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

Date:	January 4, 2021
Safety Evaluator:	Kim Swank, PharmD Division of Pharmacovigilance II
Medical Officer:	Ivone Kim, MD, FAAP Division of Pharmacovigilance I
Team Leader:	Rachna Kapoor, PharmD, MBA Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Pegasys (peginterferon alpha-2a)
Pediatric Labeling Approval Date:	October 13, 2017
Application Type/Number:	BLA 103964
Applicant:	Hoffmann-La Roche
OSE RCM #:	2020-1933

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Pegasys (peginterferon alfa-2a) in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Pegasys in U.S. pediatric patients.

On October 3, 2002, FDA first approved Pegasys for the treatment of adults with chronic hepatitis C (CHC) infection who have compensated liver disease and who have not been previously treated with interferon alfa. On August 22, 2011, the indication was extended to include pediatric patients 5 years of age and older in combination with Copegus (ribavirin) for the treatment of CHC infection. This supplement was in response to a PREA postmarketing requirement (PMR) issued on October 16, 2002 to evaluate the efficacy of Pegasys in combination with Copegus compared to Pegasys monotherapy in the treatment of CHC among children 5 to 18 years of age. On May 13, 2005, FDA approved a supplement to include treatment of adult patients with HBeAg-positive and HBe-Ag-negative chronic hepatitis B (CHB) infection who have compensated liver disease and evidence of viral replication and liver inflammation. This pediatric postmarketing pharmacovigilance safety review was prompted by pediatric labeling approved on October 13, 2017, that expanded the indication to include non-cirrhotic pediatric patients 3 years of age and older with HBeAg-positive CHB and evidence of viral replication and elevations in serum alanine aminotransferase (ALT).

DPV reviewed all U.S. serious FAERS reports with Pegasys use in the pediatric population (ages 0 through 17 years), received by FDA from October 13, 2016 through September 14, 2020. After exclusions, DPV identified one non-fatal U.S. serious pediatric case with a labeled adverse event of autoimmune disorders (myasthenia gravis). There were no new safety signals identified, no increased severity of any labeled events, and no deaths directly associated with Pegasys. The reported adverse event is consistent with the known adverse reactions described in the Pegasys labeling (i.e., autoimmune disorders).

This review did not identify any new or unexpected pediatric safety concerns for Pegasys. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with Pegasys use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Pegasys (peginterferon alfa-2a) in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Pegasys in U.S. pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Pegasys, peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon with a single branched bis-monomethoxy polyethylene glycol (PEG) chain. Pegasys is a cytokine and induces an antiviral immune response. Pegasys is indicated for the treatment of (1) adults with HBeAg-positive and HBeAg-negative chronic hepatitis B (CHB) infection who have compensated liver disease and evidence of viral replication and liver inflammation, (2) non-cirrhotic pediatric patients 3 years of age and older with HBeAg-positive CHB and evidence of viral replication and elevations in serum alanine aminotransferase (ALT), (3) adults with compensated chronic hepatitis C (CHC) infection in combination with other hepatitis C virus (HCV) drugs or as monotherapy if the patient has contraindication or significant intolerance to other HCV drugs, and (4) pediatric patients 5 years of age and older with compensated CHC infection in combination with Copegus (ribavirin).

1.1.1 Chronic Hepatitis C Infection

On October 3, 2002, FDA first approved Pegasys for the treatment of adults with CHC who have compensated liver disease and who have not been previously treated with interferon alfa. On August 22, 2011, FDA approved supplemental Biologics License Application (sBLA) 103964/S-5213 to extend the Pegasys indication to include pediatric patients 5 years of age and older in combination with Copegus for the treatment of CHC virus infection. This supplement was in response to a PREA postmarketing requirement (PMR) issued on October 16, 2002 to evaluate the efficacy of Pegasys in combination with Copegus compared to Pegasys monotherapy in the treatment of CHC among children 5 to 18 years of age. The applicant received a waiver for clinical trials in patients less than 3 years of age because the product may be unsafe and necessary studies are considered impossible or highly impracticable in this pediatric group based on discussions at a previous Advisory Committee Meeting held in 2002. Pegasys contains benzyl alcohol.[1] In neonates and infants, benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications which are sometimes fatal in neonates and infants.

The Office of Surveillance and Epidemiology (OSE) previously evaluated postmarketing adverse event reports with a serious outcome and drug utilization data for Pegasys in combination with Copegus for the treatment of CHC virus infection in pediatric patients (5 years of age and older).[2] OSE's evaluation, dated June 14, 2013, was prompted by the pediatric labeling changes on August 22, 2011, which was based on the results of Trial NV172424 and Trial NR1614. Trial NV172424 was a Phase 3, randomized prospective study that assessed the efficacy of combination therapy with Pegasys and Copegus in pediatric patients aged 5-18 years with CHC and compensated liver disease. In addition, a supporting Phase 2 study (NR 16141) of viral

kinetics, pharmacokinetics, and safety was conducted in patients aged 2-8 years with CHC and compensated liver disease. The overall safety profile in the study was similar to that observed in adults with CHC treated with combination therapy of Pegasys and Copegus. FDA presented OSE's evaluation to the Pediatric Advisory Committee (PAC) on September 19, 2013. OSE's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with Pegasys in combination with Copegus.

1.1.2 Chronic Hepatitis B Infection

On May 13, 2005, FDA approved sBLA 103964/S-5037 to include treatment of adult patients with HBeAg-positive and HBe-Ag-negative CHB who have compensated liver disease and evidence of viral replication and liver inflammation. This review was prompted by pediatric labeling approved on October 13, 2017, that expanded the indication to include non-cirrhotic pediatric patients 3 years of age and older with HBeAg-positive CHB and evidence of viral replication and elevations in serum ALT based upon the data from Trial YV25718. Supplement 5270 was submitted in response to a PREA PMR 2322-1 to *"assess the safety and efficacy of peginterferon alfa-2a versus a no-treatment control in 110 pediatric patients with HBeAg-positive chronically infected with the hepatitis B virus, who have compensated liver disease."*

The following regulatory history was reproduced from Dr. Andreas Pikis' clinical review for BLA 103964/S-5270.[3]

- *A total of 151 subjects 3 to less than 18 years of age with CHB infection and without advanced fibrosis were randomized in a 2:1 ratio to receive Pegasys (Group A, n=101) or untreated control (Group B, n=50). Subjects with advanced fibrosis were assigned to Pegasys treatment group (Group C, n=10). Subjects in Groups A and C (n=111) were treated with Pegasys once weekly for 48 weeks according to body surface area (BSA) categories. Subjects in Group B were observed for 48 weeks. Subjects in Group B had the choice to switch to treatment with Pegasys after week 48. All subjects were followed for 24 weeks post-treatment. The primary efficacy endpoint was HBeAg seroconversion at 24 weeks after the end of treatment. At this time-point, 26 patients (26%) in Group A had HBeAg seroconversion compared to 3 patients (5%) in Group B (untreated group). The safety evaluation was based on the safety data of the 111 patients treated with Pegasys. The most common adverse events reported were pyrexia, headache, abdominal pain, cough, vomiting, influenza-like illness, rash, ALT increased, and aspartate aminotransferase (AST) increased. Overall, the safety profile of Pegasys in the treatment of non-cirrhotic pediatric patients 3 years of age and older with HBeAg seropositive CHB infection were consistent with that observed in adult patients with CHB infection, as well as with pediatric patients with CHC infection. No new safety signals were identified.*

The recommended dosage of Pegasys in pediatric patients 3 years of age and older with HBeAg-positive CHB is 180 mcg/1.73 m^2 x BSA subcutaneously once weekly, to a maximum dose of 180 mcg. The recommended duration of therapy is 48 weeks.

1.2 RELEVANT LABELED SAFETY INFORMATION

The Pegasys labeling includes the following safety information (excerpted from the pertinent sections). For further Pegasys labeling, including dosage and administration for adult patients, please refer to full prescribing information.[4]

WARNING: RISK OF SERIOUS DISORDERS

Risk of Serious Disorders
Alpha interferons, including PEGASYS (peginterferon alfa-2a), may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy. *[see Warnings and Precautions (5.2, 5.5, 5.8, 5.11, 5.14, 5.16), Adverse Reactions (6.1) and Nonclinical Toxicology (13.1)]*.

----------CONTRAINDICATIONS----------

- Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome to alpha interferons, including PEGASYS, or any of its components.
- Autoimmune hepatitis
- Hepatic decompensation (Child-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment
- Hepatic decompensation with Child Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment

PEGASYS is contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol is associated with an increased incidence of neurologic and other complications which are sometimes fatal in neonates and infants.

When PEGASYS is used in combination with other HCV antiviral drugs, the contraindication applicable to those agents are applicable to combination therapies. PEGASYS combination treatment with ribavirin is contraindicated in women who are pregnant and men whose female partners are pregnant (5.1, 8.1).

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

Labeling Section	**Adverse Events**
Section 5.1 Pregnancy: use with ribavirin	• Birth defects and fetal death. Patients must avoid pregnancy (female patients or female partners of male patients). Ribavirin therapy should not be started unless a confirmed negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use two forms of effective contraception during treatment and for at least 6 months after treatment has concluded.
Section 5.2 Neuropsychiatric reactions	• Life-threatening or fatal neuropsychiatric reactions may manifest in all patients receiving therapy with PEGASYS and include suicide, suicidal ideation, homicidal ideation, depression, relapse of drug addiction, and drug overdose.

Labeling Section	Adverse Events
	These reactions may occur in patients with and without previous psychiatric illness. Use with extreme caution in all patients who report a history of depression. Neuropsychiatric adverse events observed with alpha interferon treatment include aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania.
Section 5.3 Cardiovascular disorders	• Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed. Administer with caution to patients with pre-existing cardiac disease. Because cardiac disease may be worsened by ribavirin-induced anemia, patients with a history of significant or unstable cardiac disease should not receive PEGASYS/ribavirin
Section 5.4 Bone marrow suppression	• PEGASYS suppresses bone marrow function and may result in severe cytopenias. Ribavirin may potentiate the neutropenia and lymphopenia induced by alpha interferons including PEGASYS. Very rarely, alpha interferons may be associated with aplastic anemia.
Section 5.5 Autoimmune disorders	• Development or exacerbation of autoimmune disorders including myositis, hepatitis, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, psoriasis, rheumatoid arthritis, interstitial nephritis, thyroiditis, and systemic lupus erythematosus.
Section 5.6 Endocrine disorders	• PEGASYS causes or aggravates hypothyroidism and hyperthyroidism. Hyperglycemia, hypoglycemia, and diabetes mellitus have been observed.
Section 5.7 Ophthalmologic disorders	• Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema and serious retinal detachment are induced or aggravated by treatment with PEGASYS or other alpha interferons.
Section 5.8 Cerebrovascular disorders	• Ischemic and hemorrhagic cerebrovascular events have been observed.
Section 5.9 Hepatic failure and hepatic exacerbations	• Chronic hepatitis C patients with cirrhosis may be at risk of hepatic decompensation and death. • Exacerbations of hepatitis during hepatitis B therapy are not uncommon and are characterized by transient and potentially severe increases in serum ALT.
Section 5.10 Pulmonary disorders	• Dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis, some resulting in respiratory failure and/or patient deaths.
Section 5.11 Infections	• Serious and severe infections (bacterial, viral, or fungal), some fatal, have been reported.
Section 5.12 Colitis	• Ulcerative and hemorrhagic/ischemic colitis, sometimes fatal, have been observed within 12 weeks of starting treatment.

Labeling Section	Adverse Events
Section 5.13 Pancreatitis	• Pancreatitis, sometimes fatal, has occurred.
Section 5.14 Hypersensitivity	• Severe hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been observed. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens-Johnson syndrome with varying degrees of skin and mucosal involvement and exfoliative dermatitis have been reported.
Section 5.15 Impact on growth in pediatric patients	• Growth inhibition has been observed.
Section 5.16 Peripheral neuropathy	• Peripheral neuropathy has been reported with alpha interferons were given in combination with telbivudine.

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

Adult Subjects

The most common adverse reactions (incidence greater than 40%) are fatigue/asthenia, pyrexia, myalgia, and headache (6.1).

Pediatric Subjects

The most common adverse reactions are similar to those seen in adults (6.1).

----------DRUG INTERACTIONS----------

- Drugs metabolized by CYP1A2: monitor for increased serum levels of theophylline and adjust dose accordingly (7.2)
- Methadone: monitor for signs and symptoms of methadone toxicity (7.3)
- Nucleoside analogues: closely monitor for toxicities. Reduce or discontinue the dose of PEGASYS or ribavirin or both should the events worsen (7.4)
- Zidovudine: monitor for worsening neutropenia and/or anemia with PEGASYS and/or ribavirin (7.4)

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

- Pediatric patients: safety and efficacy in CHC pediatric patients less than 5 years old and CHB pediatric patients less than 3 years old have not been established (8.4)
- Geriatric patients: neuropsychiatric, cardiac, and systemic (flu-like) adverse reactions may be more severe (8.5)
- Patients with hepatic impairment: clinical status and hepatic function should be closely monitored and treatment should be immediately discontinued if decompensation occurs (8.6)
- Patients with renal impairment: PEGASYS dose should be reduced in patients with creatinine clearance less than 30 ml/min (2.6, 8.7)
- CHB: safety and efficacy have not been established in hepatitis B patients coinfected with HCV or HIV (8.9)

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	September 15, 2020
Time period of search	October 13, 2016† - September 14, 2020
Search type	Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient: Peginterferon alfa-2a
MedDRA search terms (Version 23.0)	All Preferred Terms (PTs)
Search parameters	Age < 18 years, all outcomes, worldwide
* See Appendix A for a description of the FAERS database. † One year prior to the pediatric approval labeling date	

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 October 13, 2016 through September 14, 2020 with Pegasys.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From October 13, 2016 through September 14, 2020 with Pegasys			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1,154 (339)	938 (134)	28 (5)
Pediatrics (0 - <18 years)	12 (9)	**7 (4)**	**1** (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, or other serious important medical events.			

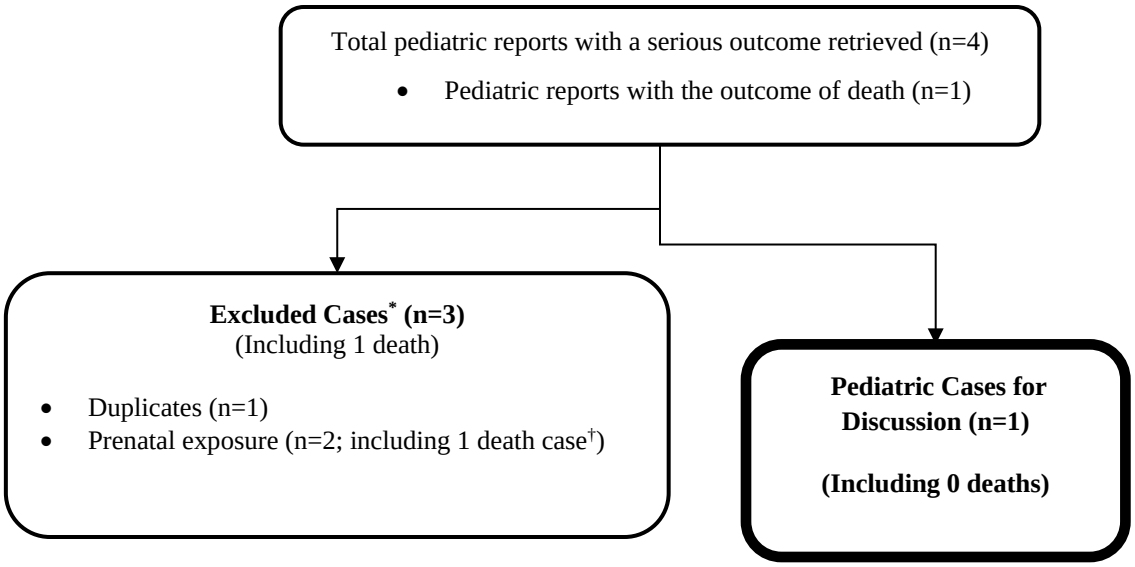
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved four U.S. serious pediatric reports from October 13, 2016 through September 14, 2020.

We reviewed all FAERS pediatric reports; however, our primary focus was on U.S. pediatric reports with a serious outcome. We did not identify any new safety concerns among the non-serious or foreign pediatric reports. We excluded reports from the case series for various reasons, such as if the report was a duplicate (n=1) or described transplacental exposure (n=2). We summarize the remaining case 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 Pegasys



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above
† The case described a male who impregnated his wife after the use of peg-interferon alfa and ribavirin for an unknown indication. The infant was born premature at 24 weeks gestation and died five days later of an unknown cause.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any fatal pediatric adverse event reports (U.S. and foreign) associated with Pegasys.

3.1.4 Summary of Non-Fatal Pediatric U.S. Serious Cases (N=1)

We identified one non-fatal serious FAERS case with Pegasys in the U.S. pediatric population. Appendix B contains the line listing of the case. The case is summarized below.

FAERS Case 14070168: An 8-year-old male (weight: 26 kg) participating in the Pediatric Immune Tolerant Trial (A1463-245) started on oral entecavir 0.375 mg daily for hepatitis B (HBV) infection. Approximately two months later, the patient started therapy with subcutaneous Pegasys injection 95 mcg every week for the treatment of HBV. The patient received entecavir and Pegasys for 11 months and 9 months, respectively. Three weeks after his last dose of Pegasys, the patient was evaluated for ptosis of his left eye. Approximately 4 months later, the patient followed-up with a neurologist who believed he had myasthenia gravis despite a negative magnetic resonance imaging (MRI) and inconclusive blood testing. The neurologist started the patient on pyridostigmine bromide for the diagnosis of myasthenia gravis one month later. The patient remained stable with therapy and was being followed by a neurologist.

Reviewer's comment: This case reported the occurrence of myasthenia gravis shortly after completion of treatment with Pegasys. Pegasys is labeled for autoimmune disorders, in the WARNINGS and PRECAUTIONS section of the label, although the adverse event of myasthenia gravis is not specifically mentioned. Based on the above information, a causal association between the development of myasthenia gravis and Pegasys treatment cannot be excluded. In addition, an exploratory search of the FAERS database and the medical literature did not identify further evidence of a new safety signal with myasthenia gravis and pediatric patients.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with Pegasys use in the pediatric population (ages 0 through 17 years), received by FDA from October 13, 2016[a] through September 14, 2020. After exclusions, DPV identified one non-fatal U.S. serious pediatric case with a labeled adverse event of autoimmune disorders (myasthenia gravis). There were no new safety signals identified, no increased severity of any labeled events, and no deaths directly associated with Pegasys. The reported adverse event is consistent with the known adverse reactions described in the Pegasys labeling (i.e., autoimmune disorders).

5 CONCLUSION

DPV did not identify any new or unexpected pediatric safety concerns for Pegasys.

6 RECOMMENDATION

DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with the use of Pegasys through routine pharmacovigilance.

[a] One year prior to pediatric approval labeling date.

7 REFERENCES

[1] Rellosa N, Smith F. Division of Antiviral Products Medical Officer's Clinical Review of BLA 103964/S-5213. July 29, 2011. Reference ID: 2981519.
[2] Gada N, Ready T, Sorbello A. Pegasys/Copegus Pediatric Postmarket Pharmacovigilance and Drug Utilization Review. June 14, 2013. Reference ID: 3325402.
[3] Pikis, A. Division of Antiviral Products Medical Officer's Clinical Review of BLA 103964/S-5270. September 5, 2017. Reference ID: 4150282.
[4] Pegasys (peginterferon alfa-2a) [package insert]. South San Francisco, CA: Hoffmann-La Roche, Inc.; Revised October 2017. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process Accessed on September 29, 2020.

8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

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=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	10/10/2017	14070168 14070074	2	US-BMS-2017-089449 US-Roche-2003969	Expedited	8	Male	U.S.	DS, OT

*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, a congenital anomaly/birth defect, or 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.
Abbreviations: DS=disability, OT=other medically significant

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KIMBERLEY A SWANK
01/04/2021 09:58:57 AM

IVONE E KIM
01/04/2021 10:00:03 AM

RACHNA KAPOOR
01/04/2021 12:20:56 PM

IDA-LINA DIAK
01/04/2021 12:29:45 PM