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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:	April 24, 2024
Reviewers:	Van Tran, PharmD, BCPPS, BCPS, MBA, Safety Evaluator Division of Pharmacovigilance I (DPV-I) Ivone Kim, MD, Medical Officer DPV-I
Team Leader:	Carmen Cheng, PharmD DPV-I
Division Director:	Monica Muñoz, PharmD, PhD, BCPS DPV-I
Product Name:	Yervoy (Ipilimumab) injection
Pediatric Labeling Approval Date:	July 21, 2017
Application Type/Number:	BLA 125377/0087
Applicant:	Bristol-Myers Squibb Company
TTT Record ID:	2024-8364

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Yervoy (ipilimumab) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance-I (DPV-I) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ipilimumab in pediatric patients.

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody, initially approved in the U.S. on March 25, 2011, for the treatment of unrespectable or metastatic melanoma in adults only. This pediatric postmarketing safety review was stimulated by pediatric labeling on July 21, 2017, that expanded the indication to include pediatric patients 12 years and older. DPV has not previously presented an evaluation of postmarking adverse event reports for ipilimumab to the Pediatric Advisory Committee.

DPV reviewed all U.S. serious FAERS reports with ipilimumab in pediatric patients less than 18 years of age from March 25, 2011, through February 22, 2024, and identified 40 reports; however, all reports were excluded from further discussion. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with ipilimumab in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Yervoy (ipilimumab) injection in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with ipilimumab in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Yervoy (ipilimumab) injection is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody initially approved in the U.S. on March 25, 2011, as an intravenous solution. Ipilimumab is currently indicated for:[1]

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older as a single agent or in combination with nivolumab.
- Adjuvant treatment of adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.
- Treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment in combination with nivolumab
- Treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Treatment of adult patients with metastatic non-small cell lung cancer expressing programmed death ligand 1 (PD-L1) (≥1%) as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations, as first-line treatment in combination with nivolumab.
- Treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy.
- Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.
- Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, as first line treatment in combination with nivolumab.

This pediatric postmarketing safety review was stimulated by pediatric labeling on July 21, 2017, that expanded the indication to include pediatric patients 12 years and older with unresectable or metastatic melanoma. On January 23, 2017, the Applicant submitted the supplemental BLA (sBLA) 125377/87 containing pediatric data and proposed revised labeling based on that data.

The following regulatory history was reproduced from Dr. Denise Casey's clinical review for sBLA 125377/87.[2]

> *Data from two pediatric clinical trials including a total of 45 patients did not establish efficacy of ipilimumab. An extrapolation of efficacy from adult data for pediatric patients 12 and older is reasonable based on disease similarity between the adult and adolescent populations and population PK analyses demonstrating that a dosing regimen of 3 mg/kg ipilimumab every 3 weeks produces similar exposures in children and adults. Study CA184070 was a multi-center, open-label, 3 + 3 dose-escalation with expansion trial of ipilimumab in 33 patients less than or equal to 21 years of age with various advanced solid tumors including melanoma. Study CA184178 was a multicenter, single-arm, open label study of ipilimumab in 12 pediatric patients 12 to < 18 years of age with previously treated or untreated, unresectable Stage III or Stage IV advanced or metastatic melanoma. Study CA184178 closed early due to poor accrual in the context of emerging adult data demonstrating increased clinical benefit in adult patients treated with ipilimumab in combination with nivolumab as compared to single-agent ipilimumab and the opening of pediatric trials of the combination regimen. Studies CA184070 and 184178 assessed antitumor activity via radiologic response rates in pediatric patients treated with a range of ipilimumab doses. Of the 17 patients 12 years and older with advanced melanoma treated, there were two partial responses (ORR=12%), one of which was durable for more than 15 months. One additional patient had a prolonged stable disease (> 22 months). In the primary trial supporting licensure, the ORR for adult patients receiving single-agent ipilimumab was 11%. These results indicate that the antitumor activity in pediatric patients as measured by ORR is similar to that in adults. It is anticipated that adolescent patients will experience similar improvements in survival despite the modest response rates observed in the pediatric trials. The safety results of ipilimumab in pediatric patients treated across Studies CA184070 and CA184178 did not identify any unique or exaggerated adverse reactions and was overall consistent with the known toxicity profile in adults. There were a limited number of pediatric patients under the age of 12 treated with ipilimumab in these trials (n=13), but the safety findings in this group, including the incidence and severity of immune mediated adverse reactions (imARs), were similar to those for adolescents and adults.*

DPV has not previously presented an evaluation of postmarking adverse event reports for ipilimumab to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

The ipilimumab labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional ipilimumab labeling information, please refer to the full prescribing information.

----------WARNINGS AND PRECAUTIONS----------

- Severe and Fatal Immune-Mediated Adverse Reactions: Immune-mediated adverse reactions (IMAR) can occur in any organ system or tissue, including the following: immune-mediated colitis, immune-mediated hepatitis, immune-mediated dermatologic adverse reactions, immune-mediated endocrinopathies, immune-mediated pneumonitis, and immune-mediated nephritis with renal dysfunction, and can occur at any time during treatment or after discontinuation. Monitor for

symptoms and signs that may be clinical manifestations of IMAR. Evaluate clinical chemistries including liver enzymes, creatinine, adrenocorticotropic hormone level and thyroid function at baseline and before each dose. In general, withhold YERVOY for severe (grade 3) and permanently discontinue for life-threatening (grade 4) immune-mediated adverse reactions. See Full Prescribing Information for additional dosage modifications. (2.3, 5.1)

- Infusion-Related Reactions: Discontinue for severe and life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion-related reactions. (2.3, 5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with YERVOY. (5.3)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception. (5.4, 8.1, 8.3)

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

Most common adverse reactions (≥5%) with YERVOY as a single agent are fatigue, diarrhea, pruritus, rash, and colitis. Additional common adverse reactions at the 10 mg/kg dose (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab are fatigue, diarrhea, rash, pruritus, nausea, musculoskeletal pain, pyrexia, cough, decreased appetite, vomiting, abdominal pain, dyspnea, upper respiratory tract infection, arthralgia, headache, hypothyroidism, constipation, decreased weight, and dizziness. (6.1)

Most common adverse reactions (≥20%) with YERVOY in combination with nivolumab and platinum-doublet chemotherapy are fatigue, musculoskeletal pain, nausea, diarrhea, rash, decreased appetite, constipation, and pruritus. (6.1)

----------USE IN SPECIFIC POPULATIONS----------

8.4 Pediatric Use

The safety and effectiveness of YERVOY have been established in pediatric patients aged 12 years and older for the following indications: as a single agent and in combination with nivolumab for unresectable or metastatic melanoma, and, in combination with nivolumab for MSI-H or dMMR mCRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Use of YERVOY for these indications is supported by evidence from adequate and well-controlled studies in adults with melanoma or MSI-H or dMMR mCRC and additional pharmacokinetic data in pediatric patients. Ipilimumab exposures in pediatric patients 12 years and older are comparable to that of adults, and the courses of melanoma and MSI-H or dMMR mCRC are similar in pediatric patients aged 12 years and older to that of adults to allow extrapolation of safety and efficacy [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.4)].

The safety and effectiveness of YERVOY have not been established in pediatric patients younger than 12 years old with unresectable or metastatic melanoma or MSI-H or dMMR mCRC.

The safety and effectiveness of YERVOY have not been established in pediatric patients for the adjuvant treatment of melanoma or for the treatment of advanced renal cell carcinoma, hepatocellular carcinoma, metastatic non-small cell lung cancer, malignant pleural mesothelioma and esophageal cancer.

In a dose-finding trial (NCT01445379), 33 patients aged 2 to 21 years (median 13 years) with relapsed or refractory solid tumors were evaluated including unresectable stage IIIc or stage IV melanoma (12), progressive or refractory sarcomas (17), renal or bladder carcinoma (3), and neuroblastoma (1). No responses in the patients with non-melanoma solid tumors and no new safety signals were observed in pediatric patients in this study.

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	February 23, 2024
Time period of search	March 25, 2011† - February 22, 2024
Search type	RxLogix Quick Query
Product terms	PAI: Ipilimumab
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † U.S. approval date Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAI=Product Active Ingredient	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

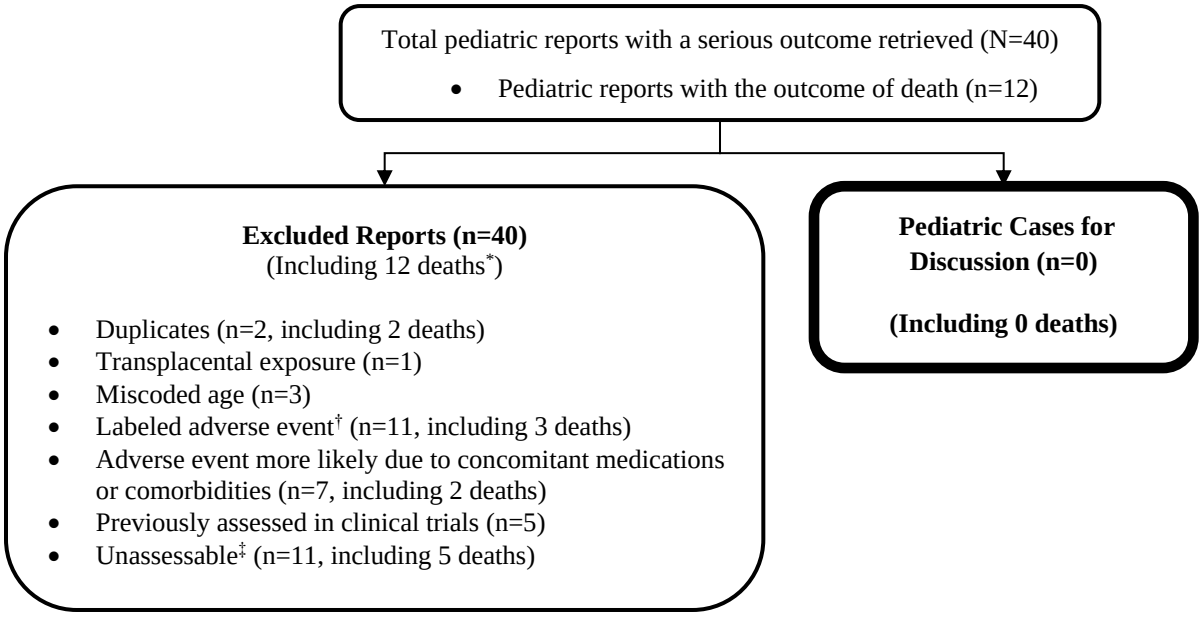
Table 2 presents the number of adult and pediatric FAERS reports from March 25, 2011 – February 22, 2024, with ipilimumab.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From March 25, 2011 – February 22, 2024 With Ipilimumab			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	24,650 (9,741)	23,352 (8,526)	5,484 (2,194)
Pediatrics (0 - < 18 years)	72 (45)	67 (40)	16‡ (12)
* 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, or other serious important medical events. ‡ See Figure 1. Two additional reports of U.S. pediatric deaths were identified among reports not reporting an age. Four additional reports of U.S. pediatric deaths were identified among reports not coded with an outcome of death. These reports are reflected in the counts of pediatric reports.			

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

Our FAERS search retrieved 40 U.S. serious pediatric reports from March 25, 2011, to February 22, 2024. We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded 40 reports from the case series for the reasons listed in Figure 1.

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



* Twelve excluded U.S. FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to ipilimumab.
† Labeled adverse event does not represent increased severity or frequency.
‡ 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.

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

There are no fatal pediatric adverse event cases for further discussion.

3.1.4 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 ipilimumab in pediatric patients less than 18 years of age from March 25, 2011, through February 22, 2024, and identified 40 reports; however, all reports were excluded from further discussion. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with ipilimumab in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Yervoy (ipilimumab) injection, for intravenous use [Prescribing Information]. Princeton, NJ: Bristol-Myers Squibb Company; February 2023. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed February 23, 2024.
2. Casey, D. Division of Oncology Products-2 Medical Officer's Clinical Review of BLA 125377/S-87. July 14, 2017. Reference ID: 4124932. Available at: https://www.fda.gov/media/107202/download. Accessed February 27, 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.

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/s/

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