

**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:** August 26, 2019

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**Product Names:** Sovaldi (sofosbuvir), Harvoni (ledipasvir/sofosbuvir)

**Pediatric Labeling  
Approval Date:** Sovaldi – 4/7/2017  
Harvoni – 4/7/2017

**Application Type/Number:** NDA 204671, NDA 205834

**Applicant/Sponsor:** Gilead Sciences, Inc.

**OSE RCM #:** 2019-1421

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## EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports in pediatric patients through 17 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with Sovaldi (sofosbuvir) and Harvoni (ledipasvir/sofosbuvir) in U.S. pediatric patients.

The FDA approved sofosbuvir on December 6, 2013 and it is indicated 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. This review was prompted by pediatric labeling approved on April 7, 2017 that expanded the indication from adults to pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 2 or 3 chronic hepatitis C infection without cirrhosis or with compensated cirrhosis in combination with ribavirin. The FDA approved ledipasvir/sofosbuvir on October 10, 2014 and it is indicated for the treatment of chronic hepatitis C genotype 1, 4, 5, or 6 infection in adults without cirrhosis or with compensated cirrhosis, adults with genotype 1 infection with decompensated cirrhosis in combination with ribavirin, and in adults with genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis in combination with ribavirin. This review was prompted by pediatric labeling approved on April 7, 2017 that expanded the indication from adults to pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 1, 4, 5, or 6 hepatitis C infection without cirrhosis or with compensated cirrhosis.

DPV reviewed all U.S. serious FAERS reports with sofosbuvir and ledipasvir/sofosbuvir use in the pediatric population through 17 years of age, received by FDA from U.S. approval dates through July 2, 2019. There were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and there were no deaths directly attributable to sofosbuvir or ledipasvir/sofosbuvir.

DPV did not identify any pediatric safety concerns for sofosbuvir or ledipasvir/sofosbuvir at this time.

DPV will continue to monitor all adverse events associated with the use of sofosbuvir and ledipasvir/sofosbuvir.

## 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) Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with sofosbuvir and ledipasvir/sofosbuvir in U.S. pediatric patients.

### 1.1 PEDIATRIC REGULATORY HISTORY

The Office of Surveillance and Epidemiology (OSE) has not previously presented a sofosbuvir or ledipasvir/sofosbuvir pediatric evaluation to the Pediatric Advisory Committee (PAC).

#### 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 and those with HCV/human immunodeficiency virus (HIV) co-infection.

This review was prompted by pediatric labeling approved on April 7, 2017 that expanded the indication from adults to 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 based upon the data from Trial GS-US-334-1112.<sup>1</sup> NDA 204671/S-6 was 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 sofosbuvir as a component of an antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.”<sup>2</sup>

The submission of the interim Clinical Study Report for GS-US-334-1112 was a partial response to a PREA PMR for the study of sofosbuvir in patients 3 to 17 years of age with chronic HCV. NDA 204671/S-6 contains pediatric data for subjects from 12 to 17 years of age. The final study report will include safety and efficacy data for patients 3 to 17 years of age and will address the entire pediatric population requested in the PREA PMR.

The following regulatory history was reproduced from Dr. Melisse Baylor’s clinical review for NDA 204671/S-6:<sup>3</sup>

*Sofosbuvir in combination with ribavirin (RBV) was evaluated in an open-label, multicenter, single-arm, pharmacokinetic (PK), safety, and efficacy trial in 50 adolescent patients in 28 centers in seven countries. The current submission only provides the results for adolescent subjects aged 12 to < 18 years of age (Group 1). The trial was conducted in two phases. The first phase was a PK lead-in phase and the second was a treatment phase. The primary objective of the PK phase was to evaluate the steady state pharmacokinetics and confirm the dose of sofosbuvir in HCV-infected pediatric patients. The primary objective of the treatment phase was to evaluate the safety and tolerability of*

*sofosbuvir and RBV treatment for 12 weeks in HCV pediatric patients with genotype 2 infection and 24 weeks in pediatric patients with genotype 3 infection. The primary efficacy endpoint was sustained virologic response (SVR12), defined as HCV RNA less than the lower limit of quantification (LLOQ), 12 weeks after discontinuation of study drug.*

*In the PK lead-in phase, subjects were required to have HCV RNA  $\geq$  1000 IU/mL at enrollment and be treatment naïve to participate. Ten subjects with HCV genotype 2 or 3 infection weighing at least 45 kg were enrolled in the PK lead-in phase in Cohort 1 to receive sofosbuvir 400 mg and RBV (weight-based) once daily for 7 days, and to undergo intensive PK evaluation on Day 7. Subjects in the PK lead-in phase immediately rolled over into the treatment phase without interruption in study treatment. After analysis of the PK data from the PK-lead-in phase and identification of the appropriate sofosbuvir dose in adolescents (400 mg daily), additional subjects were enrolled directly into the treatment phase. In Group 1, approximately 50 treatment naïve or treatment experienced subjects 12 to < 18 years of age with HCV genotype 2 (n=13) or 3 infection (n=37), including subjects from the PK lead-in phase, received the full adult dose (sofosbuvir 400 mg + RBV once daily) for 12 weeks (genotype 2) or 24 weeks (genotype 3). The SVR 12 rate was 100 % in genotype 2 subjects and 97 % in genotype 3 subjects. No subject experienced on-treatment virologic failure or relapse. The only subject counted as SVR treatment failure was lost-to-follow-up. Safety data from 50 adolescent subjects who received at least one dose of sofosbuvir were evaluated. There were no deaths up to week 12 post-treatment and no serious adverse events. The types of adverse events observed were similar to those observed in adults with chronic HCV infection who received sofosbuvir and RBV in Phase 3 studies. In summary, the exposure data from the PK analyses support the 400 mg daily dose of sofosbuvir in pediatric patients 12 years of age and older with and without cirrhosis, and the efficacy outcome as measured by sustained virologic response 12 weeks after discontinuation of treatment are consistent with results observed during trials of treatment-experienced adults.*

The recommended dosage of sofosbuvir in pediatric patients 12 years of age and older or weighing at least 35 kg is one 400 mg tablet taken orally once daily with or without food in combination with RBV. 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.

### **1.1.2 Harvoni (ledipasvir/sofosbuvir)**

Ledipasvir/sofosbuvir is 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. In 2015, the indication was extended to adults with compensated cirrhosis with genotype 4, 5, or 6 HCV infection and those with HCV/HIV 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.

This review was also prompted by pediatric labeling approved on April 7, 2017 that expanded the indication from adults to 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 based upon the data from Trial GS-US-337-116.<sup>1</sup> NDA 205834/S-017 was submitted in response to PREA PMRs 2780-1, 2983-1, and 2985-1 to “conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 to 17 years of age with chronic hepatitis C.”<sup>4</sup>

The submission for the Clinical Trial GS-US-337-116 was a partial response to the PREA PMR for the study of ledipasvir/sofosbuvir in patients 3 to 17 years of age with HCV. NDA 205834/S-017 contains data for pediatric patients 12 to 17 years of age with genotype 1 HCV infection without cirrhosis or with compensated cirrhosis. The final study report will include safety and efficacy data for patients 3 to 17 years of age and will address the entire pediatric population requested in the PREA PMR.

The following regulatory history was reproduced from Dr. Virginia Sheikh’s clinical review of NDA 205834/S-017:<sup>5</sup>

*Ledipasvir/sofosbuvir +/- RBV was evaluated in a Phase 2, open-label, multicenter, multi-cohort trial designed to evaluate the pharmacokinetics, safety, and efficacy in adolescents and children with chronic HCV. Although the trial was amended to include participants with genotypes 4, 5, and 6 after ledipasvir/sofosbuvir was approved for these genotypes in adults, this submission includes the SVR12 results from Group 1 (children ages  $\geq 12$  to  $< 18$  years of age) with genotype 1 HCV infection. The study consisted of a PK lead-in phase and a treatment phase. The PK lead-in phase evaluated and confirmed the age-appropriate ledipasvir/sofosbuvir dose by analyzing PK, safety, and antiviral activity through 10 days of dosing.*

*In Group 1, approximately 100 patients (treatment naïve with or without cirrhosis; n=80 or treatment experienced without cirrhosis; n=20) 12 to 18 years of age with HCV genotype 1 infection, including patients from the PK lead-in phase, received the full adult dose (90 mg/400 mg ledipasvir/sofosbuvir for 12 weeks). Although patients with genotypes 3, 4, 5, and 6 HCV infection were eligible to be enrolled in the study, only patients with genotype 1 were enrolled. HCV genotype does not affect ledipasvir/sofosbuvir exposure and previous trials in adults have demonstrated that equivalent ledipasvir/sofosbuvir exposure is efficacious in adults with chronic HCV genotype 4, 5, and 6. Therefore, the submitted PK data are adequate to support the efficacy of ledipasvir/sofosbuvir for treatment of HCV genotypes 4, 5, or 6 in patients 12 years of age and older. The primary efficacy endpoint was SVR 12 weeks after stopping study treatment for all enrolled and treated patients. Ninety-eight percent of enrolled patients achieved SVR12 and no patients experienced on-treatment virologic failure or relapse. The only patients who failed to achieve SVR12 were two patients who were lost-to-follow-up. No patients experienced virologic breakthrough or viral relapse. All 100 patients enrolled in the trial were included in the safety analysis. No major adverse*

*events or adverse drug reactions were reported. No deaths occurred during the study. The frequency and severity of adverse drug reactions reported in the GS-US-337-1116 trial are consistent with those observed in clinical trials of ledipasvir/sofosbuvir in adults.*

The recommended dose for ledipasvir/sofosbuvir in pediatric patients 12 years of age and older or weighing at least 35 kg is one tablet (90 mg ledipasvir and 400 mg sofosbuvir) orally once daily with or without food. The recommended duration for ledipasvir/sofosbuvir in pediatric patients is 12 to 24 weeks.

## **1.2 RELEVANT LABELED SAFETY INFORMATION**

### **1.2.1 Sovaldi (sofosbuvir)**

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.<sup>6</sup>

**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 coinfecting 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)

## **-----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.

-----**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)
- Frequent monitoring of international normalized ratio (INR) values is recommended in patients receiving warfarin. (7.1)
- Consult the full prescribing information prior to use for potential drug-drug interactions. (5.2, 5.3, 7, 12.3)

#### 8.4 Pediatric Use

The safety, pharmacokinetics, and efficacy of SOVALDI in pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 2 and 3 infection have been established. SOVALDI was evaluated in an open-label clinical trial (Study 1112), which included 50 subjects (13 genotype 2; 37 genotype 3) 12 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 12 years of age and older or weighing at least 35 kg 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 12 years of age and weighing less than 35 kg 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)

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.<sup>7</sup>

**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 coinfecting 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)

## -----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)
- Frequent monitoring of INR values is recommended in patients receiving warfarin. (7.1)
- Consult the full prescribing information prior to use for potential drug-drug interactions. (5.2, 5.3, 7, 12.3)

### **8.4 Pediatric Use**

The safety, pharmacokinetics, and efficacy with HARVONI for treatment of HCV genotype 1 infection in treatment-naïve and treatment-experienced pediatric patients 12 years of age and older without cirrhosis or with compensated cirrhosis have been established in an open-label, multicenter clinical trial (Study 1116, N=100; 80 treatment-naïve, 20 treatment-experienced) and are comparable to that observed in adults.

The safety and efficacy of HARVONI for treatment of HCV genotypes 4, 5, or 6 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis is supported by comparable ledipasvir, sofosbuvir, and GS-331—7 exposures between adults and adolescents with HCV genotype 1 and similar efficacy and

exposures across HCV genotypes 1, 4, 5, and 6 in adults [*see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.3 and 14.6)*].

The safety and efficacy of HARVONI have not been established in pediatric patients less than 12 years of age and weighing less than 35 kg, in pediatric patients with decompensated cirrhosis, or in pediatric liver transplant recipients.

## 2 METHODS AND MATERIALS

### 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1 and Table 2.

<b>Table 1. Sofosbuvir FAERS Search Strategy*</b>	
Date of Search	July 3, 2019
Time Period of Search	December 6, 2013 <sup>†</sup> - July 2, 2019
Search Type	Product-Manufacturer Reporting Summary
Product Terms	Product Active Ingredient: Sofosbuvir
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PT)
Search Parameters	Age < 18 years, all outcomes, world wide
* See Appendix A for a description of the FAERS database.	
<sup>†</sup> U.S. approval date	

<b>Table 2. Ledipasvir/sofosbuvir FAERS Search Strategy*</b>	
Date of Search	July 3, 2019
Time Period of Search	October 10, 2014 <sup>†</sup> - July 2, 2019
Search Type	Product-Manufacturer Reporting Summary
Product Terms	Product Active Ingredient: Ledipasvir/sofosbuvir
MedDRA Search Terms (Version 22.0)	All Preferred Terms (PT)
Search Parameters	Age < 18 years, all outcomes, world wide
* See Appendix A for a description of the FAERS database.	
<sup>†</sup> U.S. approval date	

## 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 December 6, 2013 through July 2, 2019 with sofosbuvir.

<b>Table 3. Total Adult and Pediatric FAERS Reports* Received by FDA from December 6, 2013 through July 2, 2019 with Sofosbuvir</b>			
	<b>All reports (U.S.)</b>	<b>Serious<sup>†</sup> (U.S.)</b>	<b>Death (U.S.)</b>
Adults ( $\geq 18$ years)	11,201 (5,461)	8,621 (2,952)	1,049 (202)
Pediatrics (0 - < 18 years)	23 (12)	<b>16 (5)</b>	1 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality <sup>†</sup> For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.			

Table 4 presents the number of adult and pediatric FAERS reports from October 10, 2014 through July 2, 2019 with ledipasvir/sofosbuvir.

<b>Table 4. Total Adult and Pediatric FAERS Reports* Received by FDA from October 10, 2014 through July 2, 2019 with Ledipasvir/sofosbuvir</b>			
	<b>All reports (U.S.)</b>	<b>Serious<sup>†</sup> (U.S.)</b>	<b>Death (U.S.)</b>
Adults ( $\geq 18$ years)	17,520 (13,372)	8,111 (4,153)	968 (353)
Pediatrics (0 - < 18 years)	28 (21)	<b>17 (10)</b>	1 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality <sup>†</sup> For the purposes of this review, the following outcomes qualify as serious: death, life- threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.			

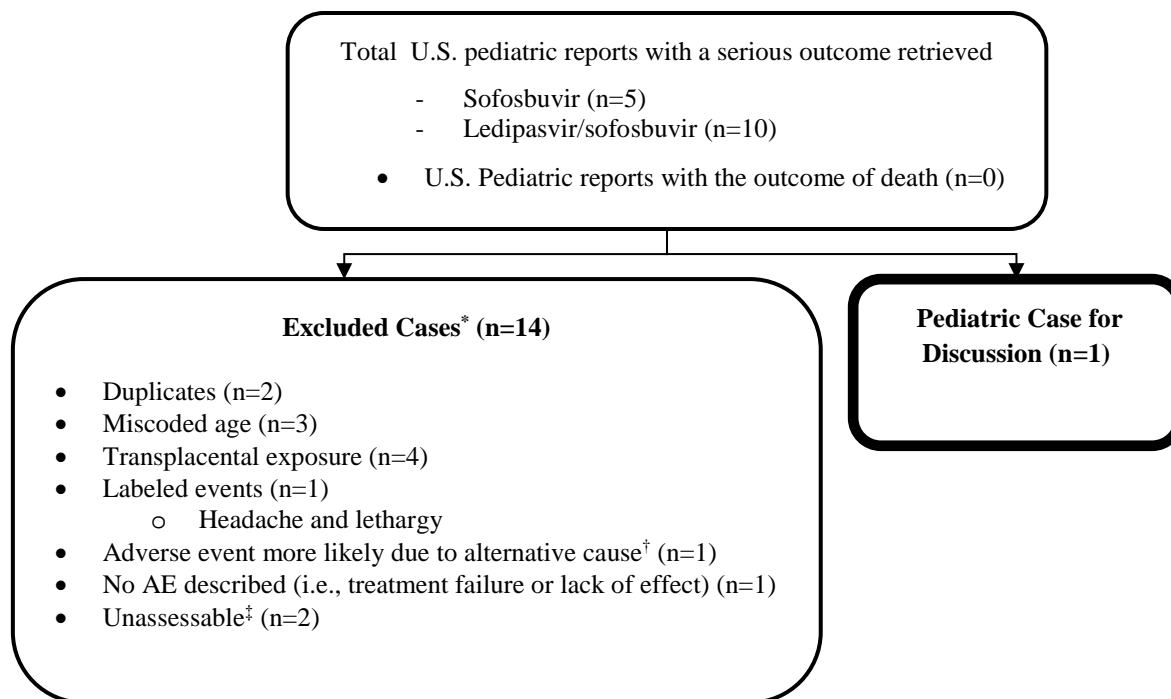
### **3.1.2 Selection of U.S. Serious Pediatric Cases in FAERS**

Our FAERS search retrieved 5 U.S. pediatric reports with a serious outcome from December 6, 2013 through July 2, 2019 with sofosbuvir, and 10 U.S. pediatric reports with serious outcome from October 10, 2014 through July 2, 2019 with ledipasvir/sofosbuvir.

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=2), report had a miscoded age (n=3), described transplacental exposure (n=4), described labeled adverse events (n=1), described adverse events more likely due to an alternative cause (n=1), did not describe an adverse event (n=1), and the case was unassessable due to limited information (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 Sofosbuvir and Ledipasvir/sofosbuvir**



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

† The case described a patient with eye discharge and photophobia from a possible eye infection.

‡ Cases 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).

### 3.1.3 Summary of Fatal Pediatric Cases (N=0)

We did not identify any U.S. fatal pediatric adverse event reports associated with sofosbuvir or ledipasvir/sofosbuvir among the 15 U.S. reports reviewed.<sup>a</sup>

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

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

**FAERS Case 13603571:** A 16-year-old female started taking ledipasvir/sofosbuvir for an unreported indication and developed autoimmune thyroiditis with hyperthyroidism during week 8 of treatment. Past medical history and concomitant medication was not provided. No other information was provided.

*Reviewers comment: Although the development of autoimmune thyroiditis and hyperthyroidism was temporally associated with ledipasvir/sofosbuvir use, because of important missing information (i.e., past medical history, concomitant medications) causality cannot be determined. In addition, autoimmune thyroid disorders are common in HCV infected patients which makes causality difficult to determine in this case.<sup>8</sup>*

<sup>a</sup> This review focuses on U.S. reports; however, DPV screened all fatal pediatric reports (i.e., non-U.S. reports) with sofosbuvir and ledipasvir/sofosbuvir use identified by the search strategy and no signal was identified. Of the two fatal non-U.S. reports, one was a miscoded age (i.e., an adult patient) and one was in a pediatric patient with acute lymphocytic leukemia who developed multi-organ failure after an allogenic stem cell transplant.

## **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 U.S. approval dates<sup>b</sup> through July 2, 2019. After exclusions, DPV identified one non-fatal U.S. serious pediatric case with an unlabeled adverse event for discussion. The case described autoimmune thyroiditis with hyperthyroidism but lacked additional information to establish causality or determine if this reflected an extrahepatic manifestation of underlying HCV infection. There were no deaths directly associated with sofosbuvir or ledipasvir/sofosbuvir use.

## **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.

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<sup>b</sup> The U.S. approval date for sofosbuvir is December 6, 2013 and October 10, 2014 for ledipasvir/sofosbuvir.

## 7 REFERENCES

- <sup>1</sup> Development Resources for Medical, Statistical, and Clinical Pharmacology Reviews of Pediatric Studies Conducted under Section 505A and 505B of the Federal Food, Drug, and Cosmetic Act, as amended by the FDA Safety and Innovation Act of 2012 (FDASIA). Available at: <https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present>. Accessed on July 15, 2019.
- <sup>2</sup> Wirth S, Rosenthal P, Gonzales-Peralta RP, Jonas MM, Balistreri WF, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2017;66(4):1102-1110.
- <sup>3</sup> Baylor, M. Clinical and Cross-Discipline Team Leader Review for Sovaldi (sofosbuvir) NDA 204671/S-6. March 27, 2017. Available at: <https://www.fda.gov/media/104827/download> Accessed on July 15, 2019.
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## 8 APPENDICES

### 8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM

#### **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)**

	<b>Initial FDA Received Date</b>	<b>FAERS Case #</b>	<b>Version #</b>	<b>Manufacturer Control #</b>	<b>Case Type</b>	<b>Age (years)</b>	<b>Sex</b>	<b>Country Derived</b>	<b>Serious Outcomes*</b>
1	6/1/2017	13603571	1	US-GILEAD-2017-0275032	Expedited	16	F	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, or a congenital anomaly/birth defect, and 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



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