Department of Health and Human Services
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Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	May 21, 2025
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Product Name:	Zepatier (elbasvir and grazoprevir)
Pediatric Labeling Approval Date:	December 9, 2021
Application Type/Number:	NDA 208261
Applicant:	Merck Sharp & Dohme
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zepatier (elbasvir and grazoprevir) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with elbasvir and grazoprevir in pediatric patients.

Zepatier is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor. Zepatier was initially approved in the U.S. on January 28, 2016. Zepatier is currently indicated for treatment of chronic HCV genotype 1 or 4 infection in adult and pediatric patients 12 years of age and older or weighing at least 30 kg.

This pediatric postmarketing safety review was prompted by pediatric labeling on December 9, 2021, which expanded the indication from use in adult patients to use in adult and pediatric patients 12 years of age and older or weighing at least 30 kg.

A pediatric safety review for Zepatier has not previously been presented to the Pediatric Advisory Committee.

DPV searched FAERS for all U.S. serious reports with elbasvir and grazoprevir in pediatric patients less than 18 years of age from January 28, 2016, through May 1, 2025, and did not identify any reports.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with elbasvir and grazoprevir in pediatric patients less than 18 years of age.

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

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Zepatier (elbasvir and grazoprevir) in pediatric patients less than 18 years of age. The Division of Pharmacovigilance (DPV) conducted this review in accordance with the Pediatric Research Equity Act (PREA). This review focuses on United States (U.S.) serious unlabeled adverse events associated with elbasvir and grazoprevir in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Zepatier is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor.[1] Zepatier was initially approved in the U.S. on January 28, 2016. Zepatier is currently indicated for treatment of chronic HCV genotype 1 or 4 infection in adult and pediatric patients 12 years of age and older or weighing at least 30 kg.[1]

This pediatric postmarketing safety review was prompted by pediatric labeling on December 9, 2021, which expanded the indication from use in adult patients to use in adult and pediatric patients 12 years of age and older or weighing at least 30 kg.[2]

A pediatric safety review for Zepatier has not previously been presented to the Pediatric Advisory Committee.

1.2 RELEVANT LABELED SAFETY INFORMATION

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

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

- Patients with moderate or severe hepatic impairment (Child-Pugh B or C). (4)
- OATP1B1/3 inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations, strong CYP3A inducers, and efavirenz. (4)
- If ZEPATIER is administered with ribavirin, the contraindications to ribavirin also apply. (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)
- ALT Elevations: Perform hepatic laboratory testing prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, perform additional hepatic laboratory testing at treatment week 12. For ALT elevations on ZEPATIER, follow recommendations in full prescribing information. (5.2)
- 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) treated with HCV NS3/4A protease inhibitor-containing regimens. Monitor for clinical and laboratory evidence of hepatic decompensation. Discontinue ZEPATIER in patients who develop evidence of hepatic decompensation/failure. (5.3)
- Risk Associated with Ribavirin Combination Treatment: If ZEPATIER is administered with ribavirin, the warnings and precautions for ribavirin also apply. (5.4)

---------- ADVERSE REACTIONS ----------
In subjects receiving ZEPATIER for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving ZEPATIER with ribavirin for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache. (6.1)

8.4 Pediatric Use

The safety, efficacy, and pharmacokinetics of ZEPATIER was evaluated in an open-label clinical trial (MK-5172-079), which included 22 subjects (n=21, genotype 1; n=1, genotype 4) 12 years of age and older who received ZEPATIER for 12 weeks. The safety, pharmacokinetics, and efficacy observed in this trial were comparable to those observed in adults *[see Dosage and Administration (2.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6)]*.

Safety and effectiveness of ZEPATIER have not been established in pediatric patients younger than 12 years of age who weigh less than 30 kg.

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	May 2, 2025
Time period of search	January 28, 2016† - May 1, 2025
Search type	RxLogix Pediatric Focused Review Alert – DPV
Product terms	Product active ingredient: elbasvir\grazoprevir, elbasvir\grazoprevir anhydrous
MedDRA search terms (Version 27.1)	All Preferred Terms
Other criteria	Case Seriousness: Serious‡ Country Derived: USA
* See Appendix A for a description of the FAERS database. † U.S. approval date ‡ 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. Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, USA=United States of America	

3 RESULTS

3.1 FAERS

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

Our FAERS search retrieved no U.S. serious pediatric reports for patients less than 18 years old from January 28, 2016, through May 1, 2025.

3.1.2 Summary of U.S. Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.3 Summary of U.S. 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 U.S. serious reports with elbasvir and grazoprevir in pediatric patients less than 18 years of age from January 28, 2016, through May 1, 2025, and did not identify any reports.

There were no new safety signals identified, no increased severity of any labeled adverse events, and no deaths directly associated with elbasvir and grazoprevir in pediatric patients less than 18 years of age.

5 CONCLUSION

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

6 REFERENCES

1. Zepatier (elbasvir and grazoprevir) tablets [package insert]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp. December 2021.
2. U.S. Food and Drug Administration. Supplemental NDA Approval Letter for NDA 208261 (S-007), Zepatier (elbasvir and grazoprevir); tablets. December 9, 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/208261Orig1s007ltr.pdf.

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.