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

Pediatric Postmarketing Pharmacovigilance Review

Date:	December 12, 2024
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Product Name:	Stelara (ustekinumab) injection
Pediatric Labeling Approval Date:	July 29, 2020; July 29, 2022
Application Type/Number:	BLA 125261
Applicant:	Janssen Biotech, Inc.
TTT Record ID:	2024-9671

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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 United States (U.S.) serious unlabeled adverse events associated with ustekinumab in pediatric patients.

Stelara (ustekinumab) injection is a human interleukin-12 and interleukin-23 antagonist. Stelara (ustekinumab) is available through two biologic license applications (BLA): BLA 125261 and BLA 761044.

FDA initially approved ustekinumab on September 25, 2009, for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. On September 29, 2013, FDA approved extending the indication for the treatment of adult patients with active psoriatic arthritis, alone or in combination with methotrexate.

FDA approved ustekinumab on September 23, 2016, for 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 factor blocker OR failed or were intolerant to treatment with one or more tumor necrosis factor blockers.

On October 13, 2017, FDA approved extending the indication for ustekinumab to include treatment of adolescent patients aged 12 – 17 years with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

On July 29, 2020, the indication for ustekinumab was expanded again to include use in children aged 6 – 11 years with moderate to severe plaque psoriasis is supported by evidence from an open-label, single-arm, efficacy, safety and pharmacokinetics study.

On July 29, 2022, the indication for ustekinumab was expanded to include treatment of pediatric patients aged 6 years and older with active psoriatic arthritis.

This pediatric postmarketing safety review was prompted by the pediatric labeling on July 29, 2020, and July 29, 2022.

On October 4, 2019, DPV completed a review of postmarketing adverse event reports with a serious outcome for ustekinumab in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with ustekinumab. On July 13, 2020, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

DPV reviewed all U.S. serious FAERS reports with ustekinumab in pediatric patients less than 18 years of age from June 1, 2019 – October 20, 2024, and identified 164 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with ustekinumab in pediatric patients less than 18 years of age.

DPV did not identify any new pediatric safety concerns for ustekinumab at this time and will continue routine pharmacovigilance monitoring for 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 United States (U.S.) serious unlabeled adverse events associated with ustekinumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Stelara (ustekinumab) injection is a human interleukin-12 and interleukin-23 antagonist. Stelara (ustekinumab) is available through two biologic license applications (BLA): BLA 125261 and BLA 761044.

FDA initially approved ustekinumab[a] on September 25, 2009, for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. On September 29, 2013, FDA approved extending the indication for the treatment of adult patients with active psoriatic arthritis, alone or in combination with methotrexate.[1]

FDA approved ustekinumab[b] on September 23, 2016, for 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 factor (TNF) blocker OR failed or were intolerant to treatment with one or more TNF blockers.[2]

On October 13, 2017, FDA approved extending the indication for ustekinumab[a] to include treatment of adolescent patients aged 12 – 17 years with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[3c]

On July 29, 2020, the indication for ustekinumab[a] was expanded again to include use in children aged 6 – 11 years with moderate to severe plaque psoriasis is supported by evidence from an open-label, single-arm, efficacy, safety and pharmacokinetics study.[5]

On July 29, 2022, the indication for ustekinumab[a,b] was expanded to include treatment of pediatric patients aged 6 years and older with active psoriatic arthritis.[6,7]

Currently, ustekinumab is indicated for the following:

Adult patients with:

- moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis
- moderately to severely active Crohn's disease
- moderately to severely active ulcerative colitis

Pediatric patients 6 years and older with:

[a] BLA 125261
[b] BLA 761004
[c] On October 18, 2019, the labeling for BLA 761044 was updated to reflect the indication for adolescent patients aged 12 – 17 years with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy based on the studies and approval for BLA 125261.[4]

- moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy
- active psoriatic arthritis

Ustekinumab is available in 45 mg/0.5 mL and 90 mg/1 mL single-dose prefilled syringes for subcutaneous injection, 45 mg/0.5 mL solution in a single-dose vial for subcutaneous injection, and 130 mg/26 mL solution in a single-dose vial for intravenous infusion.

This pediatric postmarketing safety review was prompted by the pediatric labeling on July 29, 2020, and July 29, 2022.

On October 4, 2019, DPV completed a review of postmarketing adverse event reports with a serious outcome for ustekinumab in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with ustekinumab. On July 13, 2020, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.[8]

1.2 RELEVANT LABELED SAFETY INFORMATION

The Stelara (ustekinumab) injection labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional Stelara labeling information, please refer to the full prescribing information.[9]

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

----------WARNINGS AND PRECAUTIONS----------
- Infections: Serious infections have occurred. Avoid starting STELARA® during any clinically important active infection. If a serious infection or clinically significant infection develops, discontinue STELARA® until the infection resolves. (5.1)
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL12/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 STELARA®. Initiate treatment of latent TB before administering STELARA®. (5.3)
- Malignancies: STELARA® may increase risk of malignancy. The safety of STELARA® in patients with a history of or a known malignancy has not been evaluated. (5.4)
- Hypersensitivity Reactions: If an anaphylactic or other clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue STELARA®. (5.5)
- Posterior Reversible Encephalopathy Syndrome (PRES): If PRES is suspected, treat promptly, and discontinue STELARA®. (5.6)
- Immunizations: Avoid use of live vaccines in patients during treatment with STELARA®. (5.7)
- Noninfectious Pneumonia: Cases of interstitial pneumonia, eosinophilic pneumonia, and cryptogenic organizing pneumonia have been reported during post-approval use of STELARA®. If diagnosis is confirmed, discontinue STELARA® and institute appropriate treatment. (5.8)

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

- Ulcerative colitis, induction (≥3%): nasopharyngitis (6.1)
- Ulcerative colitis, maintenance (≥3%): nasopharyngitis, headache, abdominal pain, influenza, fever, diarrhea, sinusitis, fatigue, and nausea (6.1)

8.4 Pediatric Use

Plaque Psoriasis

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

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

Use of STELARA® 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), Pharmacokinetics (12.3)].

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

Psoriatic Arthritis

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

Use of STELARA® in these age groups is supported by evidence from adequate and well controlled trials of STELARA® in adults with psoriasis and PsA, pharmacokinetic data from adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and safety data from two clinical trials in 44 pediatric patients 6 to 11 years old with psoriasis and 110 pediatric patients 12 to 17 years old with psoriasis. The observed pre-dose (trough) concentrations are generally comparable between adult patients with psoriasis, adult patients with PsA and pediatric patients with psoriasis, and the PK exposure is expected to be comparable between adult and pediatric patients with PsA [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.1, 14.2, 14.3)].

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

Crohn's Disease and Ulcerative Colitis

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

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	October 21, 2024
Time period of search	June 1, 2019† - October 20, 2024
Search type	RxLogix Pediatric Focused Review Alert – DPV

Table 1. FAERS Search Strategy*	
Product terms	Product Active Ingredient: Ustekinumab
MedDRA search terms (Version 27.0)	All Preferred Terms
Other search terms‡	Case Seriousness: Serious

* See Appendix A for a description of the FAERS database.
† Data-lock date from DPV's 2019 pediatric postmarketing pharmacovigilance review
‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
Abbreviation: MedDRA=Medical Dictionary for Regulatory Activities

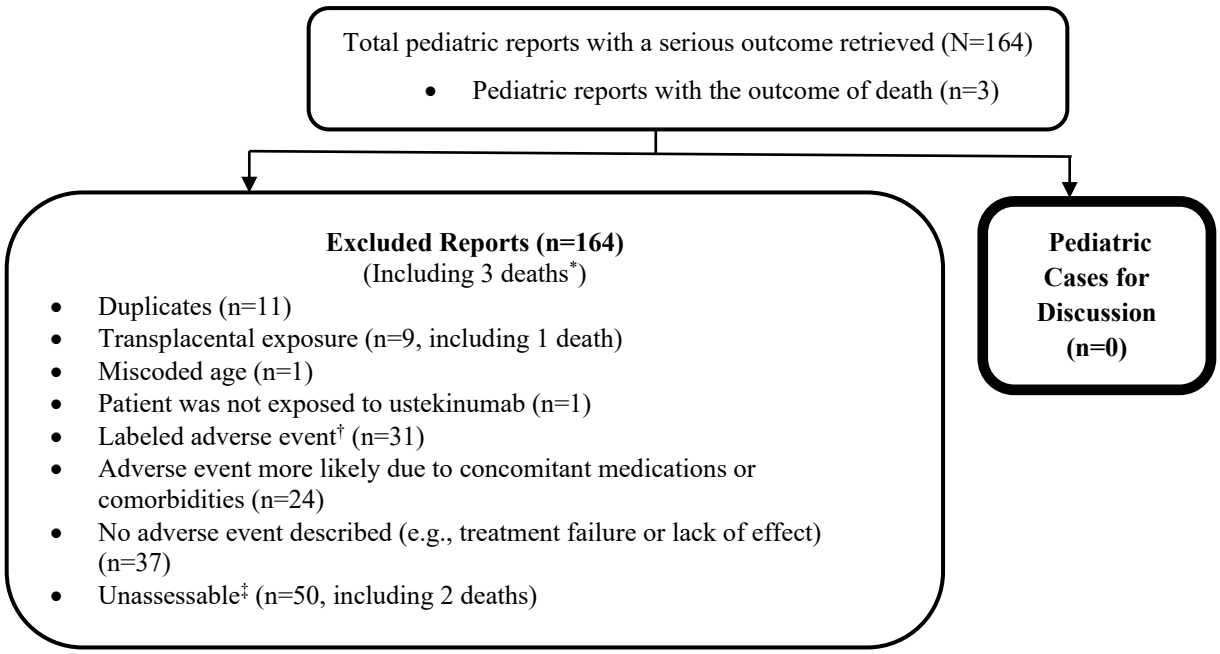
3 RESULTS

3.1 FAERS

3.1.1 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved 164 U.S. serious pediatric reports for patients less than 18 years old from June 1, 2019 – October 20, 2024.[d] We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded all 164 reports from the case series for the reasons listed in **Figure 1**. **Figure 1** presents the selection of cases for the pediatric case series.

Figure 1. Selection of U.S. Serious Pediatric Cases With Ustekinumab



* Three excluded U.S. FAERS reports described fatal outcomes. One case described fetal death with a pregnancy complicated by transplacental exposure to multiple drug products and *E coli* infection. One case described an 11-year-old child who received ustekinumab for treatment of ulcerative colitis and died following an episode of "severe vomiting." No further clinical details were available for this case. Another case reported on the death of a 16-year-old adolescent but provided no additional clinical or case information to assess causality. None of the deaths are attributable to ustekinumab based on available information.
† Labeled adverse event does not represent increased severity.

[d] Includes one pediatric report that was identified among reports not coded with an age.

‡ Unassessable: The report cannot be assessed for causality because there is insufficient information reported (i.e., unknown time to event, concomitant medications and comorbidities, clinical course and outcome), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with ustekinumab in pediatric patients less than 18 years of age from June 1, 2019 - October 20, 2024, and identified 164 reports; however, all reports were excluded from further discussion.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with ustekinumab in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for ustekinumab at this time and will continue routine pharmacovigilance monitoring for ustekinumab.

6 REFERENCES

1. Stelara (ustekinumab) injection, for subcutaneous use. [Prescribing information]. Horsham, PA; Centocor Ortho Biotech, Inc.: September 2009.
2. Stelara (ustekinumab) injection, for subcutaneous or intravenous use. [Prescribing information]. Horsham, PA; Janssen Biotech, Inc.: September 2016.
3. Approval letter. BLA 125261/S138. October 13, 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/125261Orig1s138ltr.pdf
4. Multi-Discipline Review. BLA 761044/S003. October 18, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761044Orig1s003.pdf
5. Approval letter. BLA 125261/S150. July 29, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/125261Orig1s150ltr.pdf
6. Approval letter. BLA 125261/S161. July 29, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/125261Orig1s161ltr.pdf
7. Approval letter. BLA 7610440/S010. July 29, 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/761044Orig1s010ltr.pdf
8. Pediatric Postmarketing Pharmacovigilance Review. BLA 125261, BLA 761044. October 4, 2019. Available at: https://www.fda.gov/media/140206/download
9. Stelara (ustekinumab) injection, for subcutaneous or intravenous use. [Prescribing information]. Horsham, PA; Janssen Biotech, Inc.: March 2024.

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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.