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Pediatric Postmarketing Pharmacovigilance Review

Date:	February 22, 2024
Safety Evaluator:	Kim Swank, PharmD Division of Pharmacovigilance II
Medical Officer:	Ivone Kim, MD Division of Pharmacovigilance I
Team Leader:	Rachna Kapoor, PharmD, MBA Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Mavyret (glecaprevir/pibrentasvir)
Pediatric Labeling Approval Date:	June 10, 2021
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Applicant:	AbbVie, Inc.
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mavyret (glecaprevir/pibrentasvir) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with glecaprevir/pibrentasvir in pediatric patients.

Mavyret (glecaprevir/pibrentasvir) is a direct-acting antiviral (DAA) protease inhibitor (PI) combination product and was initially approved in the U.S. on August 3, 2017. Glecaprevir/pibrentasvir is currently indicated for the treatment of adult and pediatric patients 3 years and older with 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.

This pediatric postmarketing safety review was stimulated by pediatric labeling on June 10, 2021, which expanded the indication to include pediatric patients 3 to less than 12 years of age weighing less than 45 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis using a new oral pellet formulation.

DPV searched for all serious FAERS reports with glecaprevir/pibrentasvir in the pediatric population (ages 0 through 17 years), received by FDA from August 4, 2021 through January 1, 2024, and did not identify any reports.

Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with glecaprevir/pibrentasvir in pediatric patients less than 18 years of age.

DPV will continue to monitor all adverse events associated with glecaprevir/pibrentasvir use through routine pharmacovigilance.

Reference ID: 5333071

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Mavyret (glecaprevir/pibrentasvir) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). This review focuses on serious unlabeled adverse events associated with glecaprevir/pibrentasvir in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Mavyret (glecaprevir/pibrentasvir) is a direct-acting antiviral (DAA) protease inhibitor (PI) combination product and was initially approved in the U.S. on August 3, 2017. Glecaprevir/pibrentasvir is currently indicated for the treatment of adult and pediatric patients 3 years and older with 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]

On April 30, 2019, the indication was expanded to include adolescents 12 years of age and older weighing at least 45 kg for the treatment of chronic HCV genotype 1, 2, 3, 4, 5, or 6 without cirrhosis or with compensated cirrhosis for a duration of 12 weeks and HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease 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 patients with compensated cirrhosis.

This pediatric postmarketing safety review was stimulated by pediatric labeling on June 10, 2021, which expanded the indication to include pediatric patients 3 to less than 12 years of age weighing less than 45 kg with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis using a new oral pellet formulation. The approval was supported by the safety and efficacy data from Study M16-123 Part 2. The multicenter, open-label trial included 80 pediatric subjects 3 to less than 12 years of age with chronic HCV infection. The primary efficacy outcome of sustained virologic response 12 weeks (SVR12) after treatment was achieved in 98.3% of subjects who received the recommended dose. The safety profile was overall comparable to adolescents and adults with the exception of vomiting, rash, and abdominal pain, which were observed more frequently in pediatric patients < 12 years of age. There were no deaths, drug-related serious adverse events, or concerning laboratory trends.[2]

On November 22, 2021, DPV completed a review of postmarketing adverse event reports with a serious outcome for glecaprevir/pibrentasvir in pediatric patients. DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with glecaprevir/pibrentasvir. On September 22, 2022, DPV's evaluation was presented to the Pediatric Advisory Committee via webposting.

1.2 RELEVANT LABELED SAFETY INFORMATION

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The glecaprevir/pibrentasvir labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional glecaprevir/pibrentasvir labeling information, please refer to the full prescribing information.[1]

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----------

- 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: 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)

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

- In subjects receiving MAVYRET, the most commonly reported adverse reactions (greater than 10%) are headache and fatigue. (6.1)

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

- Carbamazepine, efavirenz, and St. John's wort may decrease concentrations of glecaprevir and pibrentasvir. Coadministration of carbamazepine, efavirenz containing regimens, and St. John's wort with MAVYRET is not recommended. (5.3)
- 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. (7.3)
- Medication- Assisted Treatment (MAT) for Opioid Use Disorder. (7.4)

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

8.4 Pediatric Use

- The safety, efficacy, and pharmacokinetics of MAVYRET in HCV GT1, 2, 3, or 4 infected pediatric patients 3 years 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 (n=114) or treatment-experienced (n=13) and received MAVYRET for 8, 12 or 16 weeks (DORA-Part 1 and Part 2). 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 *[see Adverse Reactions (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 1**.

Table 1. FAERS Search Strategy*	
Date of search	January 2, 2024
Time period of search	August 4, 2021† - January 1, 2024
Search type	RxLogix Pediatric Focused Review Alert
Product terms	PAI: glecaprevir\pibrentasvir
MedDRA search terms (Version 26.1)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † The FAERS search period for the most recently completed (November 22, 2021) DPV pediatric postmarketing pharmacovigilance review for glecaprevir/pibrentasvir ended on August 3, 2021. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, PAI=Product Active Ingredient	

3 RESULTS

3.1 FAERS

3.1.1 Total Number of FAERS Reports by Age

Table 2 presents the number of adult and pediatric FAERS reports from August 4, 2021 – January 1, 2024, with glecaprevir/pibrentasvir.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From August 4, 2021 – January 1, 2024, With Glecaprevir/Pibrentasvir			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	770 (503)	482 (234)	86 (32)
Pediatrics (0 - < 18 years)	2 (2)	0 (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 no serious pediatric reports from August 4, 2021 through January 1, 2024 with glecaprevir/pibrentasvir.

3.1.3 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.4 Summary of Serious Non-Fatal Pediatric Cases (N=0)

There are no non-fatal pediatric adverse event cases for discussion.

4 DISCUSSION

DPV searched FAERS for all serious reports with glecaprevir/pibrentasvir in pediatric patients less than 18 years of age from August 4, 2021 through January 1, 2024, and did not identify any reports.

Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with glecaprevir/pibrentasvir in pediatric patients less than 18 years of age.

5 CONCLUSION

DPV did not identify any new pediatric safety concerns for glecaprevir/pibrentasvir at this time and will continue routine pharmacovigilance monitoring for glecaprevir/pibrentasvir.

6 REFERENCES

[1] Mavyret (glecaprevir/pibrentasvir) [package insert]. North Chicago, IL: AbbVie, Inc.; Revised October 2023. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=215110. Accessed on January 2, 2024.
[2] Taormina G., Viswanathan P, Mishra P. Mavyret (glecaprevir/pibrentasvir) Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Review. May 28, 2021. Available at: https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present. Accessed on January 2, 2024.

7 APPENDICES

7.1 APPENDIX A. 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 terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

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 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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RACHNA KAPOOR
02/22/2024 09:40:05 AM

IDA-LINA DIAK
02/22/2024 09:46:25 AM