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Veklury® (remdesivir) Hepatic Safety

This document is in response to your request for information regarding hepatic safety data for Veklury® (remdesivir [RDV]). This response was developed according to principles of evidence-based medicine and contains data from phase 3 clinical trials.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Summary

Product Label[1]

Perform hepatic laboratory testing in all patients before starting RDV and while receiving RDV as clinically appropriate. Determine prothrombin time in all patients before starting RDV and monitor while receiving RDV as clinically appropriate.

Transaminase elevations have been observed in healthy volunteers and have also been reported in patients with COVID-19 who received RDV. Perform hepatic laboratory testing in all patients before starting RDV and while receiving RDV as clinically appropriate. Consider discontinuing RDV if ALT levels increase to >10 × the ULN. Discontinue RDV if ALT elevation is accompanied by signs or symptoms of liver inflammation.

Clinical Data on Hepatic Safety of RDV

A review of hepatic AEs and hepatic laboratory abnormalities across three phase 3 studies (ACTT-1, PINETREE, and REDPINE) in RDV use in participants with COVID-19 demonstrated that hepatic AEs were similar between treatment groups in ACTT-1 and PINETREE, and most increases in ALT and AST levels were Grade 1 or Grade 2 in all three studies.[2]

In the SIMPLE studies, rates of Grade 3 or 4 ALT and AST elevations were similar between the 5-day RDV, 10-day RDV, and SoC groups.[3-5]

Product Labeling[1]

Warnings and Precautions

Increased risk of transaminase elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of RDV followed by 100 mg doses for up to 10 days; the transaminase elevations were mild

(Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of RDV. Transaminase elevations have also been reported in patients with COVID-19 who received RDV. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus RDV in clinical trials of RDV, discerning the contribution of RDV to transaminase elevations in patients with COVID-19 can be challenging.

Perform hepatic laboratory testing in all patients before starting RDV and while receiving RDV as clinically appropriate.

- Consider discontinuing RDV if ALT levels increase to >10 × ULN.
- Discontinue RDV if ALT elevation is accompanied by signs or symptoms of liver inflammation.

Use in Specific Populations

Hepatic impairment

No dosage adjustment of RDV is recommended for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Perform hepatic laboratory testing in all patients before starting RDV and while receiving RDV as clinically appropriate.

Pharmacokinetics

Patients with hepatic impairment

The pharmacokinetics of RDV and GS-441524 were evaluated in healthy subjects and those with moderate or severe hepatic impairment (Child-Pugh Class B or C) following a single dose of 100 mg of RDV. Relative to subjects with normal hepatic function, mean exposures (AUC_{∞}, C_{max}) of RDV and GS-441524 were similar in subjects with moderate hepatic impairment and higher in subjects with severe hepatic impairment.

For additional details, please refer to Clinical Trials Experience (Section 6.1) in the US FDA-approved prescribing information .

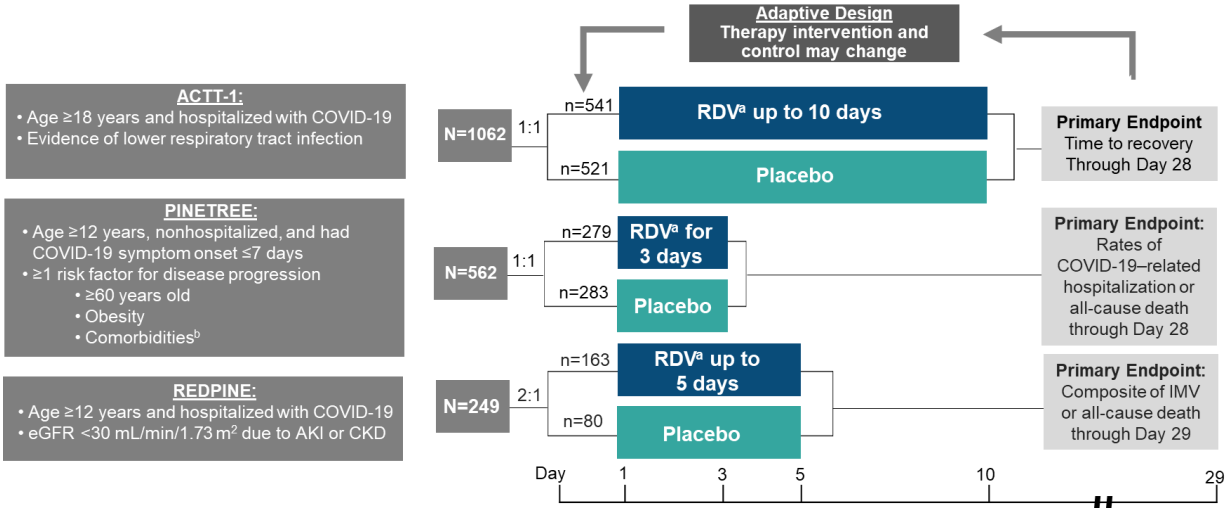
Clinical Data on Hepatic Safety of RDV

Phase 3 Placebo-Controlled COVID-19 Studies[2]

Study designs

Three phase 3 studies were reviewed to assess hepatic AEs and hepatic laboratory abnormalities in hospitalized and nonhospitalized participants with COVID-19 treated with RDV: ACTT-1, PINETREE, and REDPINE; Figure 1). In all three studies, RDV was discontinued or held if ALT and/or AST were >5 × ULN; additionally, RDV was discontinued or held in PINETREE if ALT was >3 × ULN and total bilirubin was >2 × ULN.

Figure 1. ACTT-1, PINETREE, AND REDPINE Study Designs[2]



Abbreviations: AKI=acute kidney injury; CKD=chronic kidney disease; IMV=invasive mechanical ventilation.
[a]RDV was administered as 200 mg IV on Day 1, followed by 100 mg IV once daily thereafter.
[b]Cardiovascular or cerebrovascular disease, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer, diabetes mellitus, hypertension, immune compromise, or sickle cell disease.

Results

In ACTT-1 and PINETREE, hepatic AE rates were similar between treatment groups, and rates were higher with RDV than with placebo in REDPINE (Table 1).

Table 1. ACTT-1, PINETREE, AND REDPINE: Treatment-Emergent Hepatic AEs in >1 Participant[2]

Participants, n (%)	ACTT-1		PINETREE		REDPINE	
	RDV (n=532)	Placebo (n=516)	RDV (n=279)	Placebo (n=283)	RDV (n=163)	Placebo (n=80)
Any treatment-emergent hepatic AE	71 (13.3)	80 (15.5)	1 (0.4)	4 (1.4)	12 (7.4)	2 (2.5)
Prothrombin time prolonged	26 (4.9)	8 (1.6)	0	0	0	0
AST increased	18 (3.4)	33 (6.4)	1 (0.4)	1 (0.4)	4 (2.5)	1 (1.3)
ALT increased	12 (2.3)	24 (4.7)	1 (0.4)	3 (1.1)	4 (2.5)	1 (1.3)
Blood bilirubin increased	9 (1.7)	16 (3.1)	0	0	0	0
Transaminases abnormal	7 (1.3)	11 (2.1)	0	0	0	1 (1.3)
Liver function test abnormal	3 (0.6)	3 (0.6)	0	0	1 (0.6)	0
INR increased	3 (0.6)	1 (0.2)	0	1 (0.4)	0	0
Hyperbilirubinemia	2 (0.4)	3 (0.6)	0	0	2 (1.2)	0
Liver injury	2 (0.4)	0	0	0	0	0
Blood alkaline phosphatase increased	1 (0.2)	0	0	0	1 (0.6)	0

Most hepatic laboratory abnormalities reported across all studies for increased levels of ALT and AST were Grade 1 or Grade 2. Any-grade increases of ALT, AST, and bilirubin levels were reported at lower rates in the RDV group than in the placebo group in ACTT-1 and at similar rates in PINETREE and REDPINE (Table 2).

Table 2. ACTT-1, PINETREE, AND REDPINE: Treatment-Emergent Hepatic Laboratory Abnormalities[2]

Participants, n (%)	ACTT-1		PINETREE		REDPINE	
	RDV (n=532)	Placebo (n=516)	RDV (n=279)	Placebo (n=283)	RDV (n=163)	Placebo (n=80)
Available ALT values	516	503	273	275	157	78
Any-grade ALT increased	167 (32.4)	216 (42.9)	34 (12.5)	37 (13.5)	27 (17.2)	16 (20.5)
Grade 1	103 (20)	108 (21.5)	29 (10.6)	27 (9.8)	7 (4.5)	8 (10.3)
Grade 2	48 (9.3)	77 (15.3)	4 (1.5)	8 (2.9)	12 (7.6)	3 (3.8)
Grade 3	11 (2.1)	22 (4.4)	1 (0.4)	2 (0.7)	5 (3.2)	5 (6.4)
Grade 4	5 (1)	9 (1.8)	0	0	3 (1.9)	0
Available AST values	503	492	274	275	156	78
Any-grade AST increased	167 (33.2)	216 (43.9)	20 (7.3)	18 (6.5)	35 (22.4)	15 (19.2)
Grade 1	83 (16.5)	102 (20.7)	16 (5.8)	12 (4.4)	21 (13.5)	7 (9)
Grade 2	55 (10.9)	74 (15)	3 (1.1)	5 (1.8)	5 (3.2)	5 (6.4)
Grade 3	24 (4.8)	30 (6.1)	1 (0.4)	1 (0.4)	4 (2.6)	3 (3.8)
Grade 4	5 (1)	10 (2)	0	0	5 (3.2)	0
Available bilirubin values	513	498	274	275	157	78
Any-grade hyperbilirubinemia	53 (10.3)	66 (13.3)	3 (1.1)	5 (1.8)	8 (5.1)	4 (5.1)
Grade 1	26 (5.1)	22 (4.4)	3 (1.1)	5 (1.8)	3 (1.9)	1 (1.3)
Grade 2	15 (2.9)	21 (4.2)	0	0	1 (0.6)	1 (1.3)
Grade 3	4 (0.8)	16 (3.2)	0	0	2 (1.3)	1 (1.3)
Grade 4	8 (1.6)	7 (1.4)	0	0	2 (1.3)	1 (1.3)

Note: Grading was defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017.

Overall, 26 participants with a history of chronic liver disease received RDV in the three studies, and a review of reported AEs among these participants found no safety concerns regarding the use of RDV in this population.

SIMPLE Study: RDV in Moderate COVID-19

Study design

A phase 3, two-part (Parts A and B), open-label study evaluated the efficacy of two RDV regimens (5- or 10-day course) compared with SoC in participants with moderate COVID-19. Data from participants in Part A (n=596), conducted between March 15, 2020, and June 26, 2020, are available. The primary efficacy endpoint was the efficacy of two RDV regimens with respect to clinical status compared with the SoC group, as assessed by a 7-point ordinal scale on Day 11.[3,6]

Participants with AST or ALT levels >5 × ULN at baseline were excluded. Monitoring of AST/ALT levels was conducted according to SoC practice or at least on Days 1, 3, 5, 8, 10, and 14. Doses of RDV were held if ALT levels increased to >5 × ULN or if ALT levels were >3 × ULN and total bilirubin levels were >2 × ULN (confirmed with repeat testing).[3]

Hepatic safety results[4]

AST/ALT level abnormalities occurred at a similar rate in all treatment groups. There were no significant differences in AST or ALT levels over time between participants who received RDV and those who received SoC.

Table 3. SIMPLE Study: Hepatic Safety in Participants With Moderate COVID-19[3,4]

Safety Outcomes, n/N (%)		5-Day RDV (n=191)	10-Day RDV (n=193)	SoC (n=200)
Any-grade laboratory abnormality		131/180 (73)	128/179 (72)	136/186 (73)
Grade 3		18/180 (10)	25/179 (14)	25/186 (13)
Grade 4		5/180 (3)	4/179 (2)	9/186 (5)
AST increase	Any grade	56/177 (32)	56/175 (32)	60/182 (33)
	Grade 3[a]	3/177 (2)	2/175 (1)	6/182 (3)
	Grade 4[b]	1/177 (1)	0	5/182 (3)
ALT increase	Any grade	61/179 (34)	57/177 (32)	71/182 (39)
	Grade 3[a]	4/179 (2)	6/177 (3)	11/182 (6)
	Grade 4[b]	0	0	3 (2)

[a]Grade 3 AST/ALT increase was defined as a ≥5 to <10 × ULN increase from baseline.
[b]Grade 4 AST/ALT increase was defined as a ≥10 × ULN increase from baseline.

SIMPLE Study: RDV in Severe COVID-19

Study design and demographics

A phase 3, randomized, two-part (Parts A, n=397; and B), open-label study evaluated the safety and efficacy of 5-day or 10-day RDV dosing regimens, in addition to SoC, in participants with severe manifestations of COVID-19. The primary outcome was the efficacy of two RDV regimens with respect to clinical status, assessed by a 7-point ordinal scale on Day 14.[5]

Participants with AST or ALT levels >5 × ULN at baseline were excluded. AST/ALT levels were measured on Days 1, 3, 5, 8, 10, and 14. Doses of RDV were held if ALT levels increased to >5 × ULN or if ALT levels were >3 × ULN and total bilirubin levels were >2 × ULN (confirmed with repeat testing).[5,7]

At baseline, the following median (IQR) AST levels were measured: 10-day RDV group, 46 (34–67) U/L; 5-day RDV group, 41 (29–58) U/L. The following median (IQR) ALT levels were measured: 10-day RDV group, 36 (23–58) U/L; 5-day RDV group, 32 (22–50) U/L.[5]

Hepatic safety results[5]

Participants in the 10-day and 5-day RDV groups experienced similar rates of ALT and AST increases (Table 4).

Table 4. SIMPLE Study: Hepatic Safety in Participants With Severe COVID-19[5]

Safety Outcomes, n (%)		10-Day RDV (n=197)	5-Day RDV (n=200)
AEs	ALT increased	15 (8)	11 (6)
	AST increased	13 (7)	10 (5)
	AEs that led to RDV discontinuation	20 (10)	9 (4)
Serious AEs	Aminotransferase levels increased	2 (1)	3 (2)

Most of the laboratory abnormalities were transient, and there were no significant differences in the median changes in laboratory abnormalities between treatment groups at Day 14. Participants in the 10- and 5-day RDV groups experienced similar rates of Grade ≥3 AST/ALT elevations and bilirubin increases (Table 5).

Table 5. SIMPLE Study: Grade ≥3 Hepatic Laboratory Abnormalities in Participants With Severe COVID-19[5]

Key Laboratory Abnormalities, n/N (%)		10-Day RDV (n=197)	5-Day RDV (n=200)
Any Grade ≥3 laboratory abnormality		64/191 (34)	53/195 (27)
AST elevation	Grade 3	7/190 (4)	11/94 (6)
	Grade 4	4/190 (2)	3/194 (2)
ALT elevation	Grade 3	11/191 (6)	8/194 (4)
	Grade 4	5/191 (3)	4/194 (2)
Bilirubin increased	Grade 3	3/190 (2)	1/193 (1)
	Grade 4	1/190 (1)	0

Note: Grading was defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, July 2017.

References

1. VEKLURY, Gilead Sciences Inc. VEKLURY® (remdesivir) for injection, for intravenous use. U.S. Prescribing Information. Foster City, CA.
2. Force L, Blair C, Duckworth J, et al. Hepatic Safety of Remdesivir Across Phase 3 Placebo-controlled COVID-19 Studies [Poster 524]. Paper presented at: IDWeek; October, 11-15, 2023; Boston, MA, USA.
3. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA.* 2020;324(11):1048-1057. https://jamanetwork.com/journals/jama/fullarticle/2769871
4. Criner G, Ahn MY, Huhn G, et al. Safety of Remdesivir vs Standard of Care in Patients With Moderate COVID-19 [Poster 561]. Paper presented at: IDWeek Virtual; 21-25 October, 2020.
5. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Eng J Med.* 2020:1-11.
6. ClinicalTrials.gov. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment. ClinicalTrials.gov Identifier: NCT04292730. Last Updated: 26 January, 2021. 2020.
7. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [Protocol]. *N Eng J Med.* 2020.

Abbreviations

AUC_{∞}=area under the concentration-time curve from time 0 to infinity
ACTT=Adaptive COVID-19 Treatment Trial
AE=adverse event
C_{max}=maximum observed drug concentration
DAIDS=Division of AIDS
RDV=remdesivir
SoC=standard of care
ULN=upper limit of normal

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Veklury US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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