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

Pediatric Postmarketing Pharmacovigilance Review

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Product Name:	Epclusa (velpatasvir\sofosbuvir)
Pediatric Labeling Approval Dates:	March 19, 2020, June 10, 2021
Application Type/Numbers:	NDA 208341, NDA 214187
Applicant:	Gilead Sciences, Inc.
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TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Epclusa (sofosbuvir\velpatasvir) 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) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Epclusa in pediatric patients.

The FDA approved Epclusa on June 28, 2016, for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 or 6 infection 1) without cirrhosis, 2) with compensated cirrhosis, or 3) with decompensated cirrhosis for use in combination with ribavirin. This review was prompted by pediatric labeling approved on March 19, 2020, to include pediatric patients 6 years of age and older or weighing at least 17 kg with HCV infection and on June 10, 2021, to include pediatric patients 3 years of age and older with HCV infection.

DPV reviewed all serious FAERS reports with Epclusa in the pediatric population (ages 0 through 17 years), received by FDA from June 28, 2016 through April 24, 2023. After exclusions, DPV identified one non-fatal serious pediatric case with one unlabeled adverse event for discussion. The case described auditory hallucinations with a temporal association and positive dechallenge. However, the case lacked additional important clinical information for an adequate causality assessment.

There were no new safety signals identified, no increased severity of any labeled events, and no deaths associated with Epclusa. DPV recommends no regulatory action at this time and will continue to monitor all adverse events associated with Epclusa use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Epclusa (sofosbuvir\velpatasvir) 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 Epclusa in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Epclusa is a direct-acting antiviral (DAA) combination product of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor approved on June 28, 2016, for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection 1) without cirrhosis, 2) with compensated cirrhosis, or 3) with decompensated cirrhosis for use in combination with ribavirin.

On March 19, 2020, the indication was expanded to include pediatric patients 6 years of age and older or weighing at least 17 kg based on a 24-week efficacy and safety multicenter, open-label, non-comparative trial in children 6 to less than 18 years of age with chronic HCV infection. The safety and effectiveness in pediatric subjects were comparable to those observed in adults. The most common side effects were headache, fatigue, nausea, vomiting, and cough. All events were categorized as either mild or moderate.[1]

On June 10, 2021, the indication was further expanded to include pediatric patients 3 years of age and older based on a 12-week efficacy and safety single study, open-label, non-comparator trial in children 3 to less than 6 years of age with chronic HCV infection. The safety and effectiveness in pediatric subjects were comparable to those observed in adults. The most common side effects were vomiting, product use issues (spitting up of drug), fatigue, and irritability. All events were mild or moderate in severity.[2]

This pediatric postmarketing pharmacovigilance review was prompted by the pediatric labeling changes on March 19, 2020 and June 10, 2021. DPV has not previously presented Epclusa to the Pediatric Advisory Committee.

Epclusa is available as a 400 mg/100 mg or a 200 mg/50 mg tablet and as 200 mg/50 mg or 150 mg/37.5 mg unit-dose oral pellets. The recommended dosage of Epclusa in pediatric patients is described in **Table 1**.[3]

Table 1. Dosing for Pediatric Patients 3 Years of Age and Older Using Epclusa Oral Pellets or Tablets

Body Weight (kg)	Epclusa Daily Dose	Dosing of Epclusa Oral Pellets*	Dosing of Epclusa Tablets
Less than 17	150 mg/37.5 mg per day	One 150 mg/37.5 mg packet of pellets once daily	N/A
17 to less than 30	200 mg/50 mg per day	One 200 mg/50 mg packet of pellets once daily	One 200 mg/50 mg tablet once daily
At least 30	400 mg/100 mg per day	Two 200 mg/50 mg packets of pellets once daily	One 400 mg/100 mg tablet once daily

* In pediatric patients less than 6 years of age, administer the oral pellets with food to increase tolerability related to palatability.

The recommended duration for Epclusa is 12 weeks in pediatric patients with treatment-naïve and treatment-experienced HCV infection, without cirrhosis and with compensated cirrhosis (Child-Pugh A) and 12 weeks in combination with ribavirin in pediatric patients with treatment-naïve and treatment experienced HCV infection, with decompensated cirrhosis (Child-Pugh B or C).

1.2 RELEVANT LABELED SAFETY INFORMATION

The Epclusa labeling includes the following safety information (excerpted from the pertinent sections). For further Epclusa labeling information, including dosage and administration for adult patients, please refer to full prescribing information.[3]

WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

See full prescribing information for complete boxed warning

Hepatitis B virus (HBV) reactivation has been reported, in some cases, resulting in fulminant hepatitis, hepatic failure, and death. (5.1)

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

- EPCLUSA and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated. (4)

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

- Risk of hepatitis B virus reactivation: Test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. Monitor HCV/HBV coinfected patients for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. (5.1)

- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with EPCLUSA is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended. (5.2, 7.3)

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

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed in adults and pediatric subjects 6 years of age and older with treatment with EPCLUSA for 12 weeks are headache and fatigue. (6.1)

- The most common adverse reactions (incidence greater than or equal to 10%, grade 1 or 2) observed in pediatric subjects less than 6 years of age are vomiting and product use issue (spitting up the drug). (6.1)

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with EPCLUSA and ribavirin for 12 weeks in adult patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia, and diarrhea. (6.1)

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

- P-gp inducers and/or moderate to strong CYP inducers (e.g., rifampin, St. John's wort, carbamazepine): May decrease concentrations of sofosbuvir and/or velpatasvir. Use of EPCLUSA with P-gp inducers and/or moderate to strong CYP inducers is not recommended. (5.3, 7)

- Consult the full prescribing information prior to use for potential drug interactions. (5.2, 5.3, 7)

- Clearance of HCV infection with direct acting antivirals may lead to changes in hepatic function, which may impact safety and effective use of concomitant medications. Frequent monitoring of relevant laboratory parameters (INR or blood glucose) and dose adjustments of certain concomitant medications may be necessary. (7.3)

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

Pediatric Use

The safety and effectiveness in pediatric subjects were comparable to those observed in adults. However, among the 41 pediatric subjects less than 6 years of age, vomiting and product use

issue (spitting up the drug) were reported more frequently (15% and 10%, respectively; all Grade 1 or 2) compared to subjects 6 years of age and older. Five subjects (12%) discontinued treatment after vomiting or spitting up the drug *[see Dosage and Administration (2.4, 2.5), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.8)]*.

The safety and effectiveness of EPCLUSA for treatment of HCV genotype 5 in pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis are supported by sofosbuvir, GS-331007, and velpatasvir exposures in adults and pediatric patients *[see Dosage and Administration (2.2 and 2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.8)]*. Similar rationale is used to support dosing recommendations for pediatric patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection who have decompensated cirrhosis (Child-Pugh B or C).

In patients with severe renal impairment, including those requiring dialysis, exposures of GS-331007, the inactive metabolite of sofosbuvir, are increased *[see Clinical Pharmacology (12.3)]*. No data are available regarding the safety of EPCLUSA in pediatric patients with renal impairment *[see Use in Specific Populations (8.6)]*.

The safety and effectiveness of EPCLUSA have not been established in pediatric patients less than 3 years of age.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in **Table 2**.

Table 2. FAERS Search Strategy*	
Date of search	April 25, 2023
Time period of search	June 28, 2016† - April 24, 2023
Search type	RxLogix PV Reports Quick Query
Product terms	PAI: sofosbuvir\velpatasvir
MedDRA search terms (Version 25.1)	All PT terms
* See Appendix A for a description of the FAERS database. † U.S. approval date. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, PAI=Product Active Ingredient	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 3 presents the number of adult and pediatric FAERS reports from June 28, 2016, through April 24, 2023 with Epclusa.

Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA From June 28, 2016 through April 24, 2023 With Epclusa			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	11,632 (10,033)	3,601 (2,018)	585 (268)
Pediatrics (0 - <18 years)	30 (23)	15 (8)	0 (0)

* 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.

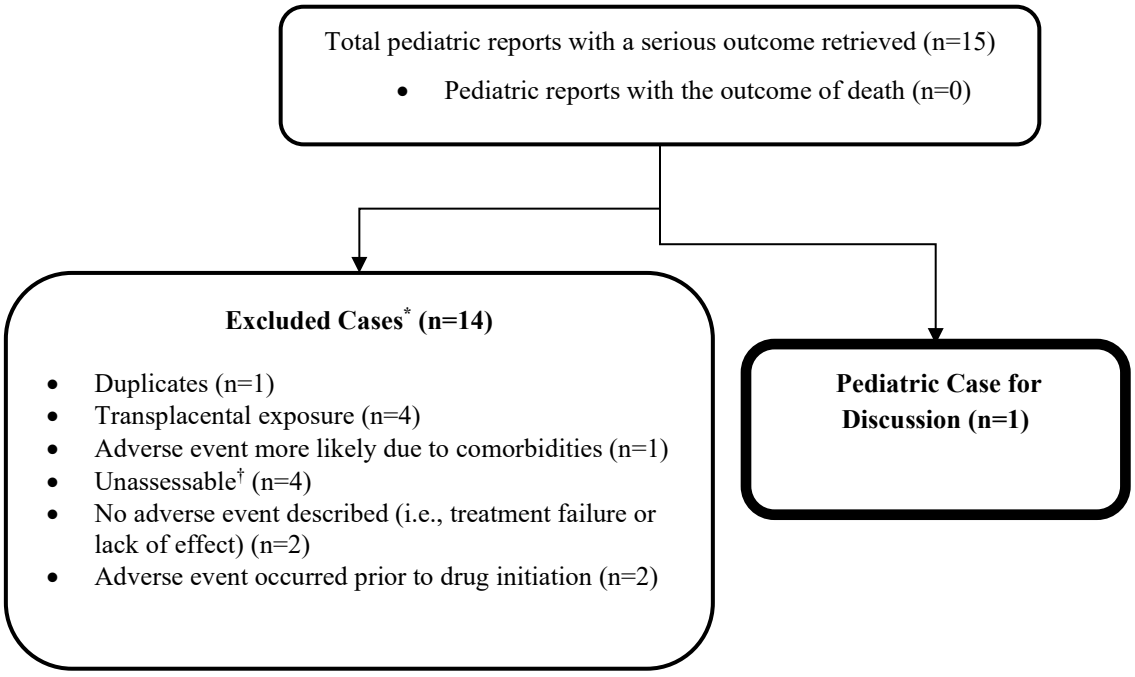
3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 15 serious pediatric reports from June 28, 2016 through April 24, 2023.

We reviewed all FAERS pediatric reports with a serious outcome. We excluded reports from the case series for the following reasons, if the adverse event was more likely due to comorbidities (n=1), reporting lack of efficacy (n=2), unassessable (n=4), transplacental exposure (n=4), duplicate report (n=1), or the event occurred prior to Epclusa 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 Pediatric Cases with Epclusa



* DPV reviewed these cases, but they were excluded from further discussion for the reasons listed above

† Unassessable: Case 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) or the information is contradictory or information provided in the case cannot be supplemented or verified.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

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

3.1.4 Summary of Non-Fatal Pediatric Serious Case (N=1)

We identified one serious FAERS case with Epclusa in the pediatric population reporting a non-fatal serious outcome. The case is summarized below.

FAERS Case #14455287, Version #2, Manufacturer Control #US-GILEAD-2018-0317406, Initial FDA Received Date 1/29/2018, United States, Serious Outcome: Other Serious

A 6-year-old female, enrolled in study GS-US-342-1143, with a past medical history of transaminitis, Dennie-Morgan fold, allergic shiners, and asthma started Epclusa once daily for the treatment of HCV. On an unknown date, the patient reported "unpleasant thoughts" and the study drug was continued. Thirty-nine days after starting Epclusa, the patient presented to the study site with a report of auditory hallucinations that started two days prior. The patient was evaluated and the investigator opted to discontinue the study medication given the development of this new adverse event. Two days after discontinuation of Epclusa, the frequency of the auditory hallucinations had decreased from multiple times on previous days to once on that day. Ten days after discontinuation of Epclusa, the auditory hallucinations had resolved. Concomitant medication included multivitamins.

Reviewers' comment: Based on a temporal association and positive dechallenge, a causal association between auditory hallucinations and Epclusa cannot be excluded. However, this case lacks sufficient clinical details, such as a description of the auditory hallucinations and diagnostic work-up of other alternative etiologies (e.g., social and environmental factors) for an adequate causality assessment. An exploratory search of the FAERS database and the medical literature did not identify further evidence of a new safety signal with auditory hallucinations and Epclusa in pediatric patients.

4 DISCUSSION

DPV reviewed all serious FAERS reports with Epclusa use in the pediatric population (ages 0 through 17 years), received by FDA from June 28, 2016[a] through April 24, 2023. After exclusions, DPV identified one non-fatal serious pediatric case with one unlabeled adverse event for discussion. The case described auditory hallucinations with a temporal association and positive dechallenge. However, the case lacked additional important clinical information for an adequate causality assessment. There were no new safety signals identified, no increased severity of any labeled events, and no deaths associated with Epclusa.

[a] U.S. approval date.

5 CONCLUSION

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

6 RECOMMENDATION

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

7 REFERENCES

[1] Tauber WB, Struble K, Birnkrant D. Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Memorandum for NDA 208341/S-14. February 18, 2020. Reference ID: 4577692.
[2] El-Kamary S, Belew Y, Mishra P. Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Review for NDA 208341/S-17 and NDA 214187. May 28, 2021. Reference ID: 4803217.
[3] Epclusa (sofosbuvir and velpatasvir) [package insert]. Foster City, CA. Gilead Sciences, Inc. Revised April 2022. Accessible at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208341. Accessed on May 2, 2023.

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.

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