Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pediatric Postmarketing Pharmacovigilance Review

Date:	January 19, 2024
Reviewers:	Kate McCartan, MD Division of Pharmacovigilance II
	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
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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Veklury (remdesivir) 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 serious unlabeled adverse events associated with remdesivir in pediatric patients.

Veklury (remdesivir) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, initially approved in the U.S. on October 22, 2020. Remdesivir is currently indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are hospitalized OR not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

This pediatric postmarketing safety review was stimulated by the pediatric labeling on January 21, 2022, and April 25, 2022. At initial approval, remdesivir was indicated for use in pediatric patients 12 years of age and older and weighing at least 40 kg for the treatment of COVID-19 requiring hospitalization. On January 21, 2022, FDA expanded the remdesivir indication to include use in patients, including pediatric patients (12 years of age and older and weighing at least 40 kg), who were not hospitalized and had mild-to-moderate COVID-19, and who were at high risk for progression to severe COVID-19, including hospitalization or death. On April 25, 2022, FDA expanded the remdesivir indication to include pediatric patients 28 days of age and older and weighing at least 3 kg.

DPV reviewed all serious FAERS reports with remdesivir in pediatric patients less than 18 years of age from February 15, 2022 through October 1, 2023, and identified nine cases for inclusion in our case series. Four cases described bradycardia with findings consistent with the findings from prior FDA assessments. Of the remaining five cases, one case described supraventricular tachycardia, two cases described unlabeled signs or symptoms of infusion-related reactions, one case described hypertension, and one case described rhabdomyolysis. These cases reported adverse events that can occur with COVID-19 itself or were missing information about latency, past medical history, concomitant medications, or outcome, therefore limiting their assessment.

Overall, there were no new safety signals identified, no increased severity or frequency of any labeled adverse events, and no deaths directly associated with remdesivir in pediatric patients less than 18 years of age. DPV will continue routine pharmacovigilance monitoring for remdesivir.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for Veklury (remdesivir) 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 serious unlabeled adverse events associated with remdesivir in pediatric patients.

1.1 PEDIATRIC REGULATORY HISTORY

Veklury (remdesivir) is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor and was initially approved in the United States on October 22, 2020.[1] Remdesivir is currently indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) who are hospitalized OR not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.[2]

This pediatric postmarketing safety review was stimulated by pediatric labeling on January 21, 2022, and April 25, 2022. At initial approval, remdesivir was indicated for use in pediatric patients 12 years of age and older and weighing at least 40 kg for the treatment of COVID-19 requiring hospitalization.[1] On January 21, 2022, FDA expanded the remdesivir indication to include use in patients, including pediatric patients (12 years of age and older and weighing at least 40 kg), who were not hospitalized and had mild-to-moderate COVID-19, and who were at high risk for progression to severe COVID-19, including hospitalization or death.[3] On April 25, 2022, FDA expanded the remdesivir indication to include pediatric patients 28 days of age and older and weighing at least 3 kg.[4]

On March 22, 2022, DPV completed a memorandum summarizing postmarketing adverse event reports for remdesivir, including a specific summary for pediatric patients, identified through February 14, 2022.[5] DPV found that the adverse events reported with the use of remdesivir for the treatment of COVID-19 in pediatric patients were similar to those identified with the use of remdesivir for the treatment of COVID-19 in all patients, with acute kidney injury and bradycardia being the two most commonly reported adverse events in both groups of patients. Overall, DPV's evaluation did not identify any new safety concerns and recommended return to routine monitoring for adverse events with remdesivir.

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

1.2 RELEVANT LABELED SAFETY INFORMATION

The remdesivir labeling contains the following safety information excerpted from the Highlights of Prescribing Information and the *Pediatric Use* subsection. For additional remdesivir labeling information, please refer to the full prescribing information.[2]

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

VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product. (4)

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

- Hypersensitivity including infusion-related and anaphylactic reactions: Hypersensitivity reactions have been observed during and following administration of VEKLURY. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent signs and symptoms of hypersensitivity. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment. (5.1)

- Increased risk of transaminase elevations: Transaminase elevations have been observed in healthy volunteers and have also been reported in patients with COVID-19 who received VEKLURY. Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate. Consider discontinuing VEKLURY if ALT levels increase to greater than 10 times the upper limit of normal. Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation. (5.2)

- Risk of reduced antiviral activity when coadministered with chloroquine phosphate or hydroxychloroquine sulfate: Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY. (5.3)

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

The most common adverse reactions (incidence greater than or equal to 5%, all grades) observed with treatment with VEKLURY are nausea, ALT increased, and AST increased. (6.1)

8.4 Pediatric Use

The safety and effectiveness of VEKLURY for the treatment of COVID-19 have been established in pediatric patients 28 days of age and older and weighing at least 3 kg, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Use in this age group is supported by the following:

- trials in adults [see Clinical Studies (14.1, 14.2, 14.3, 14.4, 14.5)]
- an open-label trial (Study 5823) in 53 hospitalized pediatric subjects [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6)].

Use of VEKLURY in pediatric patients 28 days of age and older and weighing at least 3 kg is supported by Study 5823 where 53 hospitalized pediatric subjects were treated with weight-based VEKLURY for up to 10 days in the following cohorts: subjects =12 years and weighing =40 kg (n=12); subjects <12 years and weighing =40 kg (n=5); subjects =28 days and weighing =20 to <40 kg (n=12); subjects =28 days and weighing =12 to <20 kg (n=12); and subjects =28 days and weighing =3 to <12 kg (n=12). The safety and pharmacokinetic results in pediatric subjects in this group were similar to those in adults [see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.6)].

Use of VEKLURY in pediatric patients weighing at least 40 kg is further supported by a clinical trial of VEKLURY in non-hospitalized subjects that included 3 pediatric subjects 12 years and older, and by clinical trials in hospitalized subjects that included 30 adult subjects weighing 40 to 50 kg. The safety in this weight group was comparable to adult subjects weighing greater than 50 kg. Thirty-nine pediatric patients 12 years and older and weighing at least 40 kg received VEKLURY in a compassionate use program in hospitalized subjects; the available clinical data from these patients are limited [see Adverse Reactions (6.1) and Clinical Studies (14)].

Use of VEKLURY in pediatric patients with renal impairment is supported by safety data in adults [see Adverse Reactions (6.1), Use in Specific Populations (8.6)]. Limited data are available regarding the safety of VEKLURY in pediatric patients with mild or moderate renal impairment. No data are available regarding the safety of VEKLURY in pediatric patients with severe renal impairment. In adults with severe renal impairment, including those requiring dialysis, exposures of GS-441524 and GS-704277, the metabolites of remdesivir, and betadex sulfobutyl ether sodium (SBECD) are increased [see Clinical Pharmacology (12.3)]. VEKLURY contains SBECD which, when administered intravenously, is eliminated through glomerular filtration and therefore when administered to pediatric patients with renal immaturity or renal impairment, may result in higher exposure to SBECD.

The safety and effectiveness of VEKLURY have not been established in pediatric patients younger than 28 days of age or weighing less than 3 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	October 2, 2023
Time period of search	February 15, 2022† - October 1, 2023
Search type	RxLogix Quick Query
Product terms	PAI: Remdesivir
MedDRA search terms (Version 26.0)	All Preferred Terms
* See Appendix A for a description of the FAERS database. † Data lock date from the most recently completed DPV pharmacovigilance memorandum summarizing all adverse events with remdesivir, including a specific summary for pediatric patients. 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 February 15, 2022, through October 1, 2023, with remdesivir.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA From February 15, 2022 through October 1, 2023, With Remdesivir			
	All Reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 18 years)	1,777 (697)	1,651 (596)	454 (171)
Pediatrics (0 - < 18 years)	88‡ (53)	72‡ (40)	21‡ (11)
* May include duplicates and transplacental exposures and have not been assessed for causality.			

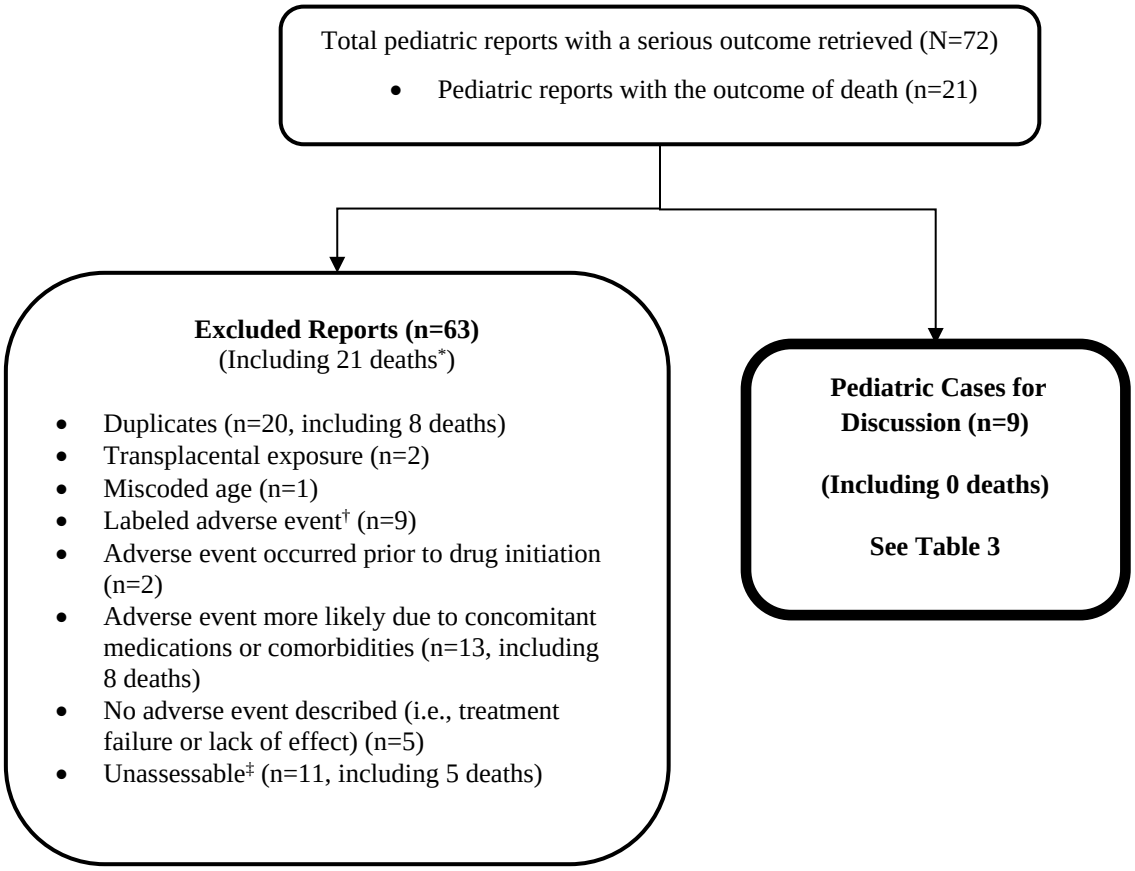
† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, or other serious important medical events.
‡ See Figure 1 below. One additional report of pediatric death was identified among reports not reporting an age. This report is reflected in the counts of pediatric reports.

3.1.2 Selection of Serious Pediatric Cases in FAERS

Our FAERS search retrieved 72 serious pediatric reports from February 15, 2022 through October 1, 2023. We reviewed all FAERS pediatric reports with a serious outcome. We excluded 63 reports from the case series for the reasons listed in Figure 1. Figure 1 presents the selection of cases for the pediatric case series.

Appendix B contains a line listing of the 9 pediatric cases in the case series.

Figure 1. Selection of Serious Pediatric Cases With Remdesivir



* Twenty-one excluded FAERS reports described fatal outcomes. None of the deaths were determined to be attributed to remdesivir. These reports were excluded for the following reasons: report was a duplicate report, adverse event was more likely due to concomitant medications or comorbidities, or the report was unassessable.
† Labeled adverse event does not represent increased severity or frequency.

‡ Unassessable: The report 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), the information is contradictory, or information provided in the report cannot be supplemented or verified.

3.1.3 Characteristics of Serious Pediatric Cases

Table 3 summarizes the nine FAERS cases in pediatric patients with remdesivir reporting a serious outcome received by FDA from February 15, 2022 through October 1, 2023.

Table 3. Characteristics of the FAERS Serious Pediatric Cases With Remdesivir Received by FDA From February 15, 2022 through October 1, 2023 (N=9)

Age	0 - < 1 month	1
	1 month - < 2 years	1
	2 - < 6 years	1
	6 - < 12 years	1
	12 - < 18 years	5
Sex	Female	5
	Male	4
Country	United States	5
	Foreign	4
Reported reason for use	COVID-19	8
	Not reported	1
Serious outcome*	Other serious	8
	Hospitalization	1
	Required intervention	1

* 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. A case can have more than one serious outcome.

3.1.4 Summary of Fatal Pediatric Cases (N=0)

There are no fatal pediatric adverse event cases for discussion.

3.1.5 Summary of Serious Non-Fatal Pediatric Cases (N=9)

We identified nine pediatric FAERS cases with remdesivir reporting a non-fatal serious outcome.

Cardiac Disorders (n=5)

Bradycardia (n=4)

- **FAERS Case #21333783:** A 17-year-old female with a past medical history of chronic kidney disease, seizures (on levetiracetam), and recent hospitalization for pneumonia was treated with remdesivir for COVID-19 and the doctor “noted bradycardia/hypotension over a period of time.” Her reported 24-hour vital sign ranges included systolic blood pressure of 88-128 mmHg, diastolic blood pressure of 45-68 mmHg, and heart rate of 53-65 bpm. Remdesivir was stopped on the second day of the planned three days of treatment and the patient’s vital signs improved to normal after the remdesivir was stopped.

- **FAERS Case #21393242:** A 2-year-old male with a past medical history of polymalformative syndrome with complex cardiopathy was admitted for adenoiditis with cellulitis of the anterior pillars and soft palate and was found to be positive for COVID-19. He was started on remdesivir and dexamethasone. Four days later, he developed bradycardia of 38-40 bpm during sleep without hemodynamic instability. The next day he was admitted to the intensive care unit (ICU) for surveillance of auricular (i.e., atrial) bradycardia. Remdesivir and dexamethasone were stopped and there was improvement in the bradycardia. Six days later, the patient was discharged from the hospital. Concomitant medications included: acetylsalicylic acid, amoxicillin/clavulanic acid, cholecalciferol, enoxaparin, esomeprazole, fluconazole, penicillin, and sildenafil.

- **FAERS Case #21684587:** A 14-year-old female with a past medical history of graft versus host disease (GVH disease) and bone marrow transplant was treated with remdesivir for three days after being admitted for mild COVID-19 symptoms. The morning after treatment with remdesivir ended, the patient experienced bradycardia of 45 bpm with "congestion," "chest discomfort/difficult retrosternal discomfort" and "slightly heavier breathing." An EKG showed sinus bradycardia at 42 bpm and pulmonary imaging (not further specified) showed "an increase in cardiac silhouette without clear signs of pulmonary surcharge." The bradycardia improved the next day (70 bpm) "despite the fact that the patient was still surcharged." The patient's weight was 2 kg above baseline but her cardiac function was in the upper limit of normal. The patient was discharged two days later. Concomitant medications included: acetaminophen, calcium carbonate and vitamin D3, cholecalciferol, cyclosporine, dexamethasone, famotidine, furosemide, lansoprazole, melatonin, morphine, piperacillin/tazobactam, polyethylene glycol, sodium chloride, valacyclovir, diphenhydramine, nystatin.

- **FAERS Case #21161736:** A 12-year-old male tested positive for COVID-19. His past medical history was notable for advanced neuronal ceroid lipofuscinosis requiring hospital admission and observation for intracerebroventricular enzyme replacement therapy every 14 days, hyperkinetic multifocal dystonic movement disorder, and colonization with *Pseudomonas aeruginosa.* Within 48 hours of testing positive for COVID-19, his respiratory symptoms worsened and three days after the initial positive test, he required admission to the pediatric ICU, requiring oxygen administration of 3 L/min via nasal cannula. On the first day of admission, he started treatment with remdesivir for COVID-19 pneumonia. On day three of admission, his clinical condition stabilized and his oxygen requirement had decreased to 1 L/min. On day four of admission, the patient developed episodes of sinus bradycardia with his heart rate dropping to 59 bpm from a baseline of 90 to 100 bpm. The bradycardia did not occur during the remdesivir infusion. Laboratory examination of cardiac biomarkers showed a slightly elevated proBNP, however, he remained hemodynamically stable during the hospital stay. No further cardiac events were reported. The patient was discharged four days after admission on 0.5 L/min oxygen and an oral cephalosporin. His respiratory condition remained stable until one month after admission when he experienced respiratory deterioration. He was treated with systemic steroid therapy, empiric antibiotic treatment, and intensified inhaled therapy. One week later, weight gain and clinical signs of fluid retention with bilateral interstitial edema and consolidation on chest X-ray were

observed. He was treated with diuretic therapy and after treatment changes, his respiratory status stabilized and it was thought he had "overcome his COVID-19 disease as well." Concomitant medications included: piperacillin/tazobactam, dexamethasone, pregabalin, tetrabenazine, valproate, lamotrigine, cannabidiol, salbutamol, fluticasone, and sodium chloride.

DPV Reviewers' Comments: Bradycardia resulting from an infusion-related reaction (IRR) is labeled for remdesivir, however, none of the four cases described specific timing of the bradycardia in relation to the remdesivir infusion. Bradycardia with remdesivir, including with pediatric patients, has been evaluated by multidisciplinary FDA staff in an Integrated Safety Assessment (ISA) in October 2021[6] and as part of the memorandum summarizing postmarketing safety adverse event reports with remdesivir completed in March 2022.[5] In the ISA, DPV identified cases of bradycardia with concerning features (e.g., bradycardia requiring treatment, second or third-degree atrioventricular block, heart rates less than 30 beats per minute), however, many of the cases lacked important details or had confounding factors so that while remdesivir was assessed as a possible cause of the bradycardia, other causes of the bradycardia could not be ruled out. The ISA also considered an assessment of other factors associated with bradycardia including bradyarrhythmias occurring in patients with COVID-19, unrelated to medication. Overall, there was insufficient evidence of a causal association between remdesivir and bradycardia and the NISS team recommended continuing routine pharmacovigilance. No regulatory action was recommended based on the ISA. In the subsequent memorandums, the findings from additional cases identified of bradycardia with remdesivir were consistent with the findings of the ISA and therefore no regulatory action was recommended based on these memorandums either. Of the four cases identified in this review, one of the cases reported hypotension with the bradycardia but without details on the severity of the hypotension and whether the patient was symptomatic. None of the remaining three cases reported symptomatic bradycardia and none of the four cases reported 2nd or 3rd degree atrioventricular block. None of the four cases reported interventions such as medications or cardiac pacing; however, two cases reported remdesivir being discontinued due to the bradycardia, including one case which also reported the need for monitoring in the ICU. The findings from the four cases in this review are consistent with the findings in the prior FDA assessments.

Supraventricular tachycardia (n=1)

- **FAERS Case #21609859:** Supraventricular tachycardia: A 1-month-old female was treated with remdesivir for COVID-19 and on the third day of treatment, the patient developed supraventricular tachycardia (SVT). The outcome for SVT was not reported. Concomitant medications and past medical history were not reported.

DPV Reviewers' Comments: The timing of the SVT in relation to the remdesivir infusion was not specified to distinguish whether these events occurred as an infusion-related reaction, for which tachycardia is labeled as a sign or symptom of IRRs. In addition to missing information with regards to concomitant medications, COVID-19 severity, and whether treatments were administered and the subsequent outcome, the case also lacked objective supportive evidence of the SVT including heart rates and EKGs. In the March 2022 FDA summary of adverse events with remdesivir[5], cases of SVT with remdesivir use were identified. Based on that assessment,

SVT was an adverse event that was assessed as not due to remdesivir and did not require further evaluation and no cases were identified in pediatric patients.

Immune System Disorders (n=2)

IRR[a] with unlabeled signs and symptoms (n=2)

- **FAERS Case #20776805:** An 18-day-old female with no reported past medical history was treated with remdesivir for an unreported indication. During the remdesivir infusion, she developed eye swelling and redness. The symptoms resolved at the completion of the infusion and recurred with the next infusion. Further remdesivir doses were held. No treatment was provided. Concomitant medications were not reported.
- **FAERS Case #21114287:** A 17-year-old male with no reported past medical history was treated with remdesivir for COVID-19. During the infusion, the patient complained of "intense chest pain" and it was noted that his "skin became reddish in tint." After the remdesivir infusion was stopped, the symptoms resolved. Rechallenge information was unknown. Concomitant medications were not reported.

DPV Reviewers' Comments: IRRs are included in the WARNINGS AND PRECAUTIONS of remdesivir labeling with rash included among the list of possible IRR signs and symptoms, however, the other symptoms described in these cases (i.e., eye swelling and redness, chest pain) are not. In both cases, the positive dechallenge supports a causal association between these unlabeled IRR symptoms and remdesivir, with the positive rechallenge in the eye swelling case providing additional support. However, assessment of these symptoms is limited in both cases with neither case reporting concomitant medications. Additionally, current labeling states, "[i]f signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment." The fact that the providers in these cases recognized these symptoms as potential clinically significant hypersensitivity reactions and initiated appropriate risk mitigation strategies suggests that the current labeling is adequate.

Vascular Disorders (n=1)

Hypertension (n=1)

- **FAERS Case #20775238:** Hypertension: A 9-year-old female was treated with remdesivir for COVID-19 and developed hypertension after the fourth dose. The outcome for hypertension was not reported. Concomitant medications and past medical history were not reported.

DPV Reviewers' Comments: The timing of the hypertension in relation to the remdesivir infusion was not specified to distinguish whether this event occurred as an infusion related reaction, for which hypertension is a labeled sign or symptom of an IRR. The case notably provided very limited information with no data to determine if there were other factors contributing to the hypertension and additionally, no objective evidence including a blood pressure measurement to confirm the reported hypertension and to assess its severity. Other missing information included

[a] Infusion-related reaction was defined as an adverse event occurring within 2 hours of administration of remdesivir.

concomitant medications, any required interventions, and outcome, which also limit evaluation of this case.

Musculoskeletal and connective tissue disorders (n=1)

Rhabdomyolysis (n=1)

- **FAERS Case #21212852:** Rhabdomyolysis: A 14-year-old male with no reported past medical history was treated with remdesivir for COVID-19 and the next day, experienced rhabdomyolysis. Creatine kinase started to increase and was "increasing by 20000 daily." Remdesivir was continued for six days and rhabdomyolysis was reported to have resolved on an unknown date. Concomitant medications were not reported.

DPV Reviewers' Comments: While the case described a temporal relationship between remdesivir initiation and rhabdomyolysis, missing information with regards to concomitant medications and dechallenge information limit the assessment of the case. We also acknowledge that cases of rhabdomyolysis associated with COVID-19 have been reported.[7] Additionally, in the March 2022 FDA summary of adverse events with remdesivir[5], seventeen cases of rhabdomyolysis with remdesivir use were identified. Based on that assessment, rhabdomyolysis was an adverse event that was assessed as not due to remdesivir and did not require further evaluation and no cases were identified in pediatric patients.

4 DISCUSSION

DPV identified nine relevant cases for inclusion in our case series. Four cases described bradycardia with findings that were consistent with those from prior FDA assessments. Of the remaining five cases, one case described SVT, two cases described unlabeled signs or symptoms of IRRs, one case described hypertension, and one case described rhabdomyolysis. These cases reported adverse events that can occur with COVID-19 itself or were missing information about latency, past medical history, concomitant medications, or outcome, therefore limiting their assessment.

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

5 CONCLUSION

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

6 REFERENCES

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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.

7.2 APPENDIX B. FAERS LINE LISTING OF THE PEDIATRIC CASE SERIES (N=9)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control # or Central Triage Unit #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
1	5/2/2022	20775238	1	FDA-CDER-CTU-2022-33264	Direct	9	F	USA	RI
2	5/2/2022	20776805	1	US-GILEAD-2022-0579192	Expedited	18 days	F	USA	OT
3	7/21/2022	21114287	1	US-GILEAD-2022-0590259	Expedited	17	M	USA	OT
4	8/15/2022	21212852	2	JP-GILEAD-2022-0593017	Expedited	14	M	JPN	OT
5	9/14/2022	21333783	1	FDA-CDER-CTU-2022-73398	Direct	17	F	USA	OT
6	9/29/2022	21393242	2	CA-GILEAD-2022-0599522	Expedited	2	M	CAN	HO, OT
7	11/17/2022	21609859	1	FDA-CDER-CTU-2022-92112	Direct	1 month	F	USA	OT
8	12/5/2022	21684587	2	CA-GILEAD-2022-0607462	Expedited	14	F	CAN	OT
9	8/2/2022 *6/15/2023*	21161736 *22605579*	2 *2*	DE-GILEAD-2022-0591528 *DE-TEVA-2023-DE-2897952*	Expedited	12	M	DEU	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control # or Central Triage Unit #	Case Type	Age (years)	Sex	Country Derived	Serious Outcomes*
	7/17/2023	*22711764*	*1*	*DE-SUN PHARMACEUTICAL INDUSTRIES LTD – 2023R1-394826*					

*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 that are blank were not marked as serious (per the previous definition) by the reporter and are coded as non-serious. A case can have more than one serious outcome.
Abbreviations: F=female, M=Male, USA=United States of America, JPN=Japan, CAN=Canada, DEU=Germany, HO=hospitalization, OT=other medically significant, RI=required intervention
Duplicates in italics

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/s/

KATE L MCCARTAN
01/19/2024 10:53:14 AM

IVONE E KIM
01/19/2024 11:04:31 AM

RACHNA KAPOOR
01/19/2024 11:10:11 AM

IDA-LINA DIAK
01/19/2024 11:37:24 AM