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

Pediatric Postmarketing Pharmacovigilance

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Product Name:	Mavyret (glecaprevir/pibrentasvir)
Pediatric Labeling Approval Dates:	April 30, 2019, September 26, 2019
Application Type/Number:	NDA 209394, NDA 215110
Applicant:	AbbVie, Inc.
OSE RCM #:	2021-1540

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mavyret (glecaprevir/pibrentasvir) 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 Mavyret in pediatric patients.

Mavyret was first approved on August 3, 2017 for adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis and for adult patients with HCV genotype 1 infection who previously have been treated with a regimen containing either an HCV nonstructural viral protein 5A (NS5A) inhibitor or a nonstructural viral protein 3/4A (NS3/4A) protease inhibitor (PI), but not both. This pediatric postmarketing pharmacovigilance review was prompted by pediatric labeling approved on April 30, 2019, which expanded the indication to include treatment of chronic HCV infection in pediatric patients 12 years of age and older weighing at least 45 kg, and pediatric labeling approved on September 26, 2019, which shortened treatment duration to 8 weeks for treatment-naïve subjects with compensated cirrhosis in adults and pediatric patients 12 years of age and older.

DPV reviewed all serious FAERS reports with Mavyret use in the pediatric population (ages 0 through 17 years), received by FDA from August 3, 2017 through August 3, 2021, and identified one non-fatal foreign serious pediatric case with an unlabeled adverse event of posterior reversible encephalopathy syndrome (PRES). However, this report had limited information for an adequate causality assessment and was confounded by a history of prior exposure to immunosuppressive therapy. An additional search of the FAERS data identified no additional reports of PRES with Mavyret. There were no new safety signals identified, no increased severity of any labeled events, and no deaths directly associated with Mavyret.

DPV will continue to monitor all adverse events associated with Mavyret use through routine pharmacovigilance.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mavyret (glecaprevir/pibrentasvir) 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 all serious adverse events associated with Mavyret in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Mavyret is a direct-acting antiviral (DAA) protease inhibitor (PI) combination product indicated for the treatment of adult and pediatric patients 3 years and older with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) and for the treatment of adult and pediatric patients 3 years and older with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV nonstructural viral protein 5A (NS5A) inhibitor or a nonstructural viral protein 3/4A (NS3/4A) PI, but not both.[1]

The recommended dosage of Mavyret in pediatric patients 3 to less than 12 years of age is based on weight (see **Table 1**). Mavyret oral pellets are recommended for pediatric patients 3 to less than 12 years old weighing less than 45 kg. Mavyret oral pellets are a fixed combination drug product containing glecaprevir 50 mg and pibrentasvir 20 mg in each packet. The recommended dosage of Mavyret in pediatric patients 12 years of age and older, or in pediatric patients weighing at least 45 kg, is three tablets at the same time once daily with food (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg). The recommended treatment duration is based on the patient population in HCV mono-infected and HCV/HIV-1 co-infected patients with compensated liver disease (with or without cirrhosis) and with or without renal impairment including patients receiving dialysis (see **Table 2**).[1]

Table 1. Mavyret Recommended Dosage in Pediatric Patients 3 Years of Age and Older

Body Weight (kg) or Age (years)	**Daily Dose of glecaprevir/pibrentasvir**	**Dosing of Mavyret**
Less than 20 kg	150 mg/60 mg per day	Three 50 mg/20 mg packets of oral pellets once daily
20 kg to less than 30 kg	200 mg/80 mg per day	Four 50 mg/20 mg packets of oral pellets once daily
30 kg to less than 45 kg	250 mg/100 mg per day	Five 50 mg/20 mg packets of oral pellets once daily
45 kg and greater OR 12 years of age and older	300 mg/120 mg per day	Three 100 mg/40 mg tablets once daily*

* Pediatric patients weighing 45 kg and greater who are unable to swallow tablets may take six 50 mg/20 mg packets of oral pellets once daily. Dosing with oral pellets has not been studied for pediatric patients weighing greater than 45 kg.

Table 2. Mavyret Recommended Treatment Duration in Patients 3 Years and Older

Recommended Duration for Treatment-Naïve Patients		
HCV Genotype 1, 2, 3, 4, 5, or 6	**No Cirrhosis:** 8 weeks	**Compensated Cirrhosis (Child-Pugh A):** 8 weeks
Recommended Duration for Treatment-Experienced Patients		
HCV Genotype 1 *Patients previously treated with an NS5A inhibitor without prior treatment with an NS3/4A PI*	**No Cirrhosis:** 16 weeks	**Compensated Cirrhosis (Child-Pugh A):** 16 weeks
Patients previously treated with an NS3/4A PI without prior treatment with an NS5A inhibitor	**No Cirrhosis:** 12 weeks	**Compensated Cirrhosis (Child-Pugh A):** 12 weeks
HCV Genotype 1,2, 4, 5, or 6 *Patients previously treated with regimens containing (peg) interferon, ribavirin, and/or sofosbuvir, but no prior treatment experiences with an NS3/4A PI or NS5A inhibitor*	**No Cirrhosis:** 8 weeks	**Compensated Cirrhosis (Child-Pugh A):** 12 weeks
HCV Genotype 3 *Patients previously treated with regimens containing (peg) interferon, ribavirin, and/or sofosbuvir, but no prior treatment experiences with an NS3/4A PI or NS5A inhibitor*	**No Cirrhosis:** 16 weeks	**Compensated Cirrhosis (Child-Pugh A):** 16 weeks
Recommended Duration for Liver or Kidney Transplant Recipients		
A 12-week treatment duration is recommended in patients 3 years of age and older who are liver or kidney transplant recipients. A 16-week treatment duration is recommended in genotype 1-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A PI or in genotype 3-infected patients who have been previously treated with regiments containing (peg) interferon, ribavirin, and/or sofosbuvir, but no prior treatment experiences with an NS3/4A PI or NS5A inhibitor.		

Mavyret was first approved on August 3, 2017 for adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis and for adult patients with HCV genotype 1 infection who previously have been treated with a regimen containing either an HCV NS5A inhibitor or an NS3/4A PI, but not both.

On October 12, 2018, the Applicant submitted supplemental NDA (sNDA) 209394/S-006. Supplement 6 was submitted in response to PREA postmarketing requirement (PMR) 3246-1 to evaluate the pharmacokinetics, safety, and treatment response (using sustained virologic response) of Mavyret for the treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 without cirrhosis or with compensated cirrhosis in pediatric patients 12 years of age and older. Approval was based on data derived from Part 1 of protocol M16-123, which was previously submitted as a partial response to the PREA PMR 3246-1. This supplement was approved on April 30, 2019, which expanded the indication to adolescents 12 years of age and older weighing at least 45 kg. The dose approved was glecaprevir 300 mg and pibrentasvir 120 mg using the adult tablet formulation.

On March 29, 2019, the Applicant submitted sNDAs 209394, S-007 and S-008. Supplemental NDA 007 provided additional safety and efficacy data (Study M16-126) for Mavyret treatment in subjects with genotype 5 and 6 HCV infection. Supplemental NDA 008 provided data from Study M16-135 of subjects with HCV genotypes 1, 2, 3, 4, 5, or 6 infection and compensated cirrhosis who were treated with Mavyret to support a shorter duration of 8 weeks of treatment. Study M16-135 enrolled adults 18 years of age and older; however, the previously reviewed pharmacokinetic and safety data in adolescents from Part 1 of Study M16-123 established the exposure and safety data of Mavyret to be similar between adults and adolescents. Because the dose of Mavyret for this indication remained unchanged, and because the disease and response to therapy is believed to be similar in adults and children, extension of the indication of 8-week dosing in treatment-naïve HCV patients with compensated cirrhosis was recommended for the adolescent population based on extrapolation of previously reviewed pharmacokinetic and safety data. On September 26, 2019, S-008 was approved, which shortened treatment duration to 8 weeks for treatment-naïve subjects with compensated cirrhosis.

This current review was prompted by pediatric labeling approved on April 30, 2019 that expanded the indication of Mavyret to include pediatric patients 12 years of age and older weighing at least 45 kg with 1) HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis for a duration of 12 weeks and 2) HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A inhibitor, but not both, for a duration of 16 weeks. On September 26, 2019, pediatric labeling was further updated to shorten the treatment duration from 12 to 8 weeks for treatment-naïve subjects with compensated cirrhosis.

The following regulatory history was reproduced from Dr. Nicholas Rister's clinical review for NDA 209394/S-006.[2]

> *Pediatric labeling was based on data from a Phase 2/3 open-label, multicenter study (Part 1) to evaluate the pharmacokinetic, efficacy, and safety of Mavyret for 8, 12, or 16 weeks in HCV genotypes, 1, 2, 3, 4, 5, or 6 infected pediatric subjects 12 to less than 18 years of age, with or without compensated cirrhosis, with or without HIV coinfection,*

who were either treatment-naïve, treatment-experienced to interferon with or without ribavirin, or treatment-experienced to sofosbuvir plus ribavirin with or without interferon. Forty-eight participants were enrolled in 8 countries and 47 received study medication. Forty-seven participants completed study treatment and all achieved sustained virologic response (SVR) 12 weeks after therapy and no participants experienced on-treatment virologic failure or relapse. Results from the study demonstrated that Mavyret was safe and well-tolerated in adolescents. Overall, the adverse events observed were similar to those observed in adult clinical trials. Subgroup analyses did not identify any populations at greater risk for adverse events; however, this assessment was limited by the small sample size in some demographic groups. No new safety signals were identified.

On June 10, 2021, the indication for Mavyret was further expanded to include the treatment of chronic HCV genotypes 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis in pediatric patients 3 to less than 12 years of age using a new oral pellet formulation.

1.2 RELEVANT LABELED SAFETY INFORMATION[1]

The Mavyret labeling includes the following safety information (excerpted from the pertinent sections). For further Mavyret labeling, 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
>
> Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with Mavyret. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct-acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated. *[see Warnings and Precautions (5.1)]*.

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

- Patients with moderate or severe hepatic impairment (Child-Pugh B or C) or those with any history of prior hepatic decompensation. (4, 5.2)
- Coadministration with atazanavir or rifampin. (4)

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

- Risk of Hepatitis B Virus Reactivation in Patients Coinfected with HCV and HBV: 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)

- Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease: Hepatic decompensation/failure, including fatal outcomes, have been reported mostly in patients with cirrhosis and baseline moderate or severe liver impairment (Child-Pugh B or C). Monitor for clinical and laboratory evidence of hepatic decompensation. Discontinue Mavyret in patients who develop evidence of hepatic decompensation/failure. (5.2)

- Risk of Reduced Therapeutic Effect Due to Concomitant Use of Mavyret with Carbamazepine, Efavirenz Containing Regimens, or St. John's Wort: Carbamazepine, efavirenz, and St. John's wort may significantly decrease plasma concentrations of glecaprevir and pibrentasvir, leading to reduced therapeutic effect of Mavyret.

----------**USE IN SPECIAL POPULATIONS**----------

- The safety, efficacy, and pharmacokinetics of Mavyret in HCV genotype 1, 2, 3, or 4 infected pediatric patients 3 years of age and older is based on data from an open-label trial in 127 subjects without cirrhosis aged 3 years to less than 18 years who were either treatment-naïve or treatment-experienced and received Mavyret for 8, 12 or 16 weeks. The adverse reactions observed in subjects 3 years to less than 18 years of age were consistent with those observed in clinical trials of Mavyret in adults with the exception of vomiting, rash, and abdominal pain upper which were observed more frequently in pediatric subjects less than 12 years of age compared to adults. (6.1)

- The safety and effectiveness of Mavyret in children less than 3 years of age have not been studied.

2 METHODS AND MATERIALS

2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 3.

Table 3. FAERS Search Strategy*

Date of search	August 4, 2021
Time period of search	August 3, 2017† - August 3, 2021
Search type	Product-Manufacturer Reporting Summary
Product terms	Product Active Ingredient: Glecaprevir/pibrentasvir
MedDRA search terms (Version 23.1)	All PT terms
Search parameters	All outcomes, worldwide, age < 18 years

* See Appendix A for a description of the FAERS database.
† U.S. approval date
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PT=Preferred Term

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 4 presents the number of adult and pediatric FAERS reports from August 3, 2017 through August 3, 2021 with Mavyret.

Table 4. Total Adult and Pediatric FAERS Reports* Received by FDA From August 3, 2017 through August 3, 2021 With Mavyret

	All reports (U.S.)	Serious† (U.S.)	Death (U.S.)
Adults (≥ 18 years)	7,891 (6,924)	2,092 (1,164)	249 (131)
Pediatrics (0 - <18 years)	10 (8)	**1 (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.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved one serious pediatric case from August 3, 3017 through August 3, 2021.

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 Cases (N=1)

We identified one FAERS case with Mavyret in the pediatric population reporting a non-fatal serious outcome.

FAERS Case Number: 18287166 (Austria)
Unlabeled Adverse Event: Posterior Reversible Encephalopathy Syndrome (PRES)
An 8-year-old male (weight: 23 kg) with a history of acute lymphatic leukemia (prior chemotherapy treatment) and HCV received 6 weeks of Mavyret 300 mg/120 mg per day for the treatment of HCV. During the sixth week of Mavyret treatment, the patient experienced posterior reversible encephalopathy syndrome (PRES). The event resolved 18 days later.
Reviewers' comment: Although this case describes a possible temporal association with Mavyret and PRES, there is insufficient information to adequately assess causality. In addition, the case is confounded by his prior exposure to immunosuppressive therapy (i.e., unspecified chemotherapy), which is a possible risk factor for the development of PRES.[3] An exploratory search of the FAERS database for the PT Posterior reversible encephalopathy syndrome retrieved no additional reports of PRES associated with Mavyret.

4 DISCUSSION

DPV reviewed all serious FAERS reports with Mavyret use in the pediatric population (ages 0 through 17 years), received by FDA from August 3, 2017[a] through August 3, 2021, and identified one non-fatal foreign serious pediatric case with an unlabeled adverse event of PRES. However, this report had limited information for an adequate causality assessment and was

[a] U.S. approval date.

confounded by a history of prior exposure to immunosuppressive therapy. There were no new safety signals identified, no increased severity of any labeled events, and no deaths directly associated with Mavyret.

5 CONCLUSION

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

6 RECOMMENDATION

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

7 REFERENCES

[1] Mavyret (glecaprevir/pibrentasvir) [package insert]. North Chicago, IL: AbbVie, Inc.; Revised June 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215110s000,209394s013lbl.pdf Accessed on August 5, 2021. March 29, 2019. Reference ID: 4411989.
[2] Rister N. Division of Antiviral Products Medical Officer's Clinical Review of NDA 209394/S-006.
[3] Neill TA. Reversible posterior leukoencephalopathy syndrome. In: UpToDate, Wilterdink JL (Ed), UpToDate, Waltham, MA. (Accessed on October 4, 2021).

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 MAVYRET PEDIATRIC CASE SERIES (N=1)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	9/21/2020	18287166	1	AT-ABBVIE-20K-009-3572802-00	Expedited	8	M	Austria	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

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/s/

KIMBERLEY A SWANK
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IVONE E KIM
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RACHNA KAPOOR
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IDA-LINA DIAK
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