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Veklury® (remdesivir) Use in Hepatic Impairment

This document is in response to your request for information regarding the use of Veklury® (remdesivir [RDV]) in patients with hepatic impairment. This response was developed according to principles of evidence-based medicine and contains information from phase 3 clinical trials and a selected phase 1 study in patients with hepatic impairment and matched control groups.

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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 Labeling[1]

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 × ULN. Discontinue RDV if ALT elevation is accompanied by signs or symptoms of liver inflammation.

No dosage adjustment of RDV is recommended for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).

Clinical Data on RDV Use in Hepatic Impairment

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. Twenty-six participants had a history of chronic liver disease: ACTT-1, n=14; REDPINE, n=11; and PINETREE, n=1. No safety concerns were identified regarding the use of RDV in this population.[2]

In a phase 1, open-label, single-dose PK study, plasma exposures to RDV and its metabolites were generally similar between participants with moderate hepatic impairment and matched individuals with normal hepatic function (Cohort 1; n=10 per matched group). Plasma exposures to RDV and GS-704277 were higher in the severe hepatic impairment group than in the matched normal hepatic function group (Cohort 2; n=6 per matched group); exposures were similar between groups for the GS-441524 metabolite. RDV was generally well tolerated across groups; 2 participants in each group per cohort reported AEs.[3]

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 × the 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.

Clinical Pharmacology

PK

Patients with hepatic impairment

The PK 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_{inf}, C_{max}) of RDV and GS-441524 were similar in subjects with moderate hepatic impairment and higher in subjects with severe hepatic impairment. The exposure differences in subjects with severe hepatic impairment are not considered to be clinically significant.

Please refer to the US FDA-approved prescribing information for additional information regarding PK of patients with hepatic impairment (Section 12.3 Pharmacokinetics).

Clinical Data on RDV Use in Hepatic Impairment

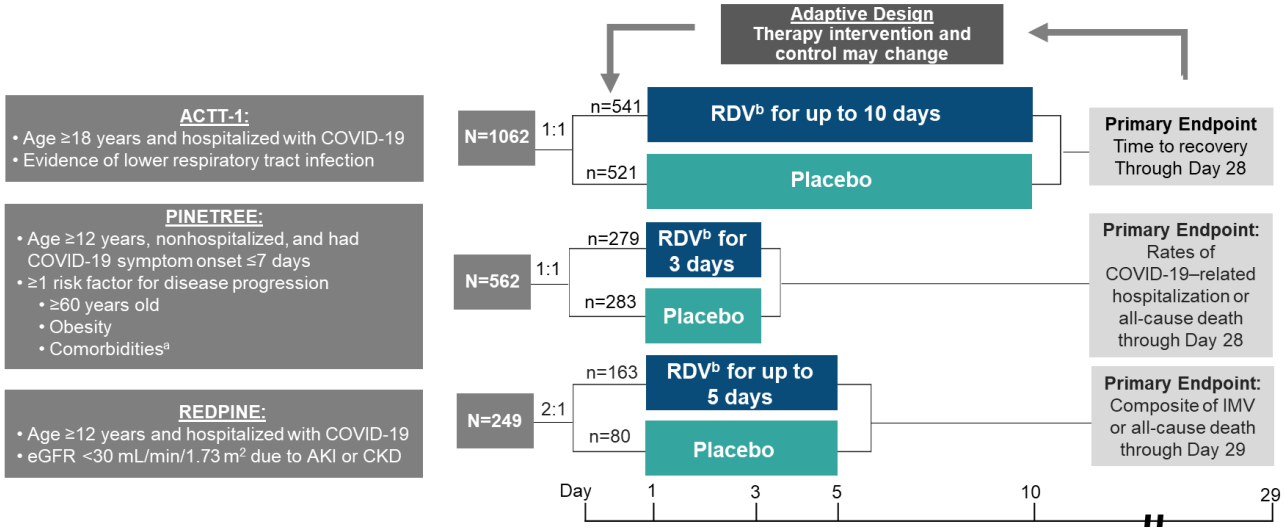
Currently, there are no Gilead studies that have evaluated the use of RDV in participants with hepatic impairment.

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. Chronic liver disease was defined in ACTT-1 by investigator per the case report form and in PINETREE and REDPINE by baseline medical history for any chronic liver disease, such as hepatic cirrhosis or nonalcoholic steatohepatitis. Overall, 26 participants who received RDV had a history of chronic liver disease: ACTT-1, n=14; REDPINE, n=11; and PINETREE, n=1.

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



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

Results

A review of AEs that were reported for the 26 participants with a history of chronic liver disease identified no safety concerns about the use of RDV in this population.

Phase 1 PK Study in Normal, Moderate, and Severe Hepatic Impairment[3]

Study design and demographics

A phase 1, open-label, multicenter study (N=32) evaluated PK profiles of RDV and its metabolites, GS-704277 and GS-441524, in participants with normal, moderate, or severe hepatic impairment. Eligible participants were aged 18 to 75 years and had $CrCl_{CG}$ ≥60 mL/min; in the participants with hepatic impairment, impairment was required to be present for >6 months, and no changes in hepatic status within 2 months of study screening were permitted. Those with normal hepatic function were matched by age (±10 years), sex, and BMI (±20%) with participants with moderate hepatic impairment (CPT Class B; n=10 per matched group) in Cohort 1 and with participants with severe hepatic impairment (CPT Class C; n=6 per matched group) in Cohort 2. Participants received a single 100-mg dose of RDV IV, and blood samples were taken before dosing, mid-infusion, and at regular intervals up to 168 hours after dosing.

Table 1. Phase 1 PK Study: Baseline Demographics and Disease Characteristics[3]

Key Demographics and Characteristics		Cohort 1		Cohort 2	
		Moderate Hepatic Impairment (n=10)	Matched: Normal Hepatic Function (n=10)	Severe Hepatic Impairment (n=6)	Matched: Normal Hepatic Function (n=6)
Age, median (range), years		59 (40–69)	60 (39–73)	56 (41–64)	56 (51–64)
Male, n (%)		6 (60)	6 (60)	2 (33.3)	2 (33.3)
Race, White/Black, n (%)		10 (100)/0	7 (70)/3 (30)	6 (100)/0	5 (83.3)/1 (16.7)
Hispanic or Latinx, n (%)		7 (70)	5 (50)	4 (66.7)	6 (100)
BMI, median (range), kg/m^2		29.8 (24–37)	28.8 (22.9–35.4)	29.1 (21.9–34.7)	28 (22.9–34.6)
eGFR, median (range)	CG, mL/min	116 (58.7–196)	105 (64–143)	104 (81.6–115)	95.7 (86.5–139)
	MDRD, $mL/min/1.73\ m^2$	89.6 (55.6–133)	88.7 (75.4–110)	78.4 (53.7–121)	88.3 (74.2–108)
Renal impairment,[a] n (%)	CG	3 (30)	2 (20)	1 (16.7)	1 (16.7)
	MDRD	5 (50)	5 (50)	5 (83.3)	5 (83.3)

[a]Defined as $eGFR_{CG}$ <90 mL/min or $eGFR_{MDRD}$ <90 mL/min/1.73 m^2.

PK results

Plasma exposures to RDV and its metabolites were generally similar between those with moderate hepatic impairment and its matched group (Table 2). Plasma exposures to RDV and GS-704277 were higher in the severe hepatic impairment group than in its matched group (Table 2); exposures for GS-441524 were similar between groups.

Table 2. Phase 1 PK Study: PK Parameters for RDV, GS-704277, and GS-441524[3]

PK Parameters		Cohort 1		Cohort 2	
		Moderate Hepatic Impairment (n=10)	Matched: Normal Hepatic Function (n=10)	Severe Hepatic Impairment (n=6)	Matched: Normal Hepatic Function (n=6)
RDV	AUC_{inf},[a] h·ng/mL	1690 (34.5)	1460 (35.6)	2850 (26.7)	1820 (24.3)
	C_{max},[a] ng/mL	3050 (37.2)	2910 (40.8)	4520 (29.1)	4570 (42.5)
	$AUC_{inf\text{-}unbound}$,[a] h·ng/mL	95.6 (53.2)	77.5 (23.3)	189 (17.6)	78.5 (24.5)
	$C_{max\text{-}unbound}$,[a] ng/mL	171 (53.4)	155 (32.2)	295 (24.8)	197 (42.8)
	T_{max},[b] h	0.25 (0.25–0.25)	0.38 (0.25–0.5)	0.5 (0.5–0.5)	0.5 (0.25–0.5)
	Cl,[a] mL/h	64,100 (26.7)	86,600 (76.2)	37,000 (22.7)	57,900 (25.2)
	$t_{1/2}$,[b] h	0.84 (0.8–1.01)	0.9 (0.68–0.91)	0.96 (0.85–1.68)	0.82 (0.76–0.9)
	V_z,[a] mL	82,800 (29.2)	104,000 (89.5)	55,800 (27.1)	66,200 (33.4)
GS-704277	AUC_{inf},[a] h·ng/mL	482 (52.3)	330 (35.2)	108 (47.8)	422 (22.4)
	C_{max},[a] ng/mL	251 (61.8)	216 (82.6)	333 (28.5)	331 (45.1)
	T_{max},[b] h	0.88 (0.75–1)	0.75 (0.5–0.75)	1 (1–1)	0.63 (0.5–0.75)
	$t_{1/2}$,[b] h	1.28 (1.02–1.87)	1.15 (0.98–1.36)	1.86 (1.33–2.16)	1.14 (0.93–1.35)
GS-441524	AUC_{inf},[a] h·ng/mL	2490 (36)	2680 (25.5)	4280 (46.7)	3040 (9.2)
	C_{max},[a] ng/mL	93 (25.9)	88 (36.2)	145 (29)	96.7 (17.7)
	T_{max},[b] h	2 (1.5–4)	2 (2–2)	2.97 (1.5–4)	2 (2–4)
	$t_{1/2}$,[b] h	23.6 (22.8–26.4)	29.5 (26.1–33)	34.7 (30–35.7)	27.7 (25.3–30.6)

Abbreviations: Cl=plasma clearance; CV=coefficient of variation; $t_{1/2}$=elimination half-life; T_{max}=time to maximum concentration; V_z=volume of distribution.
[a]Data are presented as arithmetic mean (%CV). [b]Data are presented as median (range).

GLSM ratios for AUC_{inf} and C_{max} were generally similar between the moderate hepatic impairment and matched normal hepatic function groups (Table 3). The AUC_{inf} for RDV, GS-704277, and GS-441524 in the severe hepatic impairment group were 1.56-, 2.41-, and 1.31-fold higher, respectively, than in its matched group, and the GLSM ratio for C_{max} of GS-441524 was 1.48-fold higher in the severe hepatic impairment group than in its matched group. The $AUC_{inf\text{-}unbound}$ and $C_{max\text{-}unbound}$ for RDV were 2.44- and 1.57-fold higher, respectively, in the severe hepatic impairment group than in its matched group; there were no significant differences in unbound RDV exposures between the moderate hepatic impairment group and its matched group (Table 3).

Table 3. Phase 1 PK Study: GLSM Ratios of RDV, GS-704277, and GS-441524 in Participants With Moderate or Severe Hepatic Impairment vs Matched Participants With Normal Hepatic Function[3]

GLSM Ratio (90% CI)		Moderate Hepatic Impairment (n=10)	Severe Hepatic Impairment (n=6)
RDV	AUC_{inf}, h·ng/mL	1.21 (0.87–1.67)	1.56 (1.2–2.03)
	C_{max}, ng/mL	1.1 (0.75–1.6)	1.03 (0.7–1.51)
	$AUC_{inf\text{-}unbound}$, h·ng/mL	1.15 (0.86–1.54)	2.44 (1.93–3.08)
	$C_{max\text{-}unbound}$, ng/mL	1.04 (0.73–1.48)	1.57 (1.08–2.29)
GS-704277	AUC_{inf}, h·ng/mL	1.38 (0.92–2.07)	2.41 (1.7–3.42)
	C_{max}, ng/mL	1.29 (0.54–3.08)	1.07 (0.7–1.63)
GS-441524	AUC_{inf}, h·ng/mL	0.9 (0.69–1.17)	1.31 (0.93–1.84)
	C_{max}, ng/mL	1.09 (0.86–1.38)	1.48 (1.17–1.86)

Safety

RDV was generally well tolerated; 2 participants in each group per cohort reported AEs, and no Grade 3 or 4 AEs or deaths were reported.

In Cohort 1, all AEs were Grade 1 and related to RDV. Two AEs (20%) of headache were reported in the moderate hepatic impairment group, and 1 AE (10%) each of headache and rash were reported in its matched group. Laboratory abnormalities in the moderate hepatic impairment and matched normal hepatic function groups were reported in 8 (80%) and 3 (30%) participants, respectively, and were mostly Grade 1 or 2 in severity.

In Cohort 2, all AEs were Grade 1 or 2, and none were related to RDV. Among those with severe hepatic impairment, the following AEs occurred in 1 participant (16.7%) each: abdominal pain (upper), epistaxis, herpes zoster, nausea, and pain in extremity. Among the matched participants with normal hepatic function, dry skin and neck pain each occurred in 1 participant (16.7%). Laboratory abnormalities were reported by every participant in the severe hepatic impairment and matched normal hepatic function groups and ranged from Grade 1 to 3 in severity.

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. Regan S, Humeniuk R, Caro L, et al. Pharmacokinetics of SARS-CoV-2 RNA Polymerase Inhibitor Remdesivir in Participants With Moderate and Severe Hepatic Impairment. *Clin Transl Sci.* 2025;18(2):e70159. https://www.ncbi.nlm.nih.gov/pubmed/39945591

Abbreviations

ACTT=Adaptive COVID-19 Treatment Trial
AE=adverse event
AUC_{inf}=area under the concentration-time curve from time 0 to infinity
$AUC_{inf\text{-}unbound}$=area under the concentration-time curve from time 0 to infinity for unbound remdesivir
CG=Cockcroft-Gault formula
C_{max}=maximum concentration
$C_{max\text{-}unbound}$=maximum concentration for unbound remdesivir
CPT=Child-Pugh-Turcotte
GLSM=geometric least squares mean
GS-441524=predominant circulating metabolite of remdesivir
GS-704277=intermediate metabolite of remdesivir
MDRD=Modification of Diet in Renal Disease formula
PK=pharmacokinetic(s)
RDV=remdesivir
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

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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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