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 Names:	Sovaldi (sofosbuvir), Harvoni (ledipasvir/sofosbuvir)
Pediatric Labeling Approval Date:	August 28, 2019
Application Type/Number:	NDA 204671, NDA 212480, NDA 205834, NDA 212477
Applicant:	Gilead Sciences, Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir) 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 U.S. serious, unlabeled adverse events associated with sofosbuvir and ledipasvir/sofosbuvir in pediatric patients.

The FDA approved sofosbuvir on December 6, 2013, for the treatment of chronic hepatitis C virus (HCV) genotype 1, 2, 3, or 4 infection in adult patients without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment regimen. On April 7, 2017, the indication was expanded to include pediatric patients 12 to 17 years of age or weighing at least 35 kg with HCV genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis in combination with ribavirin (RBV). This review was prompted by pediatric labeling approved on August 28, 2019 that expanded the indication to pediatric patients 3 to less than 12 years of age with chronic HCV genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis in combination with RBV. The FDA approved ledipasvir/sofosbuvir on October 10, 2014 for the treatment of chronic HCV genotype 1 infection in adults without cirrhosis or with compensated cirrhosis. In 2015, the indication was extended to adults with compensated cirrhosis with genotype 4, 5, or 6 HCV infection and those coinfected with human immunodeficiency virus (HIV) and HCV genotype 1 or 4. In 2016, the indication was further expanded to use in adults with genotype 1 or 4 HCV infection who are post-liver transplantation with compensated liver disease in combination with RBV and those with genotype 1 HCV infection with decompensated liver disease in combination with RBV regardless of transplantation status. On April 7, 2017, the indication was expanded to include pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis. This review was also prompted by pediatric labeling approved on August 28, 2019 that expanded the indication to pediatric patients 3 to less than 12 years of age with chronic HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; genotype 1 infection with decompensated cirrhosis, in combination with RBV; and genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with RBV. On August 26, 2019, DPV evaluated postmarketing adverse event reports with a serious outcome for sofosbuvir and ledipasvir\sofosbuvir. DPV's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with sofosbuvir and ledipasvir/sofosbuvir.

In this current evaluation, DPV reviewed all U.S. serious FAERS reports with sofosbuvir and ledipasvir/sofosbuvir in the pediatric population (ages 0 through 17 years), received by FDA from July 3, 2019, through October 14, 2022. After exclusions, DPV identified one non-fatal serious pediatric case with unlabeled adverse events of abnormal behavior and increased activity/energy levels with ledipasvir/sofosbuvir. However, this case lacked important information, such as concomitant medications and past medical history, for an adequate causality assessment. There were no new safety signals and no increased severity of any labeled events identified for sofosbuvir or ledipasvir/sofosbuvir at this time. DPV will continue to monitor all adverse events associated with sofosbuvir and ledipasvir/sofosbuvir use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir) 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 U.S. serious, unlabeled adverse events associated with sofosbuvir and ledipasvir/sofosbuvir in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

1.1.1 Sovaldi (sofosbuvir)

Sofosbuvir is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor approved on December 6, 2013 for the treatment of chronic hepatitis C genotype 1, 2, 3, or 4 infection in adult patients without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment regimen, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus (HIV) co-infection.[1] On April 7, 2017, the indication was expanded to include pediatric patients 12 to 17 years of age or weighing at least 35 kg with chronic HCV genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis in combination with ribavirin.

This review was prompted by pediatric labeling approved on August 28, 2019 that expanded the indication to pediatric patients 3 to less than 12 years of age with chronic HCV genotype 2 or 3 infection without cirrhosis or with compensated cirrhosis in combination with ribavirin (RBV) based on the 24 week efficacy and safety results from a single study (Study Trial GS-US-334-1112), which was a Phase 3, open-label, non-comparator trial. Supplemental new drug application (sNDA) 204671/S-14 and NDA 212480 (new oral pellets dosage form) were submitted to FDA in response to PREA postmarketing requirement (PMR) 2110-1 to "*conduct a trial to evaluate the pharmacokinetics, safety, and treatment response (using sustained virologic response) of Sovaldi (sofosbuvir) as a component of antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.*"

The following regulatory history was reproduced from Drs. Samer El-Kamary, Kimberly Struble, and Debra Birnkrant's combined clinical reviews for sNDA 204671/S-14 and NDA 212480.[2]

> *Sofosbuvir was evaluated in a two-phase, pharmacokinetic (PK), safety, and efficacy study for the treatment of pediatric subjects from 3 to less than 18 years of age with genotype 2 or 3 chronic HCV infection. The trial design was conducted in two phases: a PK lead-in phase and a treatment phase in which the safety and efficacy of sofosbuvir were evaluated. The primary objective of the PK lead-in phase was to evaluate the steady state PK and confirm the dose of sofosbuvir in HCV-infected pediatric patients. The primary objective of the second phase was to evaluate the safety and tolerability of treatment with sofosbuvir and ribavirin for 12 weeks in the HCV-infected pediatric subjects infected with genotype 2, and for 24 weeks in subjects with genotype 3. A total of 54 pediatric subjects 3 to less than 12 years of age were enrolled and received study drug (13 enrolled in the 3 to < 6 year old group and 41 in the 6 to < 12 year old group). At 12 weeks after discontinuation of study treatment, a sustained virologic response was*

demonstrated in 100% of the subjects with HCV due to genotype 2 and genotype 3; the response rate is consistent with the antiviral response observed in studies of treatment-naïve adults. All subjects who completed the treatment also achieved alanine aminotransferase (ALT) normalization. In summary, the exposure data from the PK analyses support the doses in the pediatric patients 3 to less than 12 years of age with and without cirrhosis, and the efficacy outcome as measured in trial GS-US-334-1112 by sustained virologic response 12 weeks after discontinuation of treatment are consistent with the results observed during trials of treatment experienced adults. Therefore, these results support the antiviral activity of sofosbuvir in combination with ribavirin in treatment of children 3 to less than 12 years with chronic HCV genotype 2 or genotype 3 infection. The types of adverse events observed were similar to the types of adverse events observed in adolescents and adults with chronic HCV infection who received sofosbuvir and RBV in Phase 3 studies. The most common adverse events were vomiting headache, fatigue, cough, nasopharyngitis, decreased appetite, and diarrhea. All adverse events were categorized as mild (Grade 1 or 2 adverse events). There were no drug-related serious adverse events, and no deaths. Only one child discontinued the drug due to inability to take the drug because of abnormal taste.

Sofosbuvir is available as a 400 mg or 200 mg tablet and as 150 mg or 200 mg pellets in a unit-dose packet. The recommended dosage of sofosbuvir in pediatric patients is described in **Table 1.**[1]

Table 1. Dosing for Pediatric Patients 3 Years and Older Using Sofosbuvir Tablets or Oral Pellets*

Body Weight (kg)	Dosing of Sofosbuvir Tablets or Oral Pellets	Sofosbuvir Daily Dose
At least 35	One 400 mg tablet once daily or Two 200 mg tablets once daily or Two 200 mg packets of pellets once daily	400 mg per day
17 to less than 35	One 200 mg tablet once daily or One 200 mg packet of pellets once daily	200 mg per day
Less than 17	One 150 mg packet of pellets once daily	150 mg per day

*In combination with ribavirin

The recommended duration for sofosbuvir combination therapy is 12 weeks in pediatric patients with genotype 2 HCV infection and 24 weeks in pediatric patients with genotype 3 HCV infection.[1]

1.1.2 Harvoni (ledipasvir/sofosbuvir)

Ledipasvir/sofosbuvir is a HCV NS5A inhibitor (ledipasvir) and nucleotide analog NS5B polymerase inhibitor (sofosbuvir) combination product approved on October 10, 2014 for the

treatment of chronic HCV genotype 1 infection in adults without cirrhosis or with compensated cirrhosis.[3] In 2015, the indication was extended to adults with compensated cirrhosis with genotype 4, 5, or 6 HCV infection and those with HIV/HCV/ genotype 1 or 4 co-infection. In 2016, the indication was further expanded to use in adults with genotype 1 or 4 HCV infection who are post-liver transplantation with compensated liver disease in combination with RBV and those with genotype 1 HCV infection with decompensated liver disease in combination with RBV regardless of transplantation status. On April 7, 2017, the indication was expanded to include pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis.

This review was also prompted by pediatric labeling approved on August 28, 2019 that expanded the indication to pediatric patients 3 to less than 12 years of age with chronic HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis, genotype 1 infection with decompensated cirrhosis, in combination with RBV, and genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with RBV based on the 24 week efficacy and safety results from a single study (Study Trial GS-US-337-1116), which was a Phase 3, open-label, non-comparator trial. Supplemental NDA 205834/S-29 and NDA 212477 (new oral pellets dosage form) were submitted to FDA in response to PREA PMRs 2780-1, 2983-1, and 2985-1 to *"provide data for 3 to < 18 year old HCV-infected children and to evaluate the PK, safety and HCV treatment response of ledipasvir/sofosbuvir in children 3 to < 18 years of age."*

The following regulatory history was reproduced from Drs. Samer El-Kamary, Kimberly Struble, and Debra Birnkrant's combined clinical reviews for sNDA 205834/S-29 and NDA 212477.[4]

> *Ledipasvir/sofosbuvir was evaluated in a two-phase, PK, safety, and efficacy study for the treatment of pediatric subjects 3 to less than 18 years of age with genotype 1, 4, 5, or 6 chronic HCV infection. The trial was conducted in two phases. The first phase was a 10-day PK lead-in phase, and the second was a treatment phase. The primary objective of the PK lead-in phase was to evaluate the steady state PK and confirm the dose of ledipasvir/sofosbuvir in HCV-infected pediatric patients. The second part of the study was the treatment phase; the primary objective of the treatment phase was to evaluate the safety and tolerability of treatment with ledipasvir/sofosbuvir for 12 weeks in HCV-infected pediatric subjects infected with genotype 1, 4, 5 or 6 without cirrhosis, and those with genotype 1 and cirrhosis to be treated with ledipasvir/sofosbuvir for 24 weeks. A total of 124 subjects aged 3 to less than 12 years of age with chronic HCV infection genotype 1 (n=120) and genotype 4 (n=3) were treated with ledipasvir/sofosbuvir once daily for 12 weeks (treatment naïve with/without cirrhosis or treatment experienced without cirrhosis); one subject with genotype 1 was treated with ledipasvir/sofosbuvir once daily for 24 weeks (treatment experienced with cirrhosis). The study demonstrated a high efficacy among those who received treatment. A total of 98.3% of patients with genotype 1, and 100% with genotype 4 who received the treatment achieved a sustained virological response at week 12 (SVR12). All subjects who achieved SVR12, achieved ALT normalization. The types of adverse events observed were similar to the types of adverse events observed in adolescents and adults with chronic HCV infection who received ledipasvir/sofosbuvir with our without RBV in Phase 3 studies. The most common adverse events were vomiting, headache, fatigue, nausea, pyrexia, abdominal*

pain, cough, and diarrhea. All of the adverse events were categorized as mild (Grade 1 or 2 adverse events). There were no drug-related serious adverse events, and no deaths. Only one child discontinued the drug due to inability to take the drug because of abnormal taste.

On November 15, 2019, ledipasvir/sofosbuvir was approved for the treatment of chronic HCV infection in patients with severe renal impairment, including those requiring dialysis.

Ledipasvir/sofosbuvir is a fixed-dose combination tablet available as a 90 mg/400 mg or a 45 mg/200 mg tablet and as a 45 mg/200 mg or 33.75 mg/150 mg pellet. The recommended dosage of ledipasvir/sofosbuvir in pediatric patients is described in **Table 2**.[3]

Table 2. Dosing for Pediatric Patients 3 Years and Older Using Ledipasvir/Sofosbuvir Tablets or Oral Pellets*

Body Weight (kg)	Dosing of Ledipasvir/Sofosbuvir Tablets or Oral Pellets	Ledipasvir/Sofosbuvir Daily Dose
At least 35	One 90 mg/400 mg tablet once daily or Two 45 mg/200 mg tablets once daily or Two 45 mg/200 mg packets of pellets once daily	90 mg/400 mg per day
17 to less than 35	One 45 mg/200 mg tablet once daily or One 45 mg/200 mg packet of pellets once daily	45 mg/200 mg per day
Less than 17	One 33.75 mg/150 mg packet of pellets once daily	33.75 mg/150 mg per day

*In combination with ribavirin for pediatric patients with genotype 1 infection with decompensated cirrhosis and genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis

The recommended duration of treatment for ledipasvir/sofosbuvir is described in **Table 3**.[3]

Table 3. Recommended Duration of Treatment for Ledipasvir/Sofosbuvir in Pediatric Patients 3 Years and Older

HCV Genotype	Patient Population	Treatment Duration
Genotype 1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	12 weeks*
	Treatment-experienced without cirrhosis	12 weeks
	Treatment-experienced with compensated cirrhosis (Child-Pugh A)	24 weeks†

Table 3. Recommended Duration of Treatment for Ledipasvir/Sofosbuvir in Pediatric Patients 3 Years and Older		
HCV Genotype	**Patient Population**	**Treatment Duration**
	Treatment-naïve and treatment-experienced with decompensated cirrhosis (Child-Pugh B or C)	12 weeks‡
Genotype 1 or 4	Treatment-naïve and treatment-experienced liver transplant recipients without cirrhosis or with compensated cirrhosis (Child-Pugh A)	12 weeks‡
Genotype 4, 5, or 6	Treatment-naïve and treatment-experienced, without cirrhosis or with compensated cirrhosis (Child-Pugh A)	12 weeks

* Ledipasvir/sofosbuvir for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pretreatment HCV RNA less than 6 million IU/mL.
† Ledipasvir/sofosbuvir plus ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin.
‡ In combination with ribavirin.

DPV previously evaluated postmarketing adverse event reports with a serious outcome for sofosbuvir, in pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 2 or 3 chronic HCV infection without cirrhosis or with compensated cirrhosis in combination with ribavirin, and ledipasvir/sofosbuvir, in pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 chronic HCV infection without cirrhosis or with compensated cirrhosis.[5] DPV's evaluation, dated August 26, 2019, was prompted by the pediatric labeling changes on April 7, 2017, which was based on the results of Trial GS-US-334-1112 and Trial GS-US-337-116. The overall safety profile in the studies were similar to that observed in adults with chronic HCV infection. DPV's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with sofosbuvir and ledipasvir/sofosbuvir.

1.2 Relevant Labeled Safety Information

1.2.1 Sovaldi (sofosbuvir)[1]

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

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----------

- When used in combination with peginterferon alfa/ribavirin or ribavirin alone, all contraindications to peginterferon alfa and/or ribavirin also apply to SOVALDI combination therapy. (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. Initiation appropriate patient management for HBV infection as clinically indicated. (5.1)

- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone with a sofosbuvir-containing regimen, particularly in patients also receiving beta-blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with SOVALDI is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. (5.2, 6.2, 7.1)

- Risk of reduced therapeutic effect due to use with P-gp inducers: Drugs that are P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of SOVALDI. The use of rifampin and St. John's wort with SOVALDI is not recommended. (7.1)

- Risk associated with combination treatment: Because SOVALDI is used in combination with other antiviral drugs for the treatment of HCV infection, consult the prescribing information for these drugs used in combination with SOVALDI. Warnings and Precautions related to these drugs also apply to their use in SOVALDI combination treatment.

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

- The most common adverse events (incidence greater than or equal to 20%, all grades) observed with SOVALDI in combination with ribavirin were fatigue and headache. The most common adverse events observed with SOVALDI in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia, and anemia. (6.1) The most common adverse events observed with SOVALDI in combination with ribavirin oral solution in pediatric patients was decreased appetite. (6.1)

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

- Coadministration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia. (5.2, 6.2, 7.1)
- Drugs that are intestinal P-gp inducers (e.g., rifampin, St. John's wort) may alter the concentrations of sofosbuvir. (5.3, 7, 12.3)
- Clearance of HCV infection with direct acting antivirals may lead to changes in hepatic function, which may impact safe 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. (7.1)
- Consult the full prescribing information prior to use for potential drug-drug interactions. (5.2, 5.3, 7, 12.3)

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

The safety, pharmacokinetics, and efficacy of SOVALDI in pediatric patients 3 years of age and older with genotype 2 and 3 infection have been established. SOVALDI was evaluated in an open-label clinical trial (Study 1112), which included 106 subjects (31 genotype 2; 75 genotype 3) 3 years of age and older. The safety, pharmacokinetics, and efficacy were comparable to that observed in adults [*see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)].*

The safety and efficacy of SOVALDI in pediatric patients 3 years of age and older with compensated cirrhosis is supported by comparable sofosbuvir and GS-331007 exposures between: 1) adults and adolescents without cirrhosis and 2) adults without cirrhosis and adults with compensated cirrhosis. Thus, similar efficacy would be expected for adolescent patients with compensated cirrhosis as adults with compensated cirrhosis.

The safety and efficacy of SOVALDI has not been established in pediatric patients less than 3 years of age with HCV genotype 2 or 3. The safety and efficacy of SOVALDI have not been established in pediatric patients with HCV genotype 1 or 4.

1.2.2 Harvoni (ledipasvir/sofosbuvir)Error! Bookmark not defined.

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

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----------

- If used in combination with ribavirin, all contraindications to ribavirin also apply to HARVONI combination therapy. (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. Initiation 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 HARVONI not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. (5.2, 6.2, 7.2)

- Risk of reduced therapeutic effect due to use with P-gp inducers: The concomitant use of HARVONI and P-gp inducers may significantly decrease ledipasvir and sofosbuvir plasma concentrations and may lead to a reduced therapeutic effect of Harvoni. Therefore, the use of HARVONI with P-gp inducers (e.g., rifampin, St. John's wort) is not recommended. (7.2)

- Risk associated with ribavirin combination treatment: If HARVONI is administered with ribavirin, the Warnings and Precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen. Refer to the ribavirin prescribing information for a full list of the Warnings and Precautions for ribavirin. (2.2)

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

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with HARVONI were fatigue, headache, and asthenia. (6.1)

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

- Coadministration of amiodarone may result in serious symptomatic bradycardia. Use of HARVONI with amiodarone is not recommended. (5.2, 6.2, 7.2)
- P-gp inducers (e.g., rifampin, St. John's wort): May alter the concentrations of ledipasvir and sofosbuvir. Use of HARVONI with P-gp inducers is not recommended. (5.3, 7, 12.3)
- Clearance of HCV infection with direct acting antivirals may lead to changes in hepatic function, which may impact safe 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. (7.2)
- Consult the full prescribing information prior to use for potential drug-drug interactions. (5.2, 5.3, 7, 12.3)

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

The safety, pharmacokinetics, and efficacy with HARVONI for treatment of HCV genotype 1 and 4 infection in treatment-naïve and treatment-experienced pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis have been established in an open-label, multicenter clinical trial (Study 1116, N=226; 186 treatment-naïve, 40 treatment-experienced) and are comparable to that observed in adults.

The safety and efficacy of HARVONI for treatment of HCV genotypes 5, or 6 infection in pediatric patients 3 years of age and older are supported by comparable ledipasvir, sofosbuvir, and GS-331007 exposures between adults and pediatric patients [*see Dosage and Administration (2.2 and 2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3, 14.6, 14.7)].* Similar rationale is used to support dosing recommendations for pediatric patients with HCV genotype 1 infection who have decompensated cirrhosis (Child-Pugh B or C) and for pediatric patients with HCV genotype 1 and 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis.

The safety and efficacy of HARVONI 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 4**.

Table 4. FAERS Search Strategy*	
Date of search	October 24, 2022
Time period of search	July 3, 2019† - October 14, 2022
Search type	RxLogix PV Reports Quick Query
Product terms	PAI: sofosbuvir; ledipasvir/sofosbuvir
MedDRA search terms (Version 25.0)	All Preferred Terms (PT)
* See **Appendix A** for a description of the FAERS database. † Start date was based on a previous DPV review, which had a data lock date through July 2, 2019. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term, PAI = product active ingredient, PV = pharmacovigilance	

3 RESUTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 5 presents the number of adult and pediatric FAERS reports from July 3, 2019 through October 14, 2022 with sofosbuvir.

Table 5. Total Adult and Pediatric FAERS Reports* Received by FDA From July 3, 2019 through October 14, 2022 With Sofosbuvir			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	466 (89)	444 (72)	42 (1)
Pediatrics (0 - <17 years)	6 (1)	5 (0)	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.

Table 6 presents the number of adult and pediatric FAERS reports from July 3, 2019 through October 14, 2022 with ledipasvir/sofosbuvir.

Table 6. Total Adult and Pediatric FAERS Reports* Received by FDA From July 3, 2019 through October 14, 2022 With Ledipasvir/Sofosbuvir			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	1,212 (779)	674 (244)	104 (17)
Pediatrics (0 - <17 years)	39 (32)	9 (2)	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.

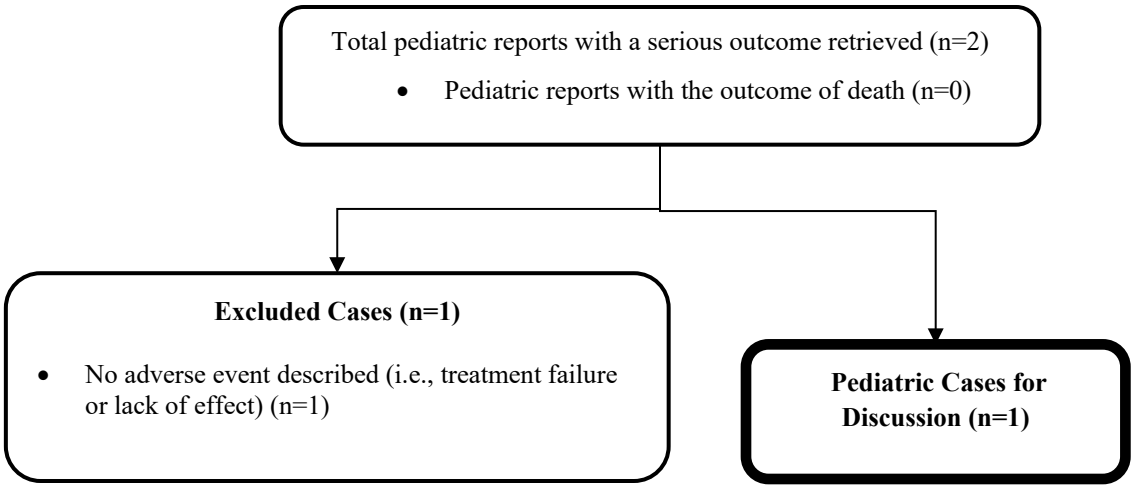
3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS

Our FAERS search retrieved no U.S. serious pediatric reports from July 3, 2019 through October 14, 2022 with sofosbuvir and two U.S. serious pediatric reports from July 3, 2019 through October 14, 2022, with ledipasvir/sofosbuvir.

We reviewed all U.S. FAERS pediatric reports with a serious outcome. We excluded one report from the case series because no adverse event was reported with the use of ledipasvir/sofosbuvir. 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 Ledipasvir/Sofosbuvir



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 U.S. Serious Case (N=1)

We identified one serious FAERS case with ledipasvir/sofosbuvir in the U.S. pediatric population reporting a non-fatal serious outcome. **Appendix B** contains a line listing of the case. The case is summarized below.

FAERS Case #20819352, United States, 2022, Serious Outcome: Other Serious

A 7-year-old male received ledipasvir/sofosbuvir for the treatment of HCV and since the beginning of therapy, his mother reported behavioral changes and behavioral "issues" that were not present prior to starting ledipasvir/sofosbuvir. The patient's mother reported that he was "getting into trouble in school" and his teachers have reported issues with increased activity level/energy.

Reviewers' comment: Abnormal behavior and increased energy are unlabeled adverse events; however, this report contains limited information, including important missing information such as the patient's past medical history and concomitant medications, which preclude an adequate assessment of this case.

4 DISCUSSION

DPV reviewed all U.S. serious FAERS reports with sofosbuvir and ledipasvir/sofosbuvir use in the pediatric population (ages 0 through 17 years) received by FDA from July 3, 2019[a] through October 14, 2022. After exclusions, DPV identified one non-fatal U.S. serious pediatric case with two unlabeled adverse events for discussion. The case described abnormal behavior and increased activity/energy levels with ledipasvir/sofosbuvir but lacked additional important information for an adequate causality assessment. There were no new safety signals identified, no increased severity of any labeled events, and no deaths directly associated with sofosbuvir or ledipasvir/sofosbuvir.

[a] The start date was based on a previous DPV review, which had a data lock date through July 2, 2019.

5 CONCLUSION

DPV did not identify any pediatric safety concerns for sofosbuvir or ledipasvir/sofosbuvir 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 sofosbuvir and ledipasvir/sofosbuvir through routine pharmacovigilance.

7 REFERENCES

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[2] El-Kamary S, Struble K, Birnkrant D. Combined Clinical Review, Cross-Discipline Team Leader Review, and Division Director Summary Memo of sNDA 204671/S-14 and NDA 212480. August 27, 2019. Reference ID: 4483174.
[3] Harvoni (ledipasvir/sofosbuvir) [package insert]. Foster City, CA. Gilead Sciences, Inc. Revised March 2020. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=205834. Accessed on December 1, 2022.
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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	5/11/2022	20819352	1	N/A	Direct	7	M	U.S.	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: OT=other medically significant, U.S. = United States, N/A = not applicable