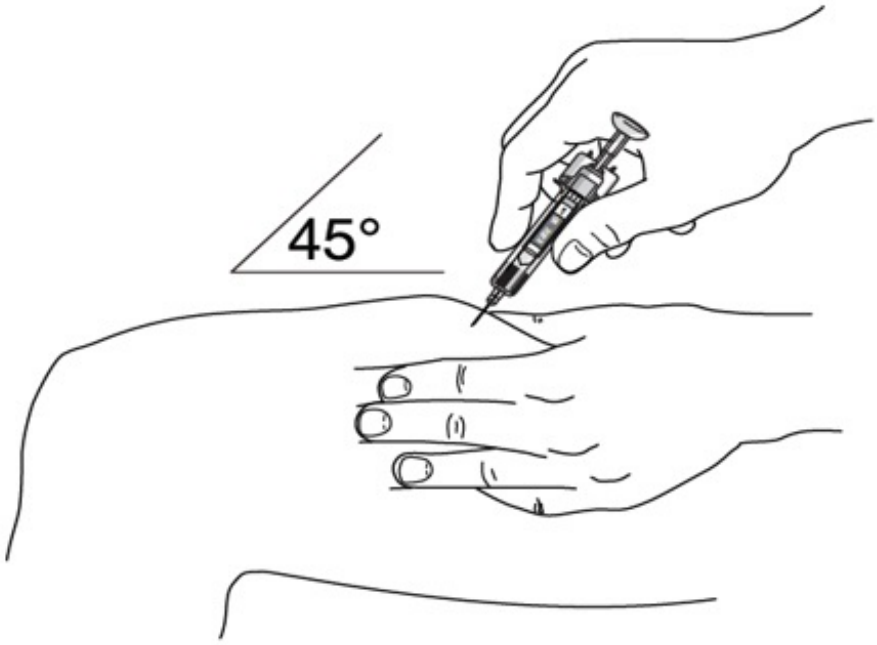


- Hold the body of the prefilled syringe in 1 hand between the thumb and index fingers. **(See Figure E)**

Figure E

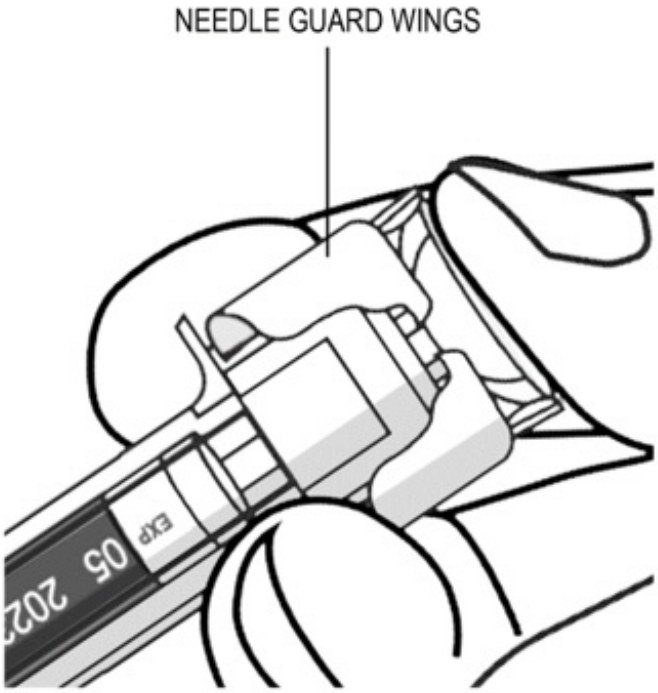
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure F)**

Figure F



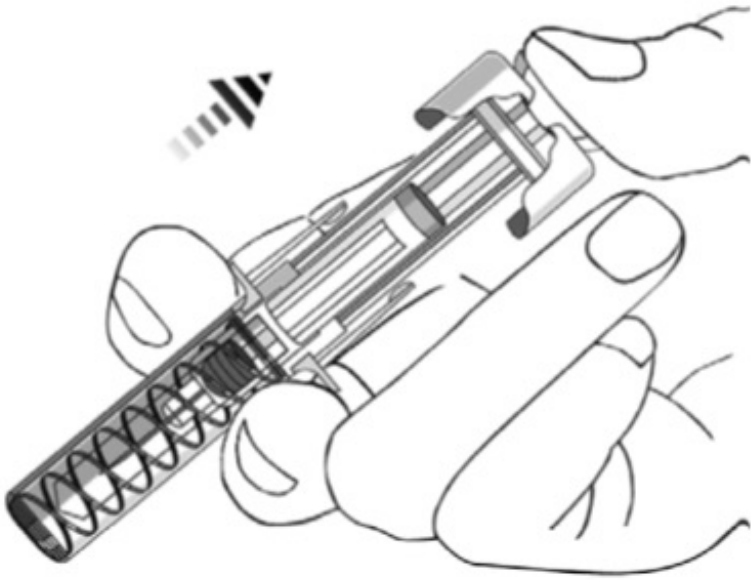
- Inject all of the liquid by using your thumb to push in the plunger until the plunger head is completely between the needle guard wings. **(See Figure G)**

Figure G



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

Figure H



- When the needle is pulled out of the skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

If the 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 a second injection right after the first. Repeat Steps 1 to 3 for the second injection using a new syringe. Choose a different site for the second injection.

Step 4: Disposing of the syringes

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

Prefilled Syringe Manufactured by:

Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License No. 1864 at Baxter Pharmaceutical Solutions, Bloomington, IN 47403 and at Cilag AG, Schaffhausen, Switzerland

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

Revised: 7/2026

For patent information: www.janssenpatents.com

INSTRUCTIONS FOR USE

Ustekinumab (yü-stə-ˈkin-ü-mab)
injection, for subcutaneous use

This Instructions for Use contains information on how to inject Ustekinumab using a vial.

Read this Instructions for Use before you start using Ustekinumab. A healthcare provider should show you how to prepare, measure the dose, and give an injection of Ustekinumab the right way.

If you cannot give the injection:
- ask a healthcare provider to help you, or
- ask someone who has been trained by a healthcare provider to give the injections.

Do not try to inject Ustekinumab until you have been shown how to inject Ustekinumab by a healthcare provider.

Important Information You Need to Know Before Injecting Ustekinumab:
- **For subcutaneous use only** (inject directly under the skin).
- Before you start, check the carton to make sure that the number of vials and strength is correct. You will have either 45 mg or 90 mg as prescribed by the healthcare provider.
  - If the dose is 45 mg or less, you will receive one 45 mg vial.
  - If the dose is more than 45 mg, you will receive two 45 mg vials **and you will need to give two injections, one right after the other.**
  - Make sure you know the proper amount (volume) to remove from the vial (s) and type of syringe(s) needed for dosing. If you do not know the amount or type of syringe(s) needed, contact your healthcare provider for further instructions.
- Check the expiration date on the vial and carton. If the expiration date has passed, do not use it. If the expiration date has passed, call the healthcare provider or pharmacist, or call 1-800-526-7736 for help.
- Check the vial for any particles or discoloration. The liquid in the vial should look clear and colorless to light yellow with a few small clear or white particles.
- Do not use if it is frozen, discolored, cloudy or has large particles. Get a new vial.
- **Do not shake the vial at any time.** Shaking the vial may damage the Ustekinumab medicine. If the vial has been shaken, do not use it. Get a new vial.
- Do not use a Ustekinumab vial more than 1 time, even if there is medicine left in the vial. After the rubber stopper is punctured, Ustekinumab can become contaminated by harmful bacteria which could cause an infection if re-used. Therefore, throw away any unused Ustekinumab after you give the injection.

- Safely throw away (dispose of) Ustekinumab vials, needles, and syringes after use. See "**Step 6: Disposing of needles, syringes, and vials.**"
- Do not re-use syringes or needles.
- To avoid needle-stick injuries, **do not** recap needles.

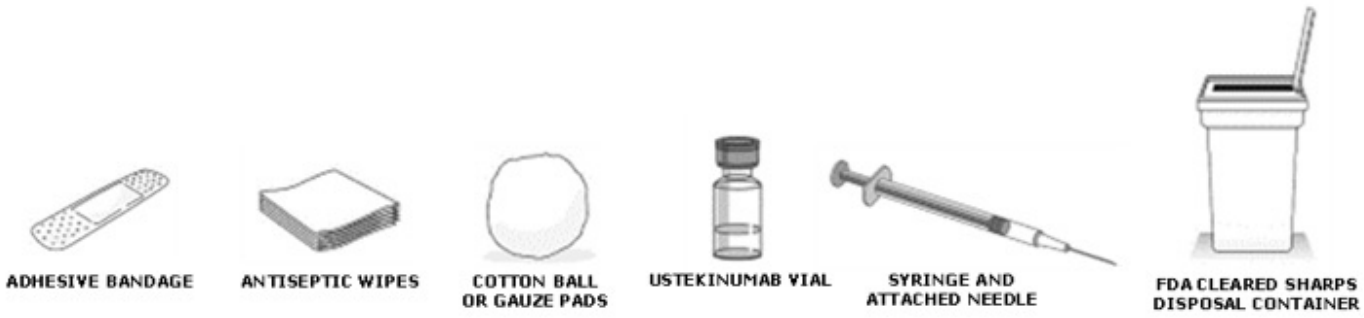
Storing Ustekinumab vials
- Store Ustekinumab vials in a refrigerator between 36 °F to 46 °F (2 °C to 8 °C).
- Store Ustekinumab vials standing up straight (upright).
- Store Ustekinumab vials in the original carton to protect from light until the time of use.
- **Do not** freeze Ustekinumab vials.

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

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

You will need:
- a syringe with the needle attached, you will need a prescription from a healthcare provider to get syringes with the needles attached from a pharmacy.
- antiseptic wipes
- cotton balls or gauze pads
- adhesive bandage
- your prescribed dose of Ustekinumab
- FDA-cleared sharps disposal container. See "**Step 6: Disposing of needles, syringes, and vials.**"

Figure A

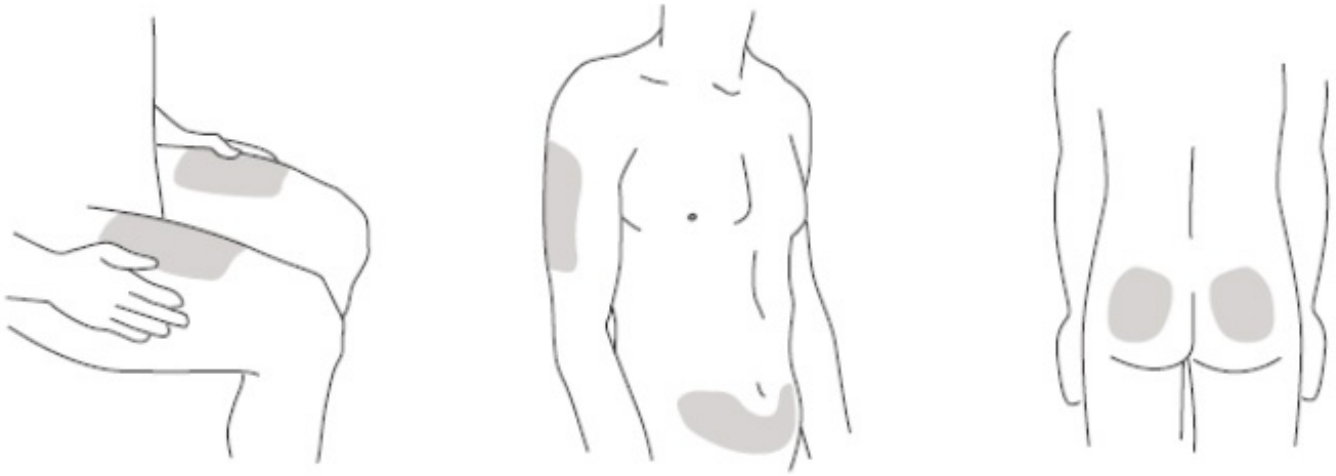


Step 1: Preparing the injection
- Choose a well-lit, clean, flat work surface.
- Wash your hands well with soap and warm water.

Step 2: Preparing the injection site
- Choose an injection site around the stomach area (abdomen), buttocks, and upper legs (thighs).
- If a caregiver is giving the injection, the outer area of the upper arms may also be used. **(See Figure B)**
- **Use a different injection site for each injection. Do not** give an injection in an area of the skin that is tender, bruised, red or hard.
- Clean the skin with an antiseptic wipe where you plan to give the injection.
- **Do not** touch this area again before giving the injection. Let the skin dry before

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

Figure B



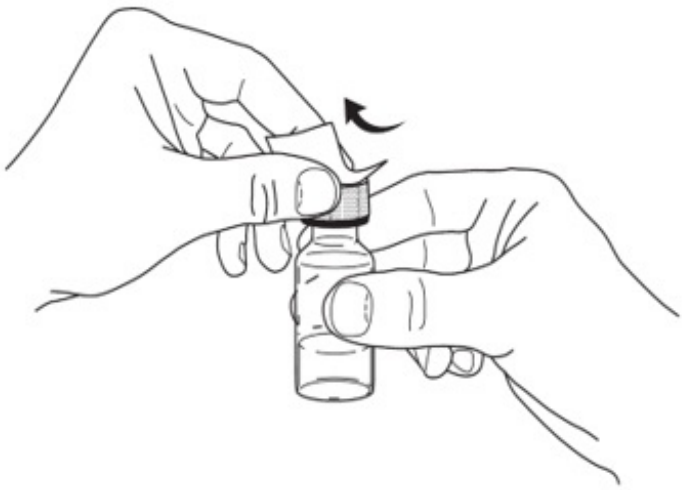
*Areas in gray are recommended injection sites.

Step 3: Preparing the vial
- Remove the cap from the top of the vial. Throw away the cap but do not remove the rubber stopper. **(See Figure C)**

Figure C

- Clean the rubber stopper with an antiseptic wipe. **(See Figure D)**

Figure D

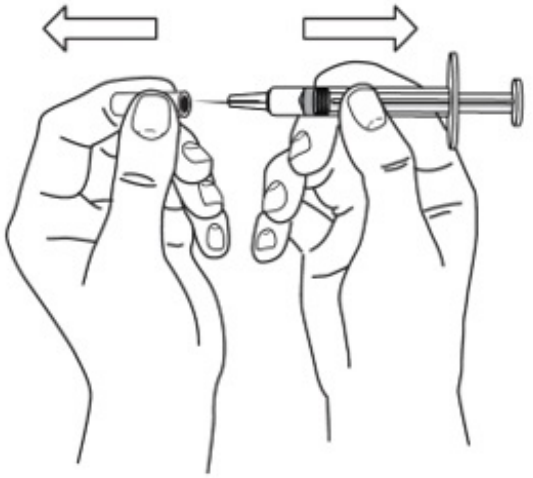


- Do not touch the rubber stopper after you clean it.
- Put the vial on a flat surface.

Step 4: Preparing the syringe

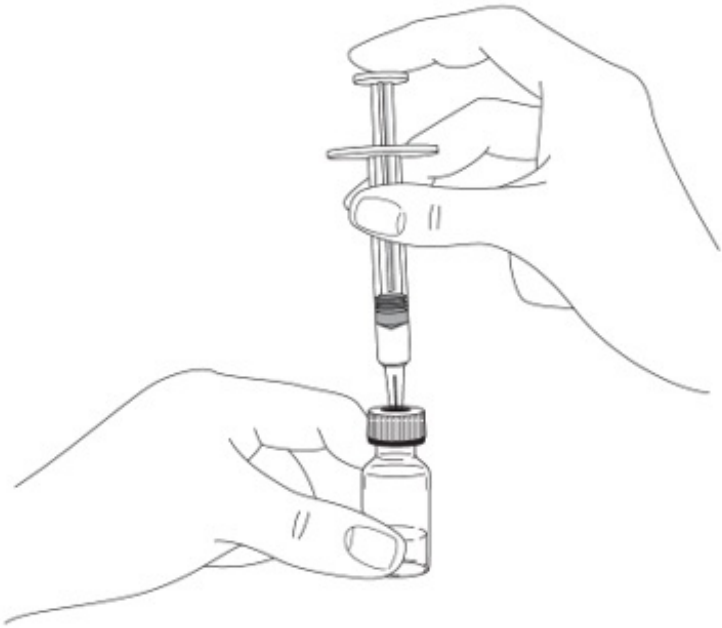
- Pick up the syringe with the needle attached.
- Remove the cap that covers the needle. **(See Figure E)**
- Throw the needle cap away. Do not touch the needle or allow the needle to touch anything.

Figure E



- Carefully pull back on the plunger to the line that matches the dose prescribed by the healthcare provider.
- Hold the vial between your thumb and index (pointer) finger.
- Use your other hand to push the syringe needle through the center of the rubber stopper. **(See Figure F)**

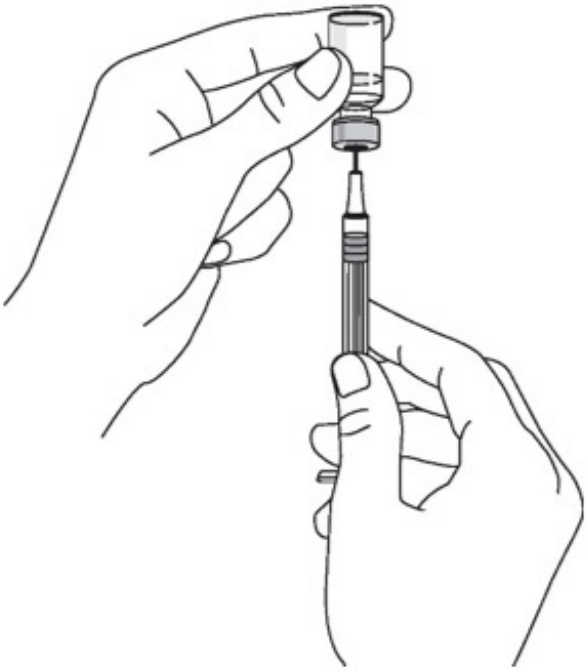
Figure F



- Push down on the plunger until all of the air has gone from the syringe into the vial.
- Turn the vial and the syringe upside down. **(See Figure G)**
- Hold the Ustekinumab vial with 1 hand.

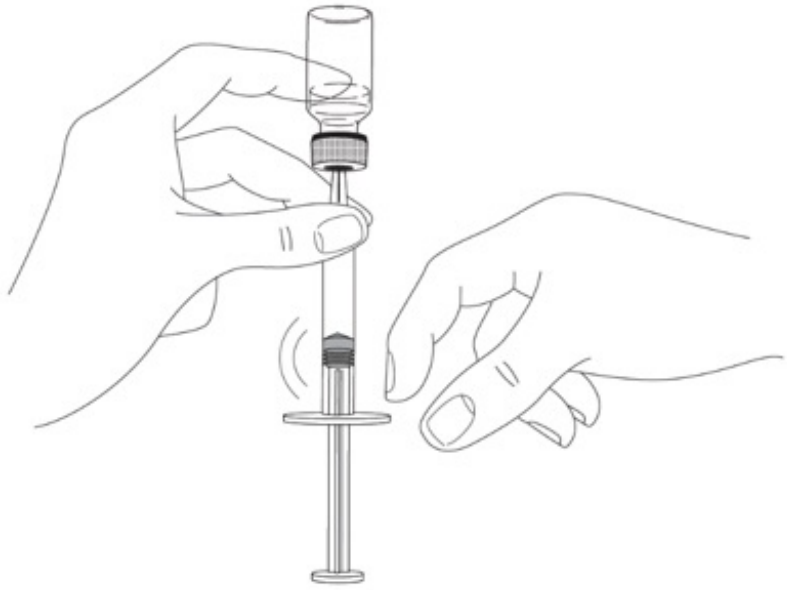
- It is important that the needle is always in the liquid in order to prevent air bubbles forming in the syringe.
- Pull back on the syringe plunger with your other hand.
- Fill the syringe until the black tip of the plunger lines up with the mark that matches the prescribed dose.

Figure G



- **Do not remove the needle from the vial.** Hold the syringe with the needle pointing up to see if it has any air bubbles inside.
- If there are air bubbles, gently tap the side of the syringe until the air bubbles rise to the top. **(See Figure H)**
- Slowly press the plunger up until all of the air bubbles are out of the syringe (but none of the liquid is out).
- Remove the syringe from the vial. Do not lay the syringe down or allow the needle to touch anything.

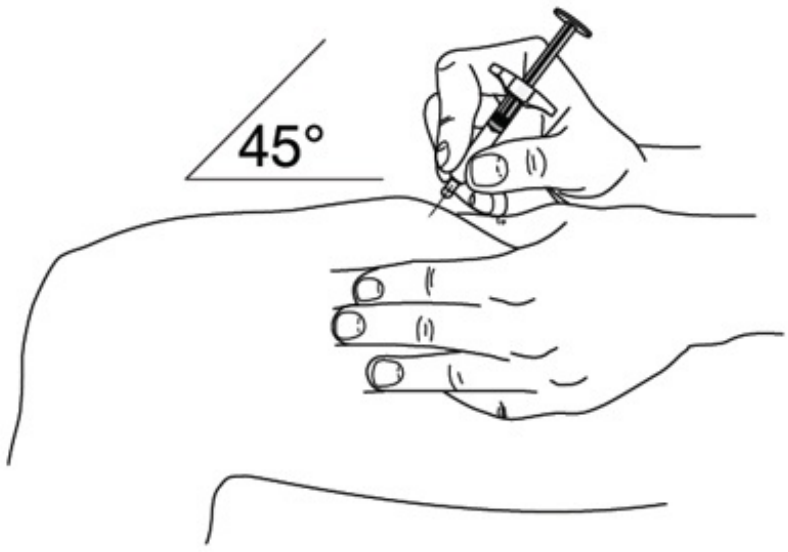
Figure H



Step 5: Injecting Ustekinumab

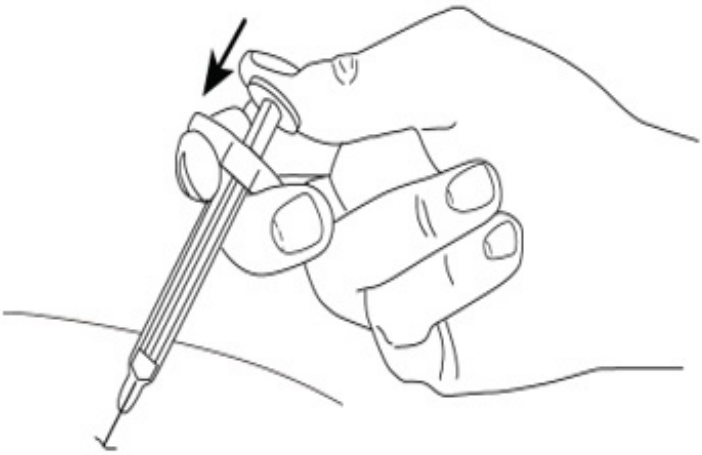
- Hold the barrel of the syringe in 1 hand, between the thumb and index fingers.
- **Do not** pull back on the plunger at any time.
- Use the other hand to gently pinch the cleaned area of skin. Hold firmly.
- Use a quick, dart-like motion to insert the needle into the pinched skin at about a 45-degree angle. **(See Figure I)**

Figure I



- Push the plunger with your thumb as far as it will go to inject all of the liquid. Push it slowly and evenly, keeping the skin gently pinched.
- When the syringe is empty, pull the needle out of the skin and then let go of the skin. **(See Figure J)**

Figure J



- When the needle is pulled out of the skin, there may be a little bleeding at the injection site. This is normal. You can press a cotton ball or gauze pad to the injection site if needed. Do not rub the injection site. You may cover the injection site with a small adhesive bandage, if necessary.

If the dose is more than 45 mg, you will receive two 45 mg vials and you will need to give a second injection right after the first. Repeat Steps 1 to 5 using a new syringe. Choose a different site for the second injection.

Step 6: Disposing of needles, syringes, and vials

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

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

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

Revised: 7/2026

For patent information: www.janssenpatents.com

PRINCIPAL DISPLAY PANEL - 45 mg/0.5 mL Vial Carton

Single-dose vial
Discard unused portion

NDC 57894-440-03

Ustekinumab
Injection

45 mg/0.5 mL
For subcutaneous use

Each vial contains 0.5 mL

Information for use and dosage–
See package insert

Rx only

ATTENTION: Dispense the enclosed
Medication Guide to each patient.

PRINCIPAL DISPLAY PANEL - 45 mg/0.5 mL Syringe Carton

Ustekinumab
Injection

45 mg/0.5 mL
For subcutaneous use

Contains one 45 mg/0.5 mL syringe

NDC 57894-440-01

Single-dose prefilled syringe – Discard unused portion

The 45 mg prefilled syringe contains:
45 mg ustekinumab, 0.5 mg L-histidine and L-histidine monohydrochloride monohydrate, 0.02 mg polysorbate 80, and 38 mg sucrose to fill a final volume of 0.5 mL

See package insert for dosing information

Rx only

ATTENTION: Dispense the enclosed Medication Guide
to each patient.

PRINCIPAL DISPLAY PANEL - 90 mg/mL Syringe Carton

Ustekinumab
Injection

90 mg/mL
For subcutaneous use

Contains one 90 mg/mL syringe

NDC 57894-441-01

Single-dose prefilled syringe – Discard unused portion

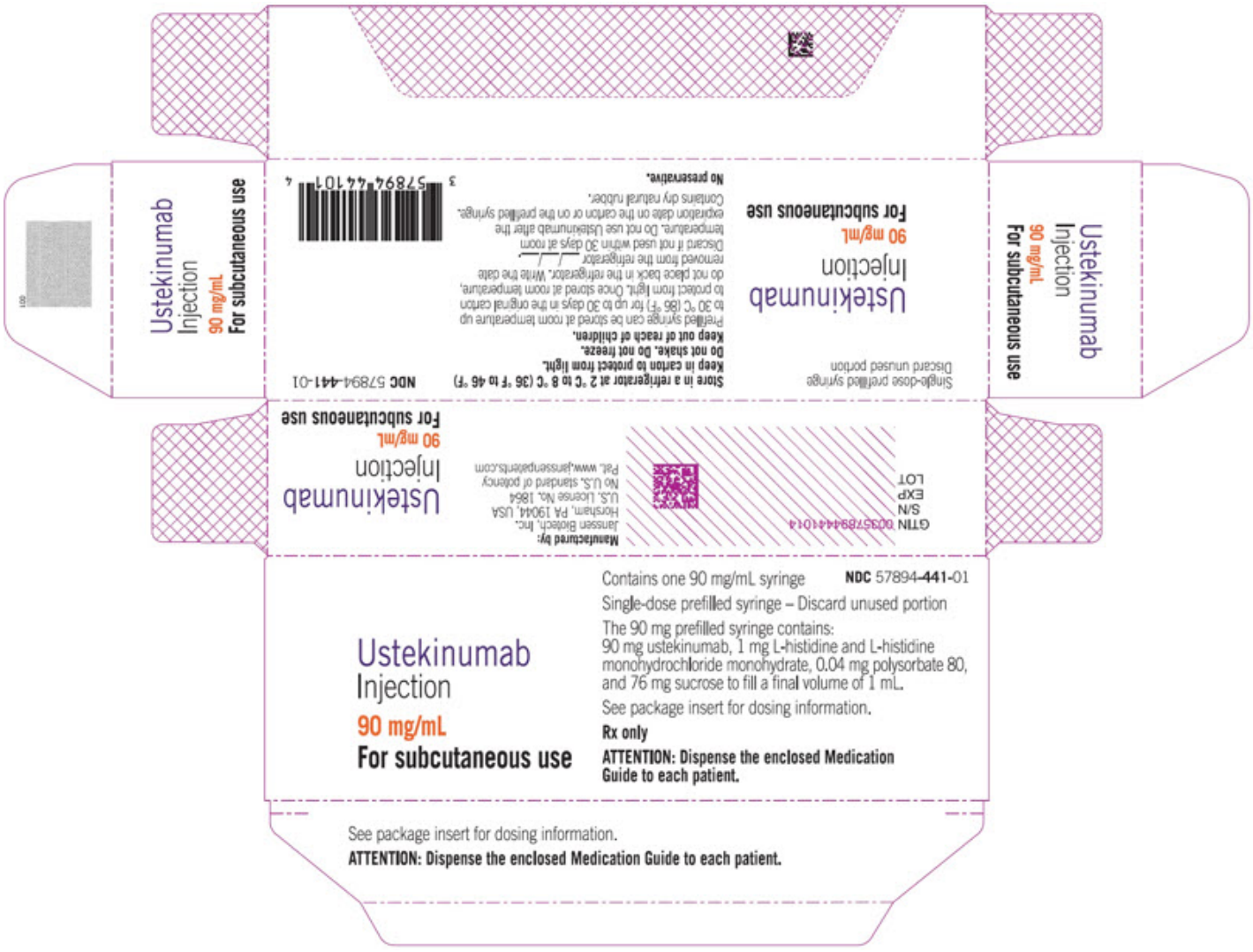
The 90 mg prefilled syringe contains:
90 mg ustekinumab, 1 mg L-histidine and L-histidine

monohydrochloride monohydrate, 0.04 mg polysorbate 80, and 76 mg sucrose to fill a final volume of 1 mL

See package insert for dosing information.

Rx only

ATTENTION: Dispense the enclosed Medication Guide to each patient.



PRINCIPAL DISPLAY PANEL - 130 mg/26 mL Vial Box

NDC 57894-444-01
Single-dose vial
Discard unused portion

Ustekinumab
Injection

130 mg/26 mL
(5 mg/mL)

For Intravenous Infusion Only

Must be diluted

ATTENTION: Dispense
the enclosed Medication
Guide to each patient.
Rx only

janssen

USTEKINUMAB

ustekinumab injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:57894-440
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
USTEKINUMAB (UNII: FU77B4U5Z0) (USTEKINUMAB - UNII:FU77B4U5Z0)	USTEKINUMAB	45 mg in 0.5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SUCROSE (UNII: C151H8M554)	38 mg in 0.5 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.02 mg in 0.5 mL
HISTIDINE (UNII: 4QD397987E)	0.5 mg in 0.5 mL
HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:57894-440-03	1 in 1 CARTON	04/01/2025	
1		0.5 mL in 1 VIAL, SINGLE-USE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		
2	NDC:57894-440-01	1 in 1 CARTON	04/01/2025	
2		0.5 mL in 1 SYRINGE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125261	04/01/2025	

USTEKINUMAB

ustekinumab injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:57894-441
Route of Administration	SUBCUTANEOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
USTEKINUMAB (UNII: FU77B4U5Z0) (USTEKINUMAB - UNII:FU77B4U5Z0)	USTEKINUMAB	90 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
SUCROSE (UNII: C151H8M554)	76 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.04 mg in 1 mL
HISTIDINE (UNII: 4QD397987E)	1 mg in 1 mL
HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:57894-441-01	1 in 1 CARTON	04/01/2025	
1		1 mL in 1 SYRINGE; Type 3: Prefilled Biologic Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125261	04/01/2025	

USTEKINUMAB

ustekinumab solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:57894-444
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
USTEKINUMAB (UNII: FU77B4U5Z0) (USTEKINUMAB - UNII:FU77B4U5Z0)	USTEKINUMAB	130 mg in 26 mL

Inactive Ingredients

Ingredient Name	Strength
EDETATE DISODIUM (UNII: 7FLD91C86K)	0.52 mg in 26 mL
HISTIDINE (UNII: 4QD397987E)	20 mg in 26 mL
HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	27 mg in 26 mL
METHIONINE (UNII: AE28F7PNPL)	10.4 mg in 26 mL

POLYSORBATE 80 (UNII: 6OZP39ZG8H)	10.4 mg in 26 mL
SUCROSE (UNII: C151H8M554)	2210 mg in 26 mL

Product Characteristics

Color	yellow (colorless to light yellow)	**Score**	
Shape		**Size**	
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:57894-444-01	1 in 1 BOX	04/01/2025	
1		26 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761044	04/01/2025	

Labeler - Janssen Biotech, Inc. (099091753)

Establishment

Name	Address	ID/FEI	Business Operations
Cilag AG		483237103	manufacture(57894-440, 57894-441, 57894-444) , analysis(57894-440, 57894-441, 57894-444)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Biologics B.V.		409612918	analysis(57894-440, 57894-441, 57894-444) , api manufacture(57894-440, 57894-441, 57894-444)

Establishment

Name	Address	ID/FEI	Business Operations
Baxter Pharmaceutical Solutions		604719430	manufacture(57894-440, 57894-441)

Establishment

Name	Address	ID/FEI	Business Operations
Janssen Sciences Ireland UC		986030167	api manufacture(57894-440, 57894-441, 57894-444) , analysis(57894-440, 57894-441, 57894-444)

Establishment

Name	Address	ID/FEI	Business Operations
PPD Development Ireland Ltd.		985036175	analysis(57894-444)