**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Surveillance and Epidemiology**

# Pediatric Postmarketing Pharmacovigilance Review

| | |
|---|---|
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| **Product Name:** | Stelara (ustekinumab) injection |
| **Pediatric Labeling Approval Date:** | October 13, 2017 |
| **Application Type/Number:** | BLA 125261, 761044 |
| **Applicant/Sponsor:** | Janssen Biotech, Inc. |
| **OSE RCM #:** | 2019-1201 |

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Stelara (ustekinumab) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious adverse events reported with ustekinumab in U.S. pediatric patients.

The FDA initially approved ustekinumab on September 25, 2009, and it is currently indicated for:

- The treatment of patients 12 years or older with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- The treatment of adult patients with active psoriatic arthritis, alone or in combination with methotrexate
- The treatment of adult patients with moderately to severely active Crohn's disease who have:
    - Failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis (TNF) blocker or
    - Failed or were intolerant to treatment with one or more TNF blockers

The FDA approved the use of ustekinumab in adolescent patients with plaque psoriasis on October 13, 2017.

We did not identify new safety signals or increased severity of labeled adverse events in pediatric patients. We reviewed all U.S. cases coded with serious outcomes reported in pediatric patients and included 41 cases, including no deaths, in our case series. Approximately half of the cases reported labeled events, such as infections or hypersensitivity reactions. These events and their severity were consistent with current ustekinumab labeling. Although gastrointestinal (GI) adverse events were frequently reported and generally not labeled, they appeared to be primarily related to the indication for use of Crohn's disease.

Although approximately 75% of the cases reported use that is currently off-label, we did not identify specific safety concerns related to off-label use, other than ustekinumab use at higher doses or more frequent dosing than recommended for that indication in adults in some cases. Ustekinumab utilization data in pediatric patients was not provided because of low visibility of pediatric use, especially by indication or prescriber specialty, in data sources available to FDA.

DPV did not identify any pediatric safety concerns for ustekinumab at this time. DPV recommends no regulatory action and will continue to monitor all adverse events reported with the use of ustekinumab.

# 1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Stelara (ustekinumab) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious adverse events reported with ustekinumab in U.S. pediatric patients.

## 1.1 PEDIATRIC REGULATORY HISTORY

Ustekinumab is a human IgG1κ monoclonal antibody that binds to the p40 subunit of the interleukin (IL)-12 and IL-23 cytokines. It is marketed for subcutaneous (SC) injection at a concentration of 90 mg/mL in single-dose vials and prefilled syringes, and for intravenous (IV) infusion at a concentration of 5 mg/mL in single-dose vials. Table 1 includes the Biologics License Application (BLA) numbers, approved indications, recommended doses, and routes of administration by FDA approval date for ustekinumab.[1]

**Table 1. Ustekinumab Biologic License Application (BLA) Numbers, Approved Indications, Recommended Doses, and Routes of Administration by FDA Approval Date**

| FDA Approval Date | BLA Number | Indication | Recommended dose and route of administration |
|---|---|---|---|
| September 25, 2009 | 125261 | Adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy | Weight <100 kg: 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks SC<br><br>Weight >100 kg: 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks SC |
| September 20, 2013 | 125261 | Adult patients (18 years or older) with active psoriatic arthritis, alone or in combination with methotrexate (MTX) | 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks SC<br><br>For patients with co-existent moderate to severe plaque psoriasis weighing >100 kg: 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks SC |

| Table 1. Ustekinumab Biologic License Application (BLA) Numbers, Approved Indications, Recommended Doses, and Routes of Administration by FDA Approval Date | | | |
|---|---|---|---|
| **FDA Approval Date** | **BLA Number** | **Indication** | **Recommended dose and route of administration** |
| September 23, 2016 | 761044 | Adult patients with moderately to severely active Crohn's disease who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed treatment with a tumor necrosis factor (TNF) blocker OR failed or were intolerant to treatment with one or more TNF blockers | Single IV weight-based infusion (see below), followed by maintenance dose of 90 mg SC 8 weeks later, then every 8 weeks thereafter:<br>≤55 kg: 260 mg<br>>55 kg-85 kg: 390 mg<br>>85 kg: 520 mg |
| October 13, 2017 | 125261 | Adolescent patients (12-17 years) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy | Weight-based doses at Weeks 0 and 4, then every 12 weeks SC:<br><60 kg: 0.75 mg/kg<br>60-100 kg: 45 mg<br>>100 kg: 90 mg |
| IV-intravenous, kg-kilograms, mg-milligrams, SC-subcutaneous | | | |

As seen in Table 1, the only currently approved pediatric indication is for the treatment of adolescent patients with moderate to severe plaque psoriasis. The safety and efficacy of two SC dose regimens of ustekinumab were evaluated in one multicenter, randomized, double-blind, placebo-controlled study (NCT01090427) in 110 subjects 12 to less than 18 years of age with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic treatment of psoriasis, or whose psoriasis was poorly controlled with topical therapy of adequate dose and duration. Moderate to severe psoriasis was defined as Psoriatic Area and Severity Index (PASI) ≥12, Physician's Global Assessment (PGA) ≥3, and body surface area (BSA) involvement ≥10%. The two dose regimens evaluated were intended to provide exposure comparable to half the adult dose of ustekinumab for plaque psoriasis and to the standard adult dose. See Table 2 for the doses evaluated in the study.

| Table 2. Weight-based Ustekinumab Doses Evaluated in Adolescent Subjects* | | |
|---|---|---|
| **Body weight** | **Half-standard dose** | **Standard dose** |
| <60 kg | 0.375 mg/kg | 0.75 mg/kg |
| 60-100 kg | 22.5 mg | 45 mg |
| >100 kg | 45 mg | 90 mg |
| * Doses were administered subcutaneously initially and 4 weeks later, then every 12 weeks thereafter.<br>kg-kilograms, mg-milligrams | | |

The primary endpoint was the proportion of subjects who achieved a PGA score of cleared or minimal at Week 12. Both dose regimens were superior to placebo ($p < 0.001$) at Week 12, but through Week 52, PGA scores of cleared or minimal and PASI 75 (a secondary endpoint)

response rates were generally higher and better sustained in the standard dose group.[2] In addition, loss of treatment response toward the end of the 12-week dosing interval was more frequently observed in the half-standard dose group. The observed ustekinumab concentrations in adolescent subjects who received the standard dose were generally comparable to adults receiving the recommended adult dose. Therefore, the data supported the standard dose regimen for adolescents.[2]

Adverse events in the study were generally similar between both ustekinumab treatment groups and placebo through Week 12, with no change in the safety profile and no new adverse reactions or safety signals identified through Week 60.[2]

The sponsor did not provide an evaluation of pediatric postmarketing reports in their safety database with the efficacy supplement for the adolescent psoriasis study. DPV has not previously completed a postmarketing pharmacovigilance review for ustekinumab in pediatric patients.

The sponsor has a Postmarketing Requirement to assess the efficacy, safety, and pharmacokinetics of ustekinumab in pediatric subjects 6 to less than 12 years of age with moderate to severe chronic plaque psoriasis. The pediatric study requirement for psoriatic arthritis was waived because necessary studies are impossible or highly impractical. The sponsor agreed to Postmarketing Commitments to conduct a dose-ranging trial and a randomized, controlled, blinded, multicenter trial to evaluate the safety and efficacy of ustekinumab in pediatric patients 2-17 years of age with moderate to severe active Crohn's disease despite conventional therapy.

### 1.2 RELEVANT LABELED SAFETY INFORMATION

The following safety information is excerpted from the ustekinumab labeling:[1]

> 4 CONTRAINDICATIONS
> STELARA® is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients.
>
> 5 WARNINGS AND PRECAUTIONS
> 5.1 *Infections*
> STELARA® may increase the risk of infections and reactivation of latent infections. Serious bacterial, fungal, and viral infections were observed in subjects receiving STELARA®.
>
> Serious infections requiring hospitalization occurred in patients with psoriasis, psoriatic arthritis and Crohn's disease in clinical studies. In patients with psoriasis, serious infections included diverticulitis, cellulitis, pneumonia, appendicitis, cholecystitis, sepsis, osteomyelitis, viral infections, gastroenteritis and urinary tract infections. In patients with psoriatic arthritis, serious infections included cholecystitis. In patients with Crohn's disease, serious or other clinically significant infections included anal abscess, gastroenteritis, ophthalmic herpes, pneumonia, and listeria meningitis.

Treatment with STELARA® should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. Consider the risks and benefits of treatment prior to initiating use of STELARA® 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 STELARA® and consider discontinuing STELARA® 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 STELARA® may be susceptible to these types of infections. Appropriate diagnostic testing should be considered, e.g., tissue culture, stool culture, as dictated by clinical circumstances.

5.3 *Pre-treatment Evaluation for Tuberculosis*
Evaluate patients for tuberculosis infection prior to initiating treatment with STELARA®.

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

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

The safety of STELARA® 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 STELARA® who had pre-existing risk factors for developing non-melanoma skin cancer. All patients receiving STELARA® should be monitored for the appearance of non-melanoma skin cancer. Patients greater

than 60 years of age, those with a medical history of prolonged immunosuppressant therapy and those with a history of PUVA treatment should be followed closely.

5.5 *Hypersensitivity Reactions*
Hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with STELARA®. If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®.

5.6 *Reversible Posterior Leukoencephalopathy Syndrome*
One case of reversible posterior leukoencephalopathy syndrome (RPLS) was observed in clinical studies of psoriasis and psoriatic arthritis. The subject, who had received 12 doses of STELARA® over approximately two years, presented with headache, seizures and confusion. No additional STELARA® injections were administered and the subject fully recovered with appropriate treatment. No cases of RPLS were observed in clinical studies of Crohn's disease.

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

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

5.8 *Concomitant Therapies*
In clinical studies of psoriasis the safety of STELARA® in combination with other immunosuppressive agents or phototherapy was not evaluated. Ultraviolet-induced skin cancers developed earlier and more frequently in mice genetically manipulated to be deficient in both IL-12 and IL-23 or IL-12 alone.

5.9 *Noninfectious Pneumonia*
Cases of interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. 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 STELARA® and institute appropriate treatment.

8 USE IN SPECIFIC POPULATIONS
8.4 *Pediatric Use*

The safety and effectiveness of STELARA® have been established in pediatric subjects 12 to 17 years old with moderate to severe plaque psoriasis. Use of STELARA® in this age group is supported by evidence from a multicenter, randomized, 60-week trial that included a 12-week, double-blind, placebo-controlled, parallel-group portion, in 110 pediatric subjects 12 years and older. The safety and effectiveness of STELARA® for pediatric patients less than 12 years of age have not been established.

# 2 METHODS AND MATERIALS

## 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 3.

**Table 3. FAERS Search Strategy***

| | |
|---|---|
| Date of Search | June 10, 2019 |
| Time Period of Search | September 25, 2009† - May 31, 2019 |
| Search Type | FDA Business Intelligence Solution (FBIS) Quick Query and FBIS Product-Manufacturer Reporting Summary |
| Product Terms | Product Active Ingredient: Ustekinumab |
| MedDRA Search Terms (Version 22.0) | All Preferred Terms |

* See Appendix A for a description of the FAERS database.
† Initial FDA approval date for ustekinumab.
MedDRA-Medical Dictionary for Regulatory Activities

# 3 RESULTS

## 3.1 FAERS

### *3.1.1 Total Number of FAERS Reports by Age*

Table 4 presents the number of adult and pediatric FAERS reports from September 25, 2009 to May 31, 2019 with ustekinumab.

**Table 4. Total Adult and Pediatric FAERS Reports* Received by FDA from September 25, 2009 to May 31, 2019 with Ustekinumab**

| | **All reports (U.S.)** | **Serious† (U.S.)** | **Death (U.S.)** |
|---|---|---|---|
| Adults (≥18 years) | 18,473 (8,334) | 12,510 (3,015) | 521 (141) |
| Pediatrics (0 - <18 years) | 299 (184) | **171 (60‡)** | 4 (1‡) |

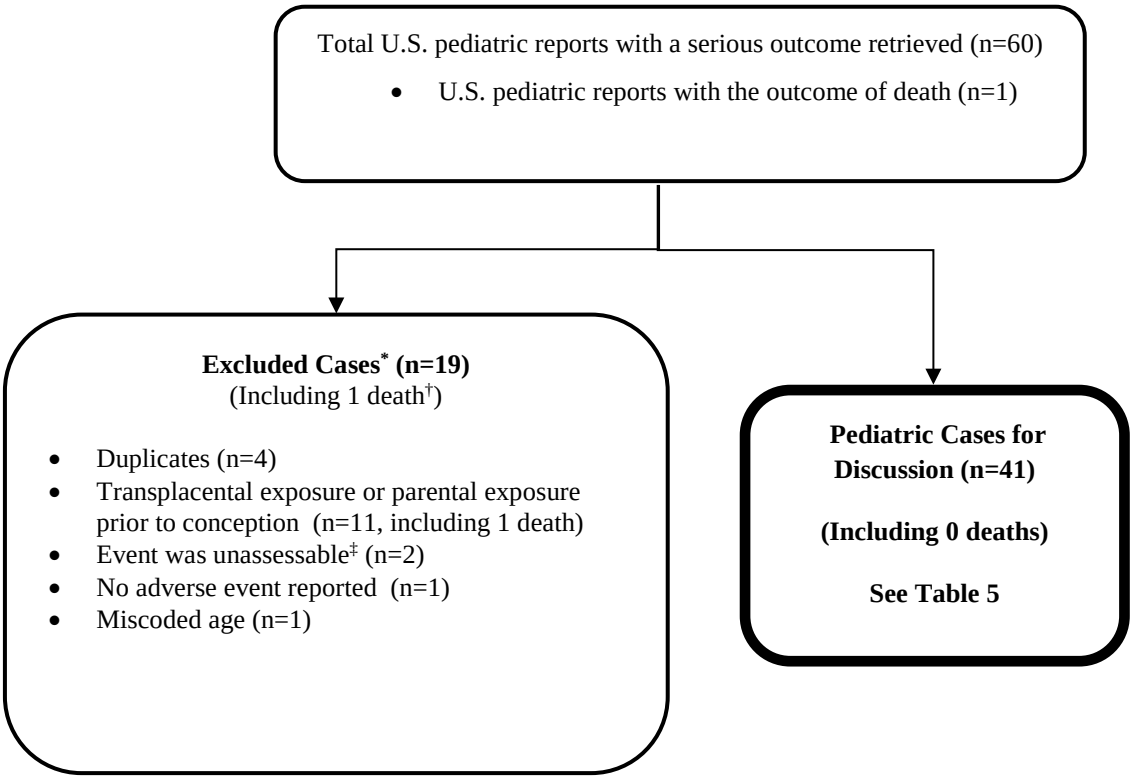
* May include duplicates and transplacental exposures, and have not been assessed for causality.
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.
‡ See Figure 1. All four reports of pediatric deaths were fetal or neonatal deaths following transplacental exposure or parental exposure prior to conception identified among reports not reporting an age.

### *3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS*

Our FAERS search retrieved 60 U.S. serious pediatric reports from September 25, 2009 to May 31, 2019. We reviewed all 60 reports and excluded 19 reports from the case series for the reasons provided in Figure 1 below. We summarize the remaining 41 cases in the sections below.

Figure 1 presents the selection of cases for the pediatric case series.

**Figure 1. Selection of Serious U.S. Pediatric Cases with Ustekinumab**




* DPV reviewed all of these cases.
† The report described a premature neonate who died shortly after birth. The neonate's father used ustekinumab 2 years prior to conception for a duration of 6 months. The report lacked additional information including transplacental exposure and neonate clinical course.
‡ Unassessable reports cannot be assessed for causality because there is insufficient information reported.

### *3.1.3 Characteristics of Pediatric Cases*

Appendix B contains a line listing of the 41 pediatric cases. Table 5 summarizes the 41 FAERS cases in U.S. pediatric patients with ustekinumab reporting a serious outcome received by FDA from September 25, 2009 to May 31, 2019.

| Table 5. Characteristics of the FAERS U.S. Serious Pediatric Cases with Ustekinumab Received by FDA from September 25, 2009 to May 31, 2019 (N=41) | | |
|---|---|---|
| Age | 2- <6 years | 1 |
| | 6- <12 years | 2 |
| | 12- <18 years | 38 |
| Sex | Female | 20 |
| | Male | 21 |
| Reported Reason for Use* (n=39) | Crohn's disease | 25 |
| | Inflammatory bowel disease | 6 |
| | Psoriasis | |
| | Plaque or not specified | 11 |
| | Pustular | 1 |
| | Psoriatic arthritis | 1 |
| Serious Outcome† | Life-threatening | 2 |
| | Hospitalization | 21 |
| | Other Serious | 21 |

* Some cases reported more than one reason for use.

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A case may have more than one serious outcome.

#### *3.1.4 Summary of Fatal Pediatric Cases (N=0)*

We did not include any fatal pediatric adverse event cases in our case series.

#### *3.1.5 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=41)*

Our case series included 41 FAERS cases with ustekinumab in the U.S. pediatric population reporting a non-fatal serious outcome. Three cases were published in the medical literature.[3,4]

All 11 cases reporting an indication of plaque psoriasis or psoriasis not otherwise specified were 12 years of age or older. The remaining 30 cases were treated for indications that are not currently approved in pediatric patients (or for some indications in adults), including six cases that reported use of the IV formulation, which is currently approved in Crohn's disease.

Approximately half of the cases reported events consistent with the known adverse reactions described in the WARNINGS AND PRECAUTIONS section of labeling, such as infections or hypersensitivity reactions. The most frequently reported unlabeled events were gastrointestinal (GI) adverse events, and these appeared to be related to the indication for use in Crohn's disease. We did not identify patterns or trends suggesting new safety signals with the serious unlabeled adverse events in our pediatric cases.

The cases are grouped below by organ system or clinical concept. In cases reporting events in more than one category, we selected the category based on the most serious event, or if the most serious event was not clear, we selected the category based on the event with the most information provided.

#### 3.1.5.1 Infections (n=16)

Sixteen cases, in patients from 12 to 17 years of age, reported infections as the most serious adverse event. Indication for ustekinumab use included Crohn's disease (6), inflammatory bowel disease (IBD; 6), Crohn's disease and psoriasis (2), psoriasis (1), and psoriasis and psoriatic arthritis (1).

Some cases reported multiple infections. Respiratory tract infections, reported in seven cases, were the most frequently reported, and included one or more of the following: pneumonia (4), methicillin-sensitive *Staphylococcus aureus* nasal mucosal infection (1), sinus infection (1), throat infection (1), and upper respiratory tract infection (1). One pneumonia case reported bronchoalveolar lavage fluid positive for Epstein-Barr virus by polymerase chain reaction, one case reported multiple caseating nodules suspicious for *Nocardia* and negative for tuberculosis, and the remaining two pneumonia cases did not report the causative organisms. GI infections, reported in four cases, included one or more of the following: perianal abscess (3; including one with adjacent cellulitis), gastroenteritis with stool cultures positive for *Salmonella* and norovirus (1), and *Clostridium difficile* infection (1). Skin and soft tissue infections included parastomal abscess (1), abscess or cyst of the ankle and shin (1), and unspecified skin and soft tissue infections (2). Other infections reported in one case each included central line infection, otitis, ovarian cyst, urinary tract infection, and viral (not otherwise specified) meningitis. One case did not identify the site of infection.

The ustekinumab dose, reported in eight cases was: 90 mg SC every 8 weeks (3), 90 mg SC every 4 weeks (1), 90 mg SC every 12 weeks (1), 90 mg SC interval not specified (1), 45 mg SC every 4 weeks (1), and 45 mg SC every 12 weeks (1). Time to onset ranged from 2 to 16 months in the 10 cases that provided this information.

Fourteen cases reported treatment for the infection or its symptoms, including one or more of the following: antimicrobials (11), surgery (5), fluids (4), corticosteroids (2), and oxygen or intubation (2).

Ten cases reported one or more factors that may have contributed to the infection, including: concomitant methotrexate (6), concomitant corticosteroids (3), history of lymphoma (1), concomitant sirolimus (1), trauma preceding skin and soft tissue infection (1), and X-linked chronic granulomatous disease (1).

Fourteen cases provided the action taken for ustekinumab. Ustekinumab was continued in six cases, and the infections improved in five cases and were ongoing in one case. Ustekinumab was stopped in eight cases. Of these eight cases, the infections improved in three cases and were ongoing in two cases; three cases did not provide follow-up.

*Reviewer's comment: Infections, including serious bacterial, fungal, and viral infections, are labeled for ustekinumab in the WARNINGS AND PRECAUTIONS section. Ten cases reported other potential risk factors for infection. The cases did not suggest increased severity, types of infections, or organisms than would be anticipated in this patient population.*

### 3.1.5.2 Gastrointestinal (n=13)

Thirteen cases, in patients from 9 to 17 years of age, reported GI adverse events as the most serious event. Indication for use was reported in 11 cases and included Crohn's disease (10) and psoriasis (1).

The events reported in the ten cases reporting use for Crohn's disease included abdominal pain, discomfort, cramping, breakthrough or worsening of Crohn's disease symptoms, bloody diarrhea, ileostomy, fistula surgery, and residual Crohn's disease.

The ustekinumab dose in the Crohn's disease patients, reported in nine cases, included: 90 mg SC every 8 weeks (5), 90 mg SC every 4 weeks (2), 90 mg SC interval not specified (1), and 390 mg IV every 8 weeks (1). The time to onset in the 10 Crohn's disease patients ranged from 1 day to 18 months from starting ustekinumab in the six cases that provided this information. One case reported treatment of the events with prednisone, and another case reported treatment with antibiotics. Two cases reported one or more other factors that were thought to contribute to the GI events, including one of each of the following: "low drug levels," noncompliance with dietary recommendations, and stress. None of the cases reported discontinuation of ustekinumab as a result of the events, and in one case the dose interval was changed from every 8 weeks to every 4 weeks.

The two cases that did not provide an indication for use reported that the patients were hospitalized for surgical procedures. The cases provided limited information, and neither case provided ustekinumab dose, medical history, or concomitant medications. One case reported a colectomy, and ustekinumab was stopped. No additional follow-up was provided. The second case reported colon surgery and ileostomy. The ustekinumab was continued, and follow-up was not provided.

A 17-year-old female treated for psoriasis experienced "a form of gastritis," dehydration, vomiting, and headache after receiving a "live flu shot" in the morning and her first ustekinumab injection later the same day. She weighed 140 pounds and her ustekinumab dose was 45 mg. She experienced a headache two hours after the ustekinumab injection and started vomiting later that evening. She had no allergies or other relevant medical history, and the report did not provide concomitant medications. She was hospitalized, but the report does not provide any diagnostic evaluation or treatment. The patient recovered, treatment with ustekinumab was continued, and no additional follow-up was provided.

*Reviewer's comment: The GI adverse events reported in these cases are not labeled for ustekinumab, but they appear to be mostly symptoms related to Crohn's disease. Based on the events reported, the two cases that did not report the indication for ustekinumab use may have been Crohn's patients. The ustekinumab labeling includes a warning to avoid administration with live vaccines. In the U.S., live attenuated influenza vaccines are approved for intranasal administration, so it is unclear if the patient received a live vaccine (as reported) or an inactivated or recombinant influenza vaccine by injection. The influenza vaccine may have contributed to the patient's symptoms, making it difficult to assess the role of ustekinumab.*

### 3.1.5.3 Hypersensitivity (n=4)

Four cases, in patients from 10 to 17 years of age, reported hypersensitivity reactions with ustekinumab use. Three of the events were described as anaphylaxis, and one, which reported

facial and eye edema and urticaria, was reported as "possibly angioedema." Indication for use included Crohn's disease (2), Crohn's disease and psoriasis (1), and psoriasis (1).

The three Crohn's patients received the IV formulation. The IV doses were not specified in two cases and was 260 mg in a 42 kg patient (the recommended adult dose for patients weighing ≤55 kg) in the third case. The time to onset was a few minutes from starting the infusion in two cases, and not reported in the third case. The psoriasis patient received 90 mg SC every 12 weeks (weight not provided), and time to onset was 18 days after the fourth dose.

Treatment of the reactions included corticosteroids (4), diphenhydramine (3), epinephrine (2), histamine-$H_2$ antagonists (2), oxygen (2), and IV hydration (1). Three of the cases reported a history of hypersensitivity reactions to other drugs or iodine. Ustekinumab was discontinued in three patients, but the fourth case, which reported anaphylaxis (symptoms not specified) after an IV dose, reported that the patient received a subsequent SC dose and experienced a variety of symptoms including fatigue, muscle pain and cramps, joint pain, irregular bowel movements, night sweats, and backaches. Ustekinumab was then stopped and symptoms improved.

*Reviewer's comment: Hypersensitivity reactions, including anaphylaxis and angioedema, are labeled for ustekinumab in WARNINGS AND PRECAUTIONS, and the potential for immunogenicity is labeled in ADVERSE REACTIONS. The labeling also includes a CONTRAINDICATION for use in patients who experience clinically significant hypersensitivity to ustekinumab or its excipients. Two cases reported a strong temporal association to ustekinumab use, one case did not report the temporal relationship (and was followed by a subsequent SC dose), and in the fourth case, the extended time to onset after the most recent dose and the patient's history of allergy to iodine make the role of ustekinumab difficult to assess.*

#### 3.1.5.4 Cardiovascular (n=1)

A 17-year-old female was hospitalized for a blood clot (not otherwise specified) approximately five months after starting ustekinumab 90 mg every 8 weeks for the treatment of Crohn's disease. Patient weight, medical history, and smoking status were not provided, and concomitant medication was reported as "birth control." Signs, symptoms, and diagnostic evaluation of the blood clot were not provided. The action taken for ustekinumab and follow-up information were not provided.

*Reviewer's comment: Ustekinumab is not labeled for thrombosis or coagulation disorders. The case provides limited information to assess the event and the role of ustekinumab. IBD is a risk factor for thromboembolic disease in both pediatric and adult patients, and thromboembolic disease is a serious extraintestinal manifestation that can complicate the course of IBD.[5,6] The patient's unspecified birth control may also have contributed.*

#### 3.1.5.5 Dermatologic (n=1)

A 4-year-old female treated with ustekinumab for pustular psoriasis experienced a severe exacerbation of her pustular psoriasis approximately 20 months after starting ustekinumab. Her ustekinumab dose was 0.9 mg/kg every 9 weeks. The report stated that the exacerbation may have been triggered by an infection or antibiotic use. The patient was hospitalized and treated with prednisone and antibiotics. Cultures were negative, and the antibiotics were stopped. The

prednisone was tapered, and her next dose of ustekinumab, which was delayed, was administered after she recovered.

*Reviewer's comment: Ustekinumab is labeled for pustular psoriasis in the ADVERSE REACTIONS section but not specifically for exacerbation of pustular psoriasis. It is not indicated for the treatment of pustular psoriasis or in patients less than 12 years of age, and the patient was receiving a dose higher than the 0.75 mg/kg every 12 weeks recommended for adolescents with plaque psoriasis less than 60 kg. The case reported infection and antibiotics as risk factors for pustular psoriasis exacerbation other than ustekinumab.*

#### 3.1.5.6 Hematologic (n=1)

A 16-year-old male experienced a platelet count of 60,000 (units not specified) an unspecified time after receiving an unspecified dose of ustekinumab for the treatment of psoriasis. Concomitant medical conditions included liver cirrhosis, and concomitant medications were not provided. Previous medications included etanercept, adalimumab, and efalizumab. The report did not provide information on the treatment of thrombocytopenia. An unspecified time after stopping ustekinumab, the patient's platelet count was 100,000.

*Reviewer's comment: Ustekinumab is not labeled for thrombocytopenia. The case provides limited information for assessment and does not include the suspected etiology of the patient's cirrhosis, the patient's platelet count prior to starting ustekinumab, the temporal relationship of the thrombocytopenia to ustekinumab use, or concomitant medications. Cirrhosis is a risk factor for thrombocytopenia.*[7]

#### 3.1.5.7 Malignancy (n=1)

A 17-year-old female who presented with thigh pain and swelling was diagnosed with a malignancy suspicious for Ewing's sarcoma two years after starting treatment with ustekinumab 90 mg SC every 4 weeks for the treatment of Crohn's disease. Concomitant medications were not reported, but past treatments included adalimumab, infliximab, and methotrexate (MTX). The patient's weight and age at diagnosis of Crohn's disease were not reported. After CT-guided biopsy of the thigh mass, flow cytometry was negative for lymphoma, and preliminary pathology showed a "small blue cell tumor." Final pathology was pending at the time of the report, and no additional follow-up was provided.

*Reviewer's comment: The ustekinumab labeling includes malignancies in WARNINGS AND PRECAUTIONS. The patient's dose of 90 mg every 4 weeks is half the approved frequency in adults with Crohn's disease of 90 mg every 8 weeks. Although the duration of the patient's other treatments for Crohn's was not provided, she was previously treated with immunosuppressants, which have been associated with increased risk for neoplastic disease.*[8]

#### 3.1.5.8 Musculoskeletal (n=1)

A 17-year-old male experienced joint pain in his knees approximately one month after starting an unspecified IV dose of ustekinumab for Crohn's disease. The case did not provide medical history, concomitant medications, or previous medications. Treatment with ustekinumab was continued, and the knee pain was ongoing for two weeks at the time of reporting.

*Reviewer's comment: Arthralgia is labeled for ustekinumab in the ADVERSE REACTIONS section in the setting of psoriatic arthritis, occurring in 3% of ustekinumab-treated subjects versus 1% of placebo-treated subjects.[1] Up to 17% of patients with IBD have arthralgias.[9]*

### 3.1.5.9 Ophthalmic (n=1)

A 17-year-old male developed iritis and sacroiliitis approximately six months after starting an unspecified dose of ustekinumab SC for the treatment of psoriasis and Crohn's disease. Medical history also included rheumatoid arthritis. Concomitant medications were not provided, but he was treated with adalimumab in the past, which did not control his psoriasis. He was treated with unspecified steroids for the iritis, but the iritis was not under control. The action taken for ustekinumab was not reported, and iritis and sacroiliitis were ongoing at the time of reporting.

*Reviewer's comment: Ustekinumab is not labeled for iritis, uveitis, sacroiliitis, or arthritis. Both uveitis and sacroiliitis can be extraintestinal manifestations of IBD and they also occur in patients with psoriasis.[10,11,12]*

### 3.1.5.10 Neurologic (n=1)

A 15-year-old female experienced hand tremors and was subsequently diagnosed with seizures approximately three months after starting ustekinumab for the treatment of psoriasis. Her weight was not reported, and she received ustekinumab 45 mg SC at Weeks 0 and 4, then every 12 weeks. The patient had no other relevant medical history, and concomitant medications were not provided. She had a family history of a cousin with seizures. She was evaluated by a pediatric neurologist, and an electroencephalogram revealed seizure activity, reported as petit mal. She was treated with lamotrigine (dose not specified) with control of seizures. Ustekinumab was continued.

*Reviewer's comment: Ustekinumab is not labeled for seizures (other than as a presenting sign of reversible posterior leukoencephalopathy syndrome). The case provides limited information to assess the contribution of ustekinumab, and the seizures were controlled with lamotrigine and use of ustekinumab continued. Information on the patient's concomitant medications was not provided, and the patient's family history of seizures may be a risk factor.*

### 3.1.5.11 Psychiatric (n=1)

A 17-year-old Caucasian male with psoriasis attempted suicide "with intent to die" 34 days after receiving an initial dose of ustekinumab 45 mg SC for the treatment of psoriasis. He weighed 68 kg. His medical history included previous suicide attempt and "anxiety disorders." The report did not provide information on concomitant medication use. He received a second dose of ustekinumab 15 days after the suicide attempt, and 33 days after the second dose, he attempted suicide again. The report did not provide the method(s) used in the suicide attempts or treatment for the suicide attempts. According to the reporting physician, the patient was suspected to be bipolar. Ustekinumab was continued, and no additional follow-up was provided.

*Reviewer's comment: Ustekinumab is not labeled for suicidal ideation and behavior (SIB). According to the ADVERSE REACTIONS section of the ustekinumab labeling, depression was reported in 1% of subjects with psoriasis receiving ustekinumab versus <1% of placebo-treated subjects. This case reports other risk factors for SIB, including psychiatric comorbidities and psoriasis. In a meta-analysis of psoriasis and suicidality, Singh, et al. found that patients with*

*psoriasis were at increased risk of suicidal ideation, attempts, and completion compared to the general population, and that younger patients and those with severe psoriasis were especially at risk.[13] The case did not provide information on concomitant medication use, and because ustekinumab was continued, did not provide evidence that symptoms improved after stopping treatment.*

## 4 DISCUSSION

We did not identify new safety signals or increased severity of labeled adverse events in pediatric patients. We reviewed all U.S. cases coded with serious outcomes reported in pediatric patients and included 41 cases, including no deaths, in our case series.

Approximately half the cases reported labeled events, such as infections or hypersensitivity reactions. These events and their severity were consistent with current ustekinumab labeling. Malignancy, which was reported in one case, is labeled for ustekinumab. Many of the cases of labeled events reported other potential risk factors that may have contributed to the events, such as concomitant or previous use of other immunosuppressants in the cases reporting infection and malignancy and a history of other allergies in the cases reporting hypersensitivity reactions.

Although GI adverse events were frequently reported and generally not labeled for ustekinumab, they appeared to be primarily related to the indication for use of Crohn's disease. For the other unlabeled adverse events, including blood clot, iritis, sacroiliitis, seizures, suicide attempt, and thrombocytopenia, one case per event was reported. The events occurred in patients with other risk factors for the event unrelated to the indication for ustekinumab use, or the patients were at risk for the event based on their underlying diagnosis, and the case did not provide compelling evidence suggesting a causal relationship to ustekinumab use.

Although approximately 75% of the cases reported use that is currently off-label, we did not identify specific safety concerns related to off-label use, other than ustekinumab use at higher doses or more frequent dosing than recommended for that indication in adults in some cases. Ustekinumab utilization data in pediatric patients was not provided because of low visibility of pediatric use, especially by indication or prescriber specialty, in data sources available to FDA.

## 5 CONCLUSION

DPV did not identify any pediatric safety concerns for ustekinumab at this time.

## 6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events reported with the use of ustekinumab.

## 7 REFERENCES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# 8 APPENDICES

## 8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

**FDA Adverse Event Reporting System (FAERS)**

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

## 8.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=41)

| | Initial FDA Received Date | FAERS Case # [Duplicate] | Version # [Duplicate] | Manufacturer Control # [Duplicate] | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 4/10/2012 | 8509803 | 1 | | Direct | 4 | Female | USA | HO |
| 2 | 11/17/2014 | 10587308 | 1 | US-JNJFOC-20141105954 | Expedited | 16 | Male | USA | OT |
| 3 | 8/7/2015 | 11349884 | 5 | US-JNJFOC-20150801870 | Expedited | 17 | Male | USA | HO |
| 4 | 10/2/2015 | 11589779 | 1 | US-JNJFOC-20150911638 | Non-Expedited | 17 | Female | USA | OT |
| 5 | 12/1/2015 | 11793183 [11793189] | 1 [1] | | Direct | 17 | Female | USA | HO |
| 6 | 3/21/2016 | 12195387 [12191201] | 3 [2] | US-JNJFOC-20160314997 [US-JNJFOC-20160312548] | Expedited | 15 | Female | USA | OT |
| 7 | 9/6/2016 | 12718226 | 1 | US-JNJFOC-20160903291 | Expedited | 13 | Female | USA | HO |
| 8 | 9/8/2016 | 12725171 | 1 | US-JNJFOC-20160901731 | Expedited | 12 | Male | USA | HO, OT |
| 9 | 10/3/2016 | 12803854 | 2 | US-JNJFOC-20160929932 | Expedited | 16 | Male | USA | OT |
| 10 | 10/21/2016 | 12873988 | 2 | US-JNJFOC-20161016261 | Expedited | 14 | Male | USA | HO, OT |
| 11 | 11/14/2016 | 12936554 | 2 | US-JNJFOC-20161104771 | Expedited | 16 | Female | USA | OT |
| 12 | 2/14/2017 | 13231043 | 2 | US-JNJFOC-20170206355 | Expedited | 17 | Female | USA | HO |

| | Initial FDA Received Date | FAERS Case # [Duplicate] | Version # [Duplicate] | Manufacturer Control # [Duplicate] | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 13 | 3/15/2017 | 13338720 | 1 | US-JNJFOC-20170312098 | Expedited | 13 | Male | USA | OT |
| 14 | 5/4/2017 | 13515020 | 2 | US-JNJFOC-20170502378 | Expedited | 17 | Male | USA | HO, LT |
| 15 | 5/9/2017 | 13531656 | 1 | | Direct | 15 | Female | USA | HO |
| 16 | 6/28/2017 | 13699229 | 7 | US-JNJFOC-20170623622 | Expedited | 16 | Male | USA | HO |
| 17 | 7/11/2017 | 13742775 | 2 | US-JNJFOC-20170705564 | Expedited | 16 | Female | USA | HO |
| 18 | 9/20/2017 | 13992689 | 2 | US-JNJFOC-20170907749 | Non-Expedited | 15 | Male | USA | OT |
| 19 | 10/10/2017 | 14069518 | 2 | US-JNJFOC-20171002416 | Expedited | 15 | Male | USA | OT |
| 20 | 1/8/2018 | 14362894 | 1 | US-JNJFOC-20171229072 | Non-Expedited | 17 | Female | USA | OT |
| 21 | 2/15/2018 | 14544179 [14544243] | 1 [1] | | Direct | 14 | Female | USA | HO |
| 22 | 3/6/2018 | 14603762 | 1 | US-JNJFOC-20180239709 | Expedited | 17 | Male | USA | OT |
| 23 | 3/21/2018 | 14665838 | 3 | US-JNJFOC-20180304769 | Expedited | 17 | Male | USA | OT |
| 24 | 3/30/2018 | 14696371 | 2 | US-JNJFOC-20180311829 | Expedited | 15 | Male | USA | OT |
| 25 | 5/9/2018 | 14869797 | 1 | US-JNJFOC-20180506954 | Expedited | 14 | Male | USA | HO |
| 26 | 6/18/2018 | 15022274 | 1 | US-JNJFOC-20180611574 | Expedited | 15 | Male | USA | OT |

| | Initial FDA Received Date | FAERS Case # [Duplicate] | Version # [Duplicate] | Manufacturer Control # [Duplicate] | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| 27 | 5/29/2018 | 15033806 | 1 | | Direct | 14 | Female | USA | HO |
| 28 | 8/20/2018 | 15296715 | 4 | US-JNJFOC-20180816233 | Expedited | 13 | Female | USA | OT |
| 29 | 11/9/2018 | 15603586 | 1 | US-JNJFOC-20181107513 | Expedited | 17 | Female | USA | HO |
| 30 | 11/26/2018 | 15656209 | 1 | US-JNJFOC-20181130398 | Expedited | 10 | Male | USA | LT |
| 31 | 1/10/2019 | 15808067 | 2 | US-JNJFOC-20190105886 | Expedited | 12 | Female | USA | HO |
| 32 | 1/23/2019 | 15857945 | 2 | US-JNJFOC-20190120251 | Expedited | 17 | Female | USA | HO |
| 33 | 2/7/2019 | 15933212 | 1 | US-JNJFOC-20190203992 | Expedited | 17 | Male | USA | HO |
| 34 | 2/11/2019 | 15952413 | 2 | US-JNJFOC-20190131589 | Non-Expedited | 9 | Female | USA | OT |
| 35 | 1/22/2019 | 15956099 | 1 | | Direct | 17 | Male | USA | HO |
| 36 | 3/17/2019 | 16082030 | 1 | US-JNJFOC-20190302355 | Non-Expedited | 17 | Male | USA | OT |
| 37 | 3/18/2019 | 16085408 | 1 | | Direct | 17 | Female | USA | HO |
| 38 | 3/4/2019 | 16162858 | 1 | | Direct | 17 | Male | USA | OT |
| 39 | 4/8/2019 | 16169482 | 2 | US-JNJFOC-20190406123 | Expedited | 16 | Male | USA | HO |
| 40 | 5/1/2019 | 16261889 | 1 | US-JNJFOC-20190438612 | Expedited | 16 | Female | USA | OT |
| 41 | 5/15/2019 | 16316800 | 1 | US-JNJFOC-20190500897 | Non-Expedited | 17 | Female | USA | OT |

| | Initial FDA Received Date | FAERS Case # [Duplicate] | Version # [Duplicate] | Manufacturer Control # [Duplicate] | Case Type | Age (years) | Sex | Country Derived | Serious Outcomes* |
|---|---|---|---|---|---|---|---|---|---|
| *As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. Those which are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case may have more than one serious outcome.<br>Abbreviations: HO=Hospitalization, LT= Life-threatening, OT=Other Medically Significant | | | | | | | | | |

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